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Iraqi Journal of Medical Sciences

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3. Chapter in book: Phillips, S.J., and Whisnant, J.P.: Hypertension and strock. In: Laragh, J.H., and Brenner, B.M. editors. Hypertension: Pathophysiology, diagnosis, and management. 2nd ed. NewYork: Raven Press; 1995. p. 465-78.

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رقم الإيداع في دار الكتب و الوثائق ببغداد ٧٠٩ لسنة ٢٠٠٠

SCIENCE AND ART IN THE PRACTICE OF MEDICINE

Khalid Abdulla *FRCP*

Medicine is said to be a mixture of science and art. The question is which part is science and which is art?

Science is knowledge based on information obtained through human senses (frequently aided with various instruments) and logical conclusions from them. Its contents are measurable and reproducible (i.e. gives the same result when repeated by the same or a different person) and it follows strict rules and laws.

Art is a human activity which depends on judgment, intuition, gift and experience. It is not readily measurable, not reproducible and does not usually obey strict rules and laws.

Science in the practice of medicine:

Modern medicine depends to a large extent on various biological sciences like physiology, biochemistry, anatomy, pathology, microbiology, pharmacology etc. It is also increasingly dependent on modern technology which in turn depends on sciences like physics, chemistry and mathematics. More importantly the modern doctor, at least the good one, is scientific in his approach to patients' problems. He does not presume that illness is produced by an evil spirit which he should rid the patient off by beating him. Or that it is the result of some change in body mixtures for which he has no evidence. Instead he will define the problem, make a preliminary hypothesis about diagnosis, collect evidence, formulate a main hypothesis, test it, if valid apply it and if not reject it and look for another one. This approach is the same that scientists follow when they tackle their problems, the so called the ***scientific method.***

Art in the practice of medicine:

The first thing a doctor does when he meets a patient is to take the history of the illness. This doctor-patient encounter contains so many things that are not measurable, not reproducible and not controlled by strict rules and laws. The look on the face of the doctor, the tone of his voice, the choice of the questions and the wording of them, the way he listens or interrupts all fall more in the realm of art than science. The doctor tries to give the proper weights for various symptoms but can he measure pain, nausea, or dizziness? Through experience he may attach great importance on some symptoms and trivialize others.

When he feels the abdomen he does not have a measure of the pressure he applies with his hand, and no units with which he accurately measures the tenderness or the consistency of an enlarged liver. If he repeats the examination or some one else does, he may give a different estimate. When he listens to the heart or the chest, he does not usually use a device which measures heart sounds, breath sounds or murmurs in an accurate and reproducible way. The same thing applies to

examination of reflexes, mentality, speech, joints, muscles, masses etc.

When he decides to do some tests, does he have strict rules which tell him what test should be done and what should not? Or is it a matter of vague ill defined judgment on how much is the test likely to be useful and how much is it likely to do harm?

The same applies when he decides on treatment. Treatment may produce benefit and may do harm. The balance between the two usually depends on that vague thing called ***'clinical judgment'*** which we cannot define, cannot measure and which may vary between different doctors and in the same doctor at different times. It is not measurable and not reproducible.

All these activities fall in the category of art. I can mention a lot more in various fields of medical practice like surgery, obstetrics, pathology etc. and about various procedures which require, beside judgment, manual skills.

This part of medicine, the art of it, is usually learned by experience and by working with someone who is good at it. Reading books and attending lectures is not the way to improve it. This is one of the defects in our medical education system. Students concentrate on the science part of medicine. We cannot blame them much if examiners do not concentrate on it when they assess students in examinations. Assessing it requires a skill which only experienced examiners have.

LATE POTENTIAL IN ACUTE MYOCARDIAL INFARCTION WITH AND WITHOUT VENTRICULAR ARRHYTHMOGENIC EVENTS

Haydar G. Ewadh* *M.Sc.*, **Amar AL-Hamdi**** *FRCP*, **Ginan AL-Dahan*** *Ph.D.*

Abstract

Signal Averaged Electrocardiography (SAECG) method has been conducted using (XYZ) leads system and a (FIR) filter of 40 Hertz cutoff frequency for signal processing.

The value of this method had been tested in 32 patients (PTS) with Acute Myocardial Infarction (AMI) compared to control group of comparable number, age and sex. The patients were devided into subgroup I with the presence of Ventricular Arrythmogenic Events (VARGE) and subgroup II without VARGE.

The Filtered QRS (FQRS) duration in the control group was 149msc.maximum, so values more than 150msc.considered prolonged. The averaged duration of the FQRS in the patients groups is significantly higher than in the control group. Moreover the subgroup I showed a prolonged FQRS in 89% of patients while subgroup II had a 52% prolonged FQRS. This gave it a sensitivity of 89% and specificity of 47% as an index of ventricular arrhythmogenicity.

Late potential (LP) was defined as a low amplitude (below 25 microvolt), high frequency signal in the last 40 mesc of the FQRS. None of the control group showed LP according to the above criteria. LP was seen in 89% in subgroup I and in 52% of subgroup II. No difference in the presence of LP was seen during the first or second week after AMI.

The presence of LP in patients with AMI is a highly sensitive index of the AMI patient s liability to develop VARGE. Further longer follow up studies are needed to correlate LP resolution and long term VARGE occurrence in AMI.

Key words: Late Potential, Acute Myocardial Infarction

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Introduction

Late potential (LP) is a low voltage, high frequency micro potential in the last 40 msc of the F.QRS. It is due to slow impulse conduction within a diseased region in the myocardium involved by ischemia. Since they are of micro level, they can not be detected by the limits of the standard Electrocardiogram (ECG)[1].

Both animals and human studies demonstrated the relationship of these LP s recorded directly from the heart or from the body surface in VT or VF following myocardial infarction[2].

Detection of LP is the focus of interest of a relatively recent technique that depends on computer for signal averaging. Signal averaging can be applied for any periodic signals and when the cardiac signals are the one of interest, it is called the Signal Averaged Electrocardiography (SAECG)[3].

The aim of this study is to confirm the method of recording LP from the body surface and to concentrate on LP in AMI, after establishing a basic normative data from normal subjects.

Patients & Methods

Thirty two healthy subjects were chosen as a control group, their age was ranging between 40-60 years with a mean of 52 years. After history, physical examination, ECG, Echocardiography and CXR they were all found free from heart disease.

The patients composed of 32 selected patients with AMI admitted to AL-Kadhimiya Teaching Hospital- Coronary Care Unit. The age range was 40-70 years, a mean of 53 years. Diagnosis of AMI was done according to the following criteria: **a:** ischemic chest pain of more than thirty minutes duration. **b:** evolving ECG changes. Patients selected should be in sinus rhythm, have no conduction delay or bundle branch block, not on antiarrythmic therapy, have normal electrolyte and not in shock state. VARGE considered being present if the patient has: sustained or non-sustained VT or recovered VF. Patients were divided into two subgroups: I with VARGE and II without VARGE.

The recording was done at time of hospital discharge 4-16 days after AMI. The recording took 10-20 minutes. The instrument used was a Dantec Counterpoint which is initially used for electromyography (EMG). The position of the electrodes was done according to the XYZ axis system where Y is in the left midclavicular line,

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Z in the anteroposterior line, the X is the horizontal line which intersects the Y at a right angle. Grounding electrode is applied to the wrist and soaked with normal saline.

The ECG signals were averaged after taking single beat as a template, all the subsequent beats were tested against the template and accepted or rejected, and the number of the averaged signals is 300-400 beats.

To simplify the analysis of the filtered QRS a single signal created from the three axes, this is the Filtered QRS (F.QRS) which is measured from the start of the ventricular depolarization to its end. The amplitude of the signal in last 40 msc of F.QRS measured in m. volts is called the L 40 which represents the Late Potential (LP). Positive late potential in this study is defined as a low amplitude signal of less than 25m volt at the last 40 msc Of the F.QRS

Results

The total number of the control group was 32; their mean age was 52 years. The patients were 32 with a mean age of 53 year. The male to female ratio was 2:1.

The maximum F.QRS duration represented by the averaged Ventricular Depolarization (VD) duration, in the control was 149 msec which was taken as the normal in this study, values more than 150 msec considered prolonged.

20/32 (63%) of the patients showed a F.QRS duration more than 150 msec, in subgroup I 8/9 (89%) had prolonged F.QRS and in subgroup II 12/23 (52%). This gives a prolonged F.QRS as a parameter to define arrythmogenicity, a sensitivity of 89% and specificity of 47%.

Positive LP was found in 21/32 (65%), in subgroup I 8/9 (89%) have a positive LP, subgroup II have a 13/23 (57%) positive LP. Accordingly positive LP has a sensitivity of 87% and specificity of 45% as an index of arrhythmogenicity (Table 1).

Table 1: Showing the incidence of prolonged F.QRS and positive LP in the control and patients group

Entity	SG. I	%	SG. II	%	Control	%	Sen.	Spe.
F.QRS >150msc	8/9	89 %	12/23	58 %	0/32	0	89%	47%
Positive LP	8/9	89 %	13/23	57 %	0/32	0	87%	45%

SG. = subgroup, Sen. = Sensitivity, Spe. = specificity

No one in the all 32 persons in the control group showed positive LP (Figure 1), notice the positive LP and the long F.QRS in AMI patients with VARGE and the negative LP and the normal F.QRS duration in the control or in patients without VARGE.

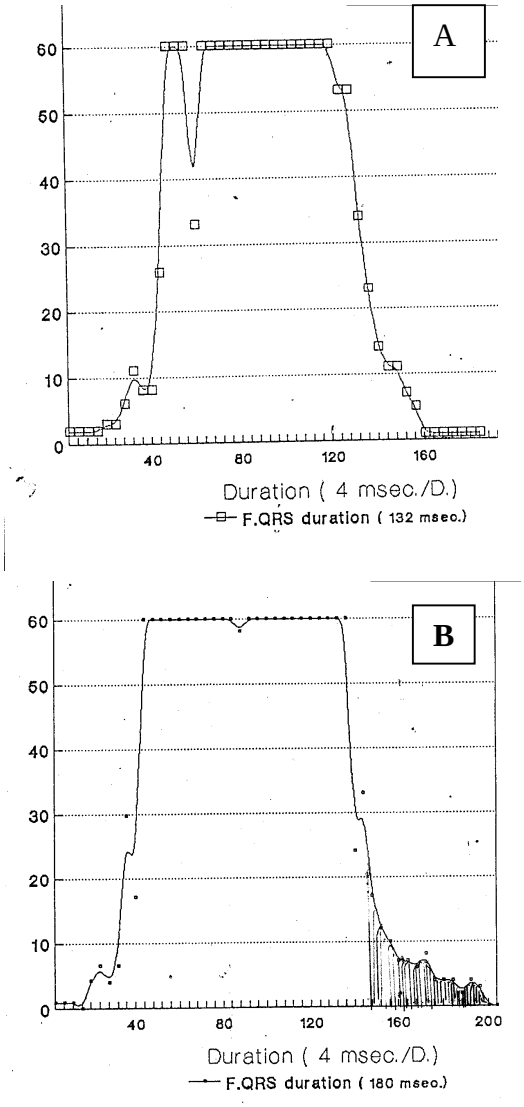

Figure 1 a: Ventricular Depolarization of heart with M.I. (no late potential, no ventricular arrhythmias), b: Ventricular Depolarization of heart with M.I. (with late potential & ventricular arrhythmias)

The incidence of the highest sensitivity and specificity parameters are the same during the first and the second week after AMI.

Discussion

For the last decade, several investigators with the use of a new processing technique showed that the SAECG can identify patients at high risk of developing ventricular arrhythmias when LP has been observed at the end of the F.QRS in the early ST-segment[1,4]. Others correlated signals with the fragmented electro grams detected

during epicardial or endocardial mapping[1,5,6]. These fragmented electrograms represent areas where conduction is slow and then re-entry can occur.

A great deal of arguments still exists regarding the lead system, signal processing and the parameters that could define LP. We used the XYZ which we believe is the most suitable currently used system. The filter type has a great effect on the identifying the LP. We used FIR filter which has not been used before our study to identify these signals. This filter can preserve the actual morphology of the VD wave allowing better identification of LP.

There are some differences in the reported incidences and prognostic values of LP in AMI which can be explained by: a, the use of different recording techniques. b, the definitions of LP. c, timing of the record in the post AMI period.

In this study the presence of LP would identify patients who developed clinically significant ventricular arrhythmias with a sensitivity of 89% and specificity of 49%. Mcguire managed to define VT in AMI with a sensitivity of 80% and specificity 72%[8]. EL-Sherif described certain criteria that would define VT with a sensitivity of 42-84% and specificity of 52-84%[11]. Kertes and Denis found less incidence of 16% in there studies[9,10]. The reason for such a difference may be due to different methods for recording and identification of LP and the definitions of LP.

In the VARGE patients we recorded positive LP before and after the occurrence of VT or VF, this finding signifies the value of the positive LP in the acute phase of MI to suggest the liability of LP positive patients to VARGE.

The use of antiarrhythmic drugs and thrombolytic therapy have a role in reducing the LP appearance and thus reduces the incidence of developing VARGE, these correlation between AMI and LP were the interest of many studies[7].

In conclusion we have been able to record LP through SAECG by using an EEG signal averaged instrument, and we confirmed that positive LP is a sensitive index for ventricular arrhythmogenicity in patients with AMI and can be well used as a routine screening test for this identification which is of great clinical diagnostic, therapeutic and prognostic value.

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S2- COMPLEX AS A NEW ANTI-LEISHMANIAL DRUG

Nada M. Al-Bashir* *B.Sc., Ph.D.*, **Ameena S.M. Juma**** *B.Sc., Ph.D.*, **Amani A.W.A.A. Razzak*** *B.Sc., Ph.D.*

Abstract

Background: Visceral leishmaniasis is a severe and often fatal disease, which is caused by the Leishmania donovani complex. S2- complex is an immunomodulator that has been used in the treatment of different cancers.

Aim: This study was conducted to evaluate the effect of S2-complex on the different stages of L. donovani and its possible future use as an anti-leishmanial drug.

Materials & Methods: Different stages of L.donovani were used. These stages are the promastigote and the amastigote (intracellular and axenic amastigotes). The direct effect of S2-complex on the promastigotes and the amastigotes was studied by the calculation of the ED_{50} value.

Results: The ED_{50} of the treated promastigotes after 3 days was 0.125 mg/ml and of the intracellular amastigotes 0.008 mg/ml and of the axenic amastigotes 0.033 mg/ml. No significant difference was found in the ED_{50} of the two types of amastigotes while a significant difference was found between the ED_{50} of the promastigotes and the amastigotes.

Conclusions: The results indicate the higher sensitivity of the amastigotes to the S2-complex in comparison to the promastigotes. Hence, S2-complex could be a possible future drug for the treatment of visceral leishmaniasis.

Keywords: Leishmania donovani, Immunomodulator drugs, S2-complex.

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Introduction

Leishmaniasis occurs throughout the tropical and subtropical regions of the world with an estimate of 12 million cases per year and 350 million people at risk[1,2]. The visceral form of leishmaniasis is a severe and often fatal disease that is caused by the L.donovani complex[3]. In Iraq, many investigators have noticed that children with visceral leishmaniasis showed marked differences in the severity of the disease as well as their response to chemotherapy[4-6].

The pentavalent antimonials, amphotericin and pentamidine are used for the treatment of leishmaniasis. Some of these agents are not effective (especially for the most virulent strains) and all have serious toxic side effects, including cardiac and/or renal failure[2,7]. Moreover, therapeutic failures have been reported in up to 15% of cases, which are either due to initial failure to respond to treatment or relapse[8] .A new oral treatment for visceral leishmaniasis has been established which had an overall cure rate greater than 90%. It was also found that it is specific and on the whole not too toxic. The major drawback is its effect on the fetus, and for this reason it cannot be used as a mass outpatient treatment[2].

Since normal immune responses in human visceral leishmaniasis are often depressed and the protective immune responses are not elicited[9], trials and experiments are needed to find either a new drug or an immunomodulator drugs to be used in combination with the existing drugs of choice for leishmaniasis.

S2-complex is an immunomodulator that has been established at College of Medicine, Al-Nahrian University. It has been used in the treatment of different cancers, for it may augment macrophages, B-cells and T-cells[10]. Thus, this study was conducted to evaluate the effect of the S2-complex on the different stages of L.donovani and its possible future use as an anti-leishmanial drug.

Materials & Methods

The parasite

Leishmania donovani (MHOM/ IQ/ 82/ BRC1) was used. The parasite was stored in liquid nitrogen and maintained by continuous passage in Balb/ C mice.

Drug efficacy

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Promastigotes: They were cultivated in RBLM medium[11]. On the day of the experiment, when the promastigotes were at the logarithmic growth phase, they were adjusted to 1 X 10^6 cells/ ml in RBLM medium, supplemented with 10% faetal calf serum (FCS). The drug was used in different concentrations (0.73, 0.365, 0.182, 0.09, 0.045, 0.022 mg/ ml of medium). The parasites were counted once daily for the following 4 days and the effect of the drug on the parasite (growth index [GI]) was determined. The GI is the mean number of the treated promastigotes divided by the number of untreated control promastigotes multiplied by 100, as .shown in the following equation[12]:

$$GI\ \% = \frac{\text{Mean number of treated promastigotes}}{\text{Mean number of untreated promastigotes (control)}} \times 100$$

Intracellular amastigotes: Mouse peritoneal macrophages were collected from Balb/ C mice and cultured in RBLM medium (Labtek 8 chamber slides) with 10 % FCS at 37°C in 5 % CO^2- air mixture. Macrophages were infected with promastigotes . Infected cultures were maintained in the medium containing different concentrations of the drug (0.365, 0.182, 0.091, 0.045 mg/ ml) for 4 days. After 4 days of exposure to the drug, the proportions of infected macrophages in Giemsa-stained preparations of each culture were determined. Axenic amastigotes: Promastigotes were grown in RBLM medium, containing 10% FCS, to reach the late logarithmic phase. An inoculum from this medium was transferred to RBLM medium supplemented with 20% FCS at a final pH of 5.2. This medium was then incubated at 37°C in 5% CO_2 for 3 days. Under these conditions, the promastigotes differentiate into amastigotes within 96 hours[11]. Fifty-percent effective dose (ED_{50}) values were calculated by linear regression analysis[13].

S2-complex

It was used as an immunopotentiating agent and prepared at the Medical Research Centre, College of Medicine, at the end of 1990.

Statistical analyses

The data were analyzed using the F-test[14].

Results

* The effect of S2-complex on the promastigotes:

Table 1 demonstrates the decrease in the total number of the promastigotes with the increasing concentrations of S2-complex at the time of exposure. The total number of live promastigotes, after 3 days, reached 6.2 X 10^6 cells/ ml in the control group compared to (1.36, 2.2, 2.6, 3.3, 3.96, 4.3) X 10^6 cells/ ml, using the S2-complex concentrations ranging from 0.73-0.022 mg/ ml respectively. The generation time was found to be 27 hours in the control group, while it was 34 hours at the concentration 0.022 mg/ ml and 160 hours at 0.73 mg/ ml.

Table 1: The effect of S2- complex on invitro culture of L.donovani BRC (AA3) promastigotes

Days after drug administration	Total No. of parasite cells (ml (X10 ^{6}) Drug concentration (mg/ml)						
	0.73	0.365	0.182	0.09	0.045	0.022	0 (control)
Day I	1.60± 0.42	1.85± 0.23	1.98± 0.11	2.30± 0.60	2.54± 0.07	2.65± 0.63	2.90± 0.09
Day 2	1.78± 0.24	1.96± 0.32	2.20± 0.69	2.50± 0.84	2.94± 0.50	3.01± 0.92	3.50± 11.20
Day 3	1.36± 0.94	2.20± 0.83	2.60± 0.69	3.30± 1.03	3.96± 1.02	4.30± 0.61	6.20± 1.87
Day 4	1.46± 0.50	1.91± 1.13	3.05± 0.73	5.96± 0.53	8.03± 0.63	9.73± 1.38	15.66± 6.77
Day 5	0.80± 0.41	3.83± 0,61	5.11± 0.23	7.65± 1.39	12.16± 1.72	17.50± 1.87	33.66± 3.60

-Data is presented as(mean ± SD) from 9 experiments.

-Log-phase promastigotes were seeded at 1x10^6 cells/ml in culture media with different concentrations of S2-complex as described in materials and methods. The viable cells were counted in a haemocytometre at different intervals as indicated.

Figure 1 shows the decrease in the growth index from 100% at 0 time and 0 concentration to 21.93% at 0.73 mg/ ml concentration and 69.35% at 0.022 mg/ ml. The ED_{50} and ED_{90} were found to be 0.125 and 1.46 mg/ ml respectively.

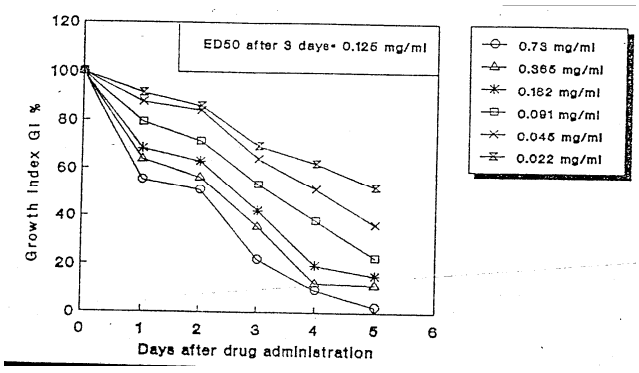

Figure 1: The effect of S2 complex on the growth of L.donovani BRC1 (AA3) promastigotes in culture at 25°C

*The effect of S2-complex on the amastigotes:

- Axenic amastigotes:

Table 2 demonstrates the total number of axenic amastigotes, cultivated at 37°C and 5% CO_2, after 3 days, which is 9.16 X 10^6 cells/ ml in the control group. The total number was (1.43, 1.96, 2.91, 4.21) X 10^6 cells/ ml using the S2-complex concentrations of 0.365-0.045 mg/ ml respectively. Moreover, the generation time was found to increase from 22.7 hours in the control group to 34.78 hours at the lowest concentration (0.045 mg/ ml) and 141 hours at the highest concentration (0.365 mg/ ml). This reflects the decrease in the growth index from 100% at 0 time and 0 concentration to 45.96 % at 0.045 mg/ ml concentration and 15.61% at 0.365 mg/ ml concentration. In addition, the ED_{50} and ED_{90} were found to be 0.03 and 0.697 mg/ ml respectively.

Table 2: The effect of various concentrations of S2-complex on the growth of the cultured axenic amastigotes

Days after drug administration	Total No. of parasite cells /ml (X10 ^{6})				
	Drug concentration (mg/ml)				
	0.365	0.182	0.09	0.045	0 (control)
Day I	1.48± 0.29	1.65± 0.52	1.76± 0.69	2.15± 0.63	3.00±0.5
Day 2	1.83± 0.55	2.01± 0.29	2.65± 0.32	3.33± 0.36	4.58±0.97
Day 3	1.43± 0.36	1.96± 0.16	2.91± 0.78	4.21± 0.44	9.16±4.40

-Data is presented as(mean ± SD) from 9 experiments.
-Log-phase amastigotes were seeded at 1xl06 cells/ml in culture media with different concentrations of S2-complex as described in materials and methods. The viable cells were counted in a haemocytometre at different intervals as indicated.

All these changes are demonstrated in figure 2.

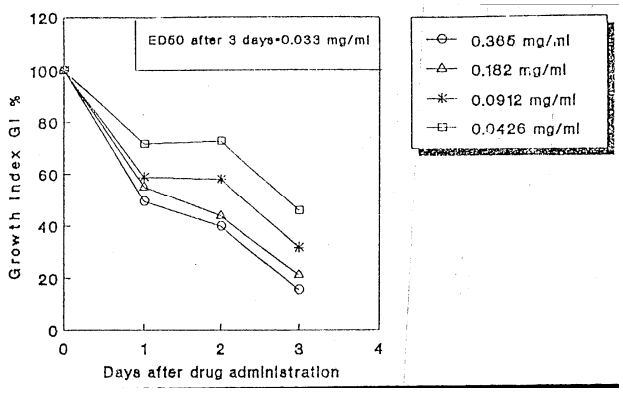

Figure 2: The effect of S2 complex on the growth of L.donovani BRC1 (AA3) amstigotes in culture at 37°C

- Intracellular amastigotes:

Similar results to the axenic amastigotes were found in the intracellular amastigotes. The exposure of the parasite to the S2- complex led to the decrease in the number of multiplying parasites inside the macrophages, in addition to the decrease in the percentage of infected macrophages, as shown in table 3.

Table 3: The effect of S2- complex on in vitro culture of L.donovani BRC1 (AA3) amastigoites in mouse peritoneal macrophages

Days after drug adm.	Drug concentration 0.365mg/ml		Drug concentration 0.182 mg/ml		Drug concentration 0.09 mg/ml		Drug concentration 0.045 mg/ml		control	
	% No. of IM	A/M	% No. of IM	A/M	% No. of IM	A/M	% No. of IM	A/M	% No. of IM	A/M
Day I	24.0 ± 2.60	2.46 ± 0.22	28.33 ± 0.45	2.83 ± 0.47	28.16 ± 2.78	3.23 ± 0.87	33.5 ± 5.28	4.05 ± 0.50	48.64 ± 5.82	4.90 ± 0.77
Day 2	12.66 ± 4.50	1.75 ± 0.84	22.0 ± 4.73	2.66 ± 1.00	30.33 ± 9.15	3.56 ± 0.97	32.83 ± 5.56	3.13 ± 0.53	53.3 ± 2.50	6.31 ± 0.80
Day 3	9.16 ±3.37	1.21 ± 0.39	14.5 ± 4.80	2.11 ± 0.34	20.83 ± 5.30	2.25 ± 0.65	33.3 ± 3.26	3.23 ± 0.47	75.95 ± 9.59	10.5 ± 2.73

IM = infected macrophages, A/M = amastigotes/macrophage
-Data is presented as (mean ± SD) from 9 experiments.

This also led to the decrease in the percentage of parasite survival index from 100% to 13.7% at the 0.045 mg/ ml and 1.38% at 0.365 mg/ ml of S2-complex concentration. The ED_{50} and ED_{90} were found to be 0.008 and 0.06 mg/ ml respectively, as shown in figure 3.

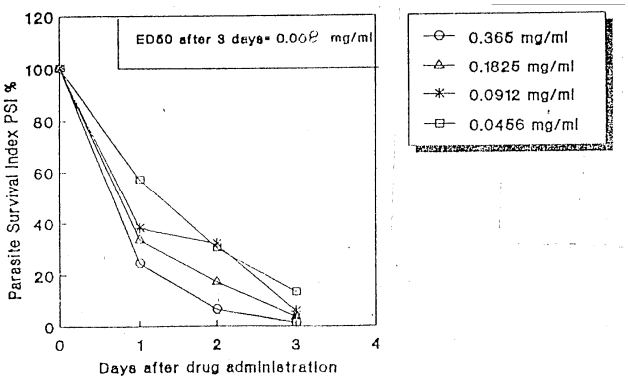

Figure 3: The effect of S2 complex on the growth of L.donovani BRC1 (AA3) amstigotes in BALB/c mouse peritoneal macrophages at 37°C

Figure 4A represents the intracellular amastigotes, where their numbers have decreased in comparison to the control (figure 4C). The figure shows the lysis and digestion of the parasite and not direct killing (the action of other anti-leishmanial drugs). Figure 4B demonstrates the increase in the number of lysed and digested parasites in the tissue culture of infected macrophages, followed-up for more than 5 days.

There was no significant difference in the effect of S2-complex on the intracellular and axenic amastigotes and on the axenic amastigotes and promastigotes. A significant difference ($P \leq 0.05$) was found in the effect of S2-complex on the promastigotes and intracellular amastigotes.

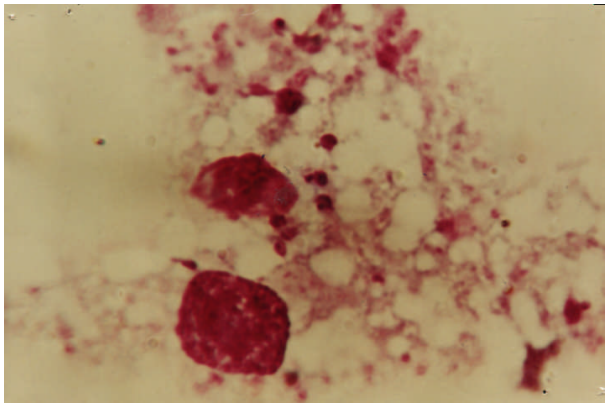

Figure 4-A: L.donavani, amastigote in mouse peritoneal macrophages treated with S2 complex at 0.182 mg/ml for 3 days (x 1500).

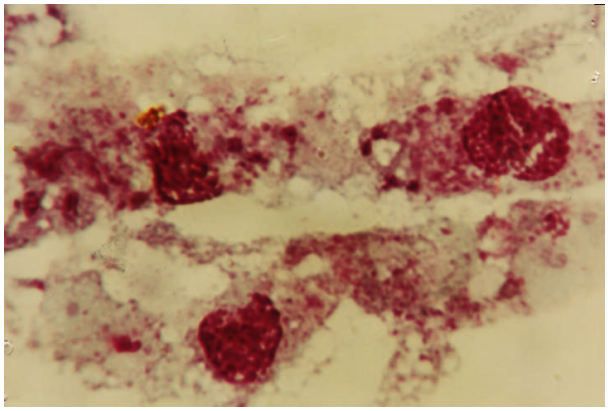

Figure 4-B: L.donavani, amastigote in mouse peritoneal macrophages treated with S2 complex at 0.042 mg/ml for 5 days (x 1500).

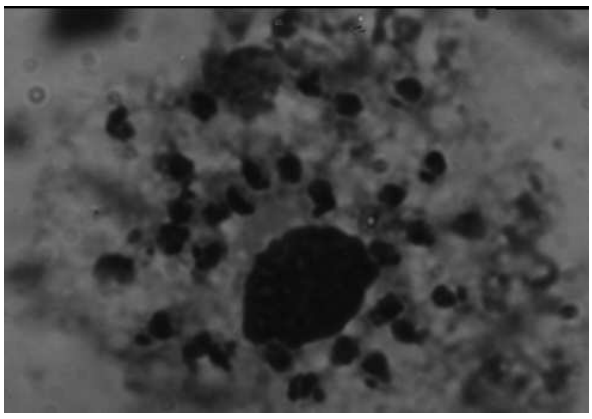

Figure 4-C: L.donavani, amastigote in mouse peritoneal macrophages xxz 1500

Discussion

It is remarkable that as the twentieth century is drawn to a close, the only recognized treatment for leishmaniasis is a heavy metal. In 1940, organic antimonial compounds were developed as a treatment and these remain the consensus treatment of choice for all forms of leishmaniasis. The toxic side effects of all these drugs drew the attention to search for a new safe or less toxic drug like an immunomodulator.

The results indicate the direct effect of S2-complex on the growth of all stages of Leishmania donovani parasite, the amastigotes (intracellular and axenic) and promastigotes. Its effect is similar to the effect of other drugs used in the treatment of leishmaniasis; it may also have another indirect effect by stimulating macrophages to release other factors that help to lyse and digest the parasite. This indicates the role of S2-complex in stimulating the macrophages to produce lymphokines like interferon-γ and interleukin-2. This is similar to what was seen when macrophages were infected with L.donovani and subjected to BCG[15].

The significant difference in the effect of S2-complex on the promastigotes and intracellular amastigotes confirms the possible stimulating effect of S2-complex on macrophages that were cultivated invitro. Its effect was more pronounced on the intracellular amastigotes when compared to its effect on the axenic amastigotes and promastigotes, which are extracellular.

S2-complex might be converted to metabolic compounds more powerful than the original compound itself. This occurs when using other drugs like pentavalent antimonial compounds that convert* from the pentavalent SbV compound to the trivalent SbIII compound, the latter being more toxic inside the macrophages[16]. Hence, the intracellular parasite is affected more than the extracellular parasite, even though the absorption of the drug by axenic amastigotes is more than that of the intracellular amastigotes and promastigotes. This again indicates the similarity between the axenic amastigotes and promastigotes[17].

S2-complex has both a direct and an indirect effect on L.donovani in all of its growth stages, the intracellular and axenic amastigotes and promastigotes. It acts directly by killing the

parasite and indirectly by possibly stimulating the production of lymphokines by macrophages, thereby enhancing the lysis and digestion of the parasite by macrophages.

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SERUM AND CEREBROSPINAL FLUID MAGNESIUM LEVELS IN PYOGENIC AND TUBERCULAR MENINGITIS IN IRAQI CHILDREN

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Introduction

Serum and cerebrospinal fluid (C.S.F.) magnesium levels were estimated in 20 control cases, 12 cases of tubercular meningitis (TBM) and 20 cases of pyogenic meningitis. Normally, the CSF magnesium level was higher than serum magnesium which was independent of age or sex, where as the serum and CSF magnesium levels were low initially in both forms of meningitis and reach normal value upon recovery. The serum and CSF values gradually rise as the clinical and biochemical recovery proceeds. Magnesium estimation helps to know the progress of the disease and the response to treatment. It is not possible to differentiate tubercular from pyogenic meningitis on the basis of magnesium estimation only.

The estimation of serum and CSF magnesium in tubercular and pyogenic meningitis and in other acute neurological states was done by different workers[1].

According to them the magnesium level falls in CSF and serum in bacterial meningitis[2-4]. The present work was conducted to find out the normal level of serum and CSF magnesium in healthy control groups and its alterations in TBM and pyogenic meningitis in children. Changes in magnesium levels have been correlated with the prognosis.

Patients & Methods

The study was conducted on children below 14 years of age who were admitted to the Central Hospital for Children because of being suspected to have meningitis. The children of the control group were suspected of having meningitis but their CSF aspirate latter proved to be clear (free of meningitis). Hence their CSF was used as a control for comparison with the C.S.F. of children proved to have meningitis.

Twenty cases of tubercular and 20 cases of pyogenic meningitis were studied. All these cases were confirmed clinically by history, physical examination and with the help of all the relevant laboratory investigations. Lumber puncture was done with aseptic measures and the CSF was subjected to biochemical, cytological and bacteriological study. Estimation of magnesium in serum and CSF was done using Titan yellow as modified by Neill and Neely[5] and by afomic absorption method for comparison. Serial estimation of magnesium level was done every five days right from admission till discharge in five cases of TBM and four cases of pyogenic meningitis.

Results

CSF parameters in the control tuberculous meningitis and pyogenic meningitis were measured as in Table 1.

Table 1: CSF parameters in normal cases, tuberculous meningitis and pyogenic meningitis

CSF parameters	Normal (Control)	Tuberculous Meningitis	Pyogenic Meningitis
Color	Clear	Cloudy	Cloudy
Cell count	0-4/mm^3	Lymphocytes 50-5000	Polymorphs 100-5000
Glucose	2/3 blood level	Decreased	Decreased
protein	< 500mg/l	Increased	Increased

In control there were 12 males and 8 females the serum magnesium level ranged from 1.80 to 2.50 mEq/l, (mean 1.92 mEq/l, S.D. ±0.02) and CSF magnesium level ranged from 2.40 to 320 mEq/l, (mean 2.80 mEq/l, S.D. ± 0.20) (Table 2).

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Table 2 : Serum and CSF magnesium levels in controls

Age (years)	Serum Mg Meq/L		CSF Mg Meq/L	
	Range	Mean±SD	Range	Mean±SD
0-1	1.80-2.10	1.93±0.13	2.55-3.00	2.78±0.15
2-3	1.80-2.35	1.90±0.15	2.40-3.10	2.81±0.21
4-5	1.83-2.42	2.02±0.23	2.45-3.20	2.79±0.26
6-10	1.80-2.24	1.96±0.16	2.52-3.12	2.77±0.21
11-14	1.80-2.50	1.99±0.29	2.65-3.10	2.81±0.14
1-14	1.80-2.50	1.92±0.02	2.40-3.20	2.80±0.20

At the time of admission, in TBM the mean magnesium level of serum was 1.70 mEq/l, S.D. ± 0.28 and C.S.F. was 2.31 mEq/l, S.D. ±0.30. At the time of discharge the mean serum magnesium level was 2.00 mEq/l, S.D. ±0.14 and CSF magnesium was 2.67 mEq/l, S.D. ±0.36. In pyogenic meningitis at the time of admission the mean magnesium level in serum was 1.84 mEq/l, S.D. ±0.31 and in CSF it was 2.18 mEq/l, S.D. ±0.31. At the time of discharge the mean serum magnesium was 1.90 mEq/l, S.D. ±0.26 and CSF was 2.70 mEq/1, S.D. ±0.27 (Table 3).

Table 3: Serum and CSF magnesium levels in tubercular and pyogenic meningitis

Type of meningitis		On admission		On discharge	
TBM	Mean±S.D	1.70±0.28	2.31±0.30	2.00±0.14	2.67±0.36
	Range	1.25-2.24	1.65-2.93	1.78-2.25	1.95-3.10
Pyogenic meningitis	Mean±S.D	1.84±0.31	2.18±0.31	1.90±0.26	2.70±0.27
	Range	1.65-2.15	1.65-2.15	1.74-3.10	2.25-3.10

The mean CSF magnesium in TBM was 2.87 mEq/1, when the CSF chloride was more than 700 mg% and it decreased to 1.82 mEq/l, as the CSF chloride level came down to below 600mg% (Table 4).

Table 4: Relationship of CSF magnesium and chloride in TBM

Cholride in Mg%	Mg value in Meq/1		No. of cases
<600	Range	1.62-1.95	9
	Mean	1.82	
600-700	Range	2.05-2.80	18
	Mean	2.40	
> 700	Range	2.80-2.03	5
	Mean		

In pyognic meningitis when the CSF protein raised to 90 mg% (Table 5) the magnesium level ranged between 1.50 to 2.05 mEq/1 with mean of 1.85 mEq/l but when the protein was <90 mg%, the CSF magnesium ranged from 2.10 to 2.90 mEq/l with a mean value of 2.90 mEq/l.

Serial values of magnesium in serum and CSF in a representative case of TBM and pyogenic meningitis each have been shown in table 1.

Discussion

In the control group there is no significant difference in serum and CSF magnesium values among the different age groups and sexes (P> 0.05). The mean serum magnesium was 1.92 mEq/1, S.D. 0.02 and mean CSF magnesium level was 2.80 mEq/l, S. 0. 0.20. The CSF magnesium level was higher than serum level. The difference is statistically significant (P< 0.001). Similar observations have been made by other workers[6]. The higher concentration of magnesium in C.S.F. as compared to that of serum may be due to contribution by the perivascular and perineural spaces or the cells of choroid plexus actively regulating the transfer of ions and crystaloids[7]. Both serum and CSF levels of magnesium were significantly low in tubercular meningitis at the time of admission as compared to controls (P<0.001). The rise of magnesium levels in serum and CSF at the time of discharge after recovery, from their original values is also significant (P<0.001). In pyogenic meningitis both serum and CSF magnesium levels at the time of admission were low as compared to control values.

The low CSF magnesium values are statistically significant (p value<0.001). On discharge both serum and CSF values increased to normal levels. The difference between serum and CSF magnesium values at the time of admission and discharge are statistically significant (P<0.001). Similar observations have been reported. The findings in the present work as well as the observations of previous workers showed that CSF magnesium tends to approximate the blood plasma levels in obedience with Cohen's law, as the TBM and pyogenic meningitis present an altered state of blood brain barrier[6,7]. These changes were regarded as a consequence of an increased permeability of the cells of choroid plexus and cerebrospinal blood vessels when those were damaged by invading organisms or toxins.

The correlation between CSF magnesium and chloride levels revealed that CSF magnesium level in TBM decreased proportionally with the fall of chlorides (Table 3). When the chloride level was more than 700 mg% the mean CSF magnesium was 2.87 mEq/l and it came down to 1.82 mEq/1 when the chloride level decreased to 600mg%. There is a strong correlation between magnesium and chloride levels statistically (r = + 0.90).

The relationship between CSF magnesium and protein in pyogenic meningitis showed that as the protein level increased the magnesium level decreased in CSF The rise of CSF protein was inversely proportional to the fall of magnesium in pyogenic meningitis. No definite correlation was observed in those cases where the protein was less than 90mg%. Similar observation was made by Mishra et al[3].

Serial estimation of serum and CSF magnesium on every fifth day after hospitalization showed that as the patients were improving the serum and CSF magnesium levels were increasing and ultimately attained the normal values at the time of discharge. In case of pyogenic meningitis the serum magnesium was not very much decreased and it maintained more or less the same level from the onset till recovery, where as CSF magnesium level followed the same pattern as observed in cases of tubercular meningitis. This coincides with the findings of Mishra et al[3].

Serum and CSF magnesium estimations in pyogenic and tubercular meningitis helps to know the progress of the disease and the response to treatment but it is not always possible to differentiate between both conditions on the basis of magnesium estimation only.

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PREVALENCE OF TORCH AGENTS IN COMPLICATED PREGNANCIES

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Abstract

In order to shed a light on the prevalence of TORCH agents among complicated pregnancies, a study was carried out on 87 women with complicated pregnancies (abortion, preterm labor, intrauterine fetal death, stillbirth, and congenital anomalies). Compared with 20 women, age-matched control group.

Sera of all women were tested by ELISA for toxoplasma , rubella , and HCMV-IgM antibodies, cervical swabs were examined for the detection of HSV antigen.

Results demonstrated that infection with TORCH agents in Iraqi pregnant women was a recognized cause of maternal and neonatal morbidity, and the risk of complications during pregnancy was particularly associated with toxoplasmosis as increased in abortion rate and fetal death. A high risk of preterm labor and stillbirth were found to be due to rubella infection, while infection with HCMV was significantly associated with congenital malformation, however, 50% of cases with history of habitual abortion were significantly associated with HSV infection.

Key wards: TORCH, Abortion, Intrauterine fetal death, Stillbirth, Congenital anomalies.

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Introduction

Infections during pregnancy are important because of the deleterious effects they may have on the developing fetus and in the new born[1]. When an infectious agent (virus, bacteria, or parasite) crosses placenta, serious damage may be done to the fetus[2,3].

In utero infections may result in fetal death, premature birth, intrauterine growth retardation or persistent postnatal infection with subsequent developmental malformations[4,5].

The most common agents implicated in congenital infections are: Toxoplasma gondii, rubella virus, human cytomegalovirus (HCMV), and herpes simplex virus (HSV), the so called TORCH agents[6,7].

Of the distressing situations encountered in medical practice, the loss of a wanted pregnancy or the birth of a malformed infant are among the most poignant which indeed carry the hardship for both child and parents, so we conducted the study among Iraqi women with complicated pregnancies to shed some light on the seroprevalence of recent infection with toxoplasma, rubella virus, and HCMV, by the detection of IgM antibodies; and the prevalence of HSV by antigen detection from cervical swabs.

Materials & Methods

Eighty seven women their age rang from 20-45 years with recent history of abortion, intrauterine fetal death (IUFD), preterm labor, and stillbirth, or congenital anomalies diagnosed by ultrasound were included in this study. They were currently attending Obstetric and Gynecology Department-Al-Kadhimiya Teaching Hospital, out patient clinic during the period of November 1998-April 1999. 20 healthy women with previous normal obstetric history were also included as age match control group.

Five ml. blood samples was harvested from patients and controls, centrifuged for 10min X 3000 rpm, then sera were separated and divided into 0.5ml aliquots and kept at -20^{o}C till tested.

Swabs from cervical region were also taken from each subject, placed in plastic sleeve of the swab holder and kept at -20^{o}C till tested for HSV antigen detection.

All sera were tested for the identification of class specific IgM antibodies by ELISA for toxoplasma, rubella virus, and HCMV, using the following commercially available kits:

1. An indirect sandwich-type enzyme immunoassay for the qualitative determination of IgM antibodies directed against Toxoplasma gondii (Sanofi; PLATELIA TOXO IgM, 72750).
2. Qualitative determination of IgM class antibodies to rubella virus (SENTINEL CH.; Cat. 340017).
3. Qualitative detection of IgM antibodies to cytomegalovirus (BIOKET; Code 3000-1212).

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An enhanced enzyme immunoassay for direct detection of herpes simplex virus antigen (type 1 and 2) (Wellcozyme. WZ02), was also used in this study.

Statistical Analysis: Results were expressed as percentage, range, and mean±SD. Statistical significance was assessed using the chi-square test, Yates correction for continuity if the number in any expected class was five or less. Results were considered significant at $P < 0.05$. Z-test was used to determine a statistical significant difference; odd ratio was used to measure of relative risk.

Results

Figure 1, demonstrate that toxoplasma IgM was observed to be positive in 25 (28.7%) among complicated pregnancies compared with seropositive in one case of control group (5%). Statistical significant difference was clearly noticed ($P<0.05$), the risk of toxoplasmosis as 7.5 times in causing complication during pregnancy.

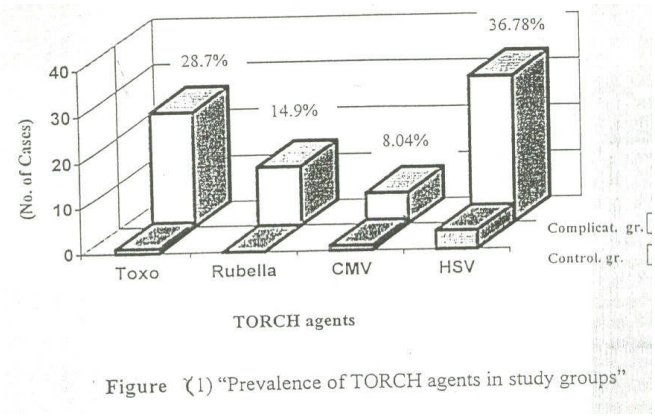

Figure (1) "Prevalence of TORCH agents in study groups"

Rubella IgM positive cases of complicated pregnancy was found in 13(14.9%) cases compared with negative control which was statistically not significant.

Only 7(8.04%) of complicated pregnancy showed positive IgM to HCMV in comparison to one healthy case (5%) in control group which statistically not significant. The risk of HCMV infection was 1.6 times in causing complication during pregnancy.

Cervical swabs were examined for detection of HSV antigens, HSV observed to be positive in 32 (36.78%) of complicated pregnancy compared to only 4(20%) in control group. No statistical significant difference was observed. The risk of HSV infection was 2.3 times in causing complication during pregnancy.

The pattern of age distribution among women with history of complicated pregnancy ranges from 20-45 with mean of (26.19±6) years. They were proved to have recent toxoplasmosis, rubella, CMV, and HSV infection with a percentage of (64%); (46%); (57%); and (43.7%) respectively among age group range from 20-24 years only , with mean (22.02±2) years, as clearly shown in Figure 2a and b. Statistical significant difference were observed ($P < 0.05$) compared to control group.

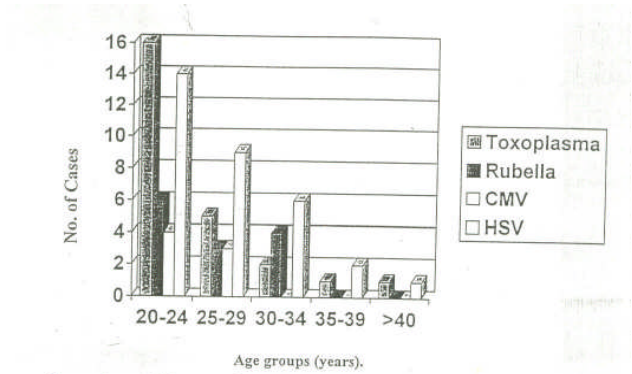

Figure (2 .a) "Pattern of age distribution of TORCH agents among complicated pregnancies"

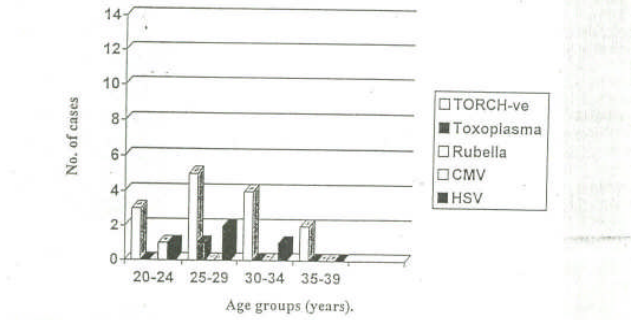

Figure (2 .b) "Age distribution of TORCH agents among control group"

Table 1 shows that 62 women with history of abortion, 20(32%) of them serologically proved to have toxoplasmosis, and 11(17.7%) proved to have German measles with statistical significant difference compared to control group ($P <0.05$), whereas no significant correlation among aborted women with HCMV recent infection 3(4.83%), and HSV infection 28(45.16%) compared to control group.

The overall infection rat as demonstrated by specific IgM antibodies to toxoplasma was significantly associated with second trimester abortion 13(59.09%) ($P<0.05$), while no significant association between rubella recent

infection and abortion that occur in first trimester 9(22.5%), and second trimester 2(9.09%) compared to control group, the results show also that there were no significant difference of first trimester abortion due to HCMV infection, and HSV infection with first and second trimester abortion compared to control group as shown in table 2.

Table 1: Prevalence of TORCH agents among different cases of complicated pregnancies

Agent	Abortion N=62	Preterm labor N=19	IUFD N=28	Stillbirth N=10	Cong. Anoma. N=13	Control N=20
Toxopl N=25	20* 32%	5 26.3%	8* 27.5%	3 30%	2 15.38	1 5%
Rubella N=13	11* 17.7%	4* 21%	2 7%	2* 20%		0
CMV N=7	3 4.83%	2 10.5%	2 7%	1 10%	6** 46.14	1 5%
HSV N=32	28 45.16%	5 26.3%	8 28.5%	3 30%		4 20%

Most of cases have two or more complications and two or three agents. IUFD = Intra uterine fetal death. N = Total number of cases.
*** P< 0.05, ** P< 0.001**

Table 2: Correlation of miscarriage (in trimester) with TORCH agents

Abortion/trimester	Toxopl. N=20	Rubella N=11	CMV N=3	HSV N=28	Total
First trimester	7 17.5%	9 22.5%	3 7.5%	21 43.75%	40
Second trimester	13* 59.05%	2 9.09%	-	7 31.8%	22

* $X^2 = 9.897$, $P < 0.05$
Some of women with recent abortion have combined TORCH agents.

Table 3 illustrates that 5(38.5%) cases with single spontaneous abortion proved to have toxoplasmosis and 4(30.7%) cases of the same problem are due to rubella infection. No statistical significant difference was observed compared to control group.

Table 3: Prevalence of TORCH agents among different types of miscarriage

Type of miscarriage	Toxopl. N=20	Rubella N=11	CMV N=3	HSV N=28	Total
Single spontaneous	5 38.5%	4 30.7%	2 15.38%	2 15.38%	13
Habitual	13 32.5%	6 15%	1 2.5%	20* 50%	40
Missed	2 22.2%	1 11.1%	-	6 66.6*	9

* Z – test = 2.69 (significant)
- Some of women with recent abortion have combined TORCH agents

Twenty (50%) cases with recurrent spontaneous abortion are significantly associated with HSV infection compared to control group (P<0.05), although, toxoplasma infection encounter to 13(32.5%) cases of habitual abortion, but it seems to be with statistical significant difference compared to control group.

Of 19 women with history of preterm labor 5(26.3%) of them were found to be seropositive to toxoplasma, 4(21%) cases infected with rubella virus; 2(10.5%) cases proved to have HCMV-IgM antibodies; and 5(26.3%) of preterm labor cases had HSV infection. No statistical significant difference was observed apart from those cases Infected with rubella virus (P<0.05) as compared to control group (table 1).

Out of 28 women with history of IUFD, 8(28.5%) of them proved serologically to have toxoplasmosis; 2(7%) cases were seropositive to rubella specific IgM antibodies 2(7%) cases recently infected with HCMV; and 8(28.5%) cases were found to have HSV antigens. No statistical significant difference was noticed compared to control group apart from those cases who were recently infected with toxoplasma (P<0.05) (table 1).

From 10 women with history of stillbirths 3(30%); 2(20%); 1(10%); and 3(30%) of cases were found to be infected with TORCH agents. No statistical significant difference was observed compared to control group except those cases associated with rubella infection (P<0.05).

There was a highly significant association (P<0.001) between HCMV infection and congenital anomalies 6(46.15%) compared to control group and compared to 2(15.3%) cases infected with toxoplasma.

Discussion

The present study has shown that infections with TORCH agents in Iraqi pregnant women are a recognized cause of pregnancy troubles.

Serological data on the prevalence of Toxo-IgM antibodies detected in 28.7% of complicated pregnancies which were statistically significant. The over all risk of maternal complication are 7.5 times in those women with serological evidence of this infection.

On the other hand, previous workers in Iraq, reported 40% using toxoplasmin test[8], hence a similar finding was registered a positivity of 39% among pregnant women examined by

immunoflouorescent antibody test[9], which relatively high in comparing to our results. Investigators in Egypt postulated that 65% of cases had Toxo-IgM using ELISA[6]. Many observers in the world detected Toxo-IgM antibodies among pregnant women using ELISA rang from 13%-43%[10-13]. The discrepancy in results in comparison to our study is rather due to the less number of cases taken, also the difference arise from laboratory methods used. To prevent toxoplasma infection during pregnancy serological tests should be carried out and medical instructions given as not eating under cooked meat and washing row vegetables and fruits well before consumption are a very successful procedures in preventing toxoplasma infection during pregnancy.

Among the study groups 14.9% of complicated cases are proved to have recent rubella infection. Data presented in other studies showed that the evidence of rubella IgG seropositivity among pregnant women was apparently higher as measured by haemagglutination inhibition test[14,15]. Nevertheless a retrospective studies showed that the overall infection demonstrated by specific IgM antibodies was lower than our result in women recently infected with rubella virus[16,17]. In England and Wales, rubella infection was confirmed in 25% of pregnant women[18]. These differences could be explained that rubella infection should be more expected in cases with pregnancy troubles.

In looking at the seroprevalence of HCMV, 8.04% of cases were seropositive. Our figure in agreement to that described by other investigators[19,20]. Previous studies in Iraq[16] and in Egypt[6] demonstrated a higher percentage of women with bad obstetric history serologically diagnosed as having recent HCMV infection. Thus, extreme difference to our results might due to many factors, as low sample size taken, geographical distribution, social class, and economic status of population.

Virological swabs taken from the cervix indicated that maternal herpes infection encounter to 36.78% of cases and 20% among control group. Although precise figures are non available in Iraq on the frequency of herpetic disease during pregnancy, nevertheless HSV DNA was detected in cervical smear from pregnant women support our view[21], this indicates that DNA hybridization test is more sensitive than ELISA. However data from many studies were conducted on neonatal herpes suggested that pregnant women were more susceptible to genital herpes[13,22,23].

Grouping the studied women (20-45 years) in age spans of four years demonstrated that all age groups are affected but the higher positivity rates of TORCH agents among age group of 20-24 years. This finding is in agreement with results reported by others[9,15,24,25]. On this occasion the observations were proved to be correct as confirmation of the same results came from other countries all over the world[20,26].

Several points should be noted in interpreting the figures shown in table 1, in that most cases have two or more complications and mixed agents at the same time, the effect is now assessed in relation to the total impact upon the fetus (abortion, preterm labor, intrauterine fetal death, stillbirth and congenital defects). A significant proportion of positive Toxo-IgM titer was found in 20(32%) cases with abortion nearly similar finding was reported[6,24,27,28], in contrast to other studies[19,29] that revealed a lower prevalence rate of Toxo-IgM using immunofluorescent test. Many studies denoted the association and the participation of T.gondii infection to the etiology of spontaneous abortion[30-32].

In this study, 11(17.7%) of cases had rubella infection which significantly associated with abortion, this percentage is higher in comparison to results reported in Iraq[17], who claimed that the abortion might due to other causes rather than rubella infection, but support to our view is given by other workers[33,34]. Follow-up of patients after rubella epidemics is mandatory, from which the risk of reinfection should be calculated.

Serologically proved HCMV infection among recently aborted female was found to be 3(4.83%), its in agreement with other investigator findings[6], as supported by HCMV-IgM antibodies in sera of aborted women, however, a high positivity rate of HCMV associated with abortion range from 12.5%-30.8% reported by others[19,20,25,35]. Moreover, our results point to the fact that the majority of cases of abortion could be due to causes other than HCMV infection, in addition to the limited number of study groups.

The percentage of aborted women with HSV infection was 45.16. This result was first

reported in Iraq. The postulation of other workers revealed, the association of HSV infection with abortion[21,36].

As shown in table 2 Toxo-IgM antibodies were significantly associated with 59.09% of cases with second trimester abortion. These results were confirmed by many studies that reflected the incidence of fetal infection, and damage increase from 59%-65% in mid trimester[37-40].

On the other hand, the result shows no significant association between rubella recent infection and the gestational age where abortion occurs, as 22.5% occurs in first trimester, where as 9.09% occurs in second trimester. With regard to pregnancy outcome, a high percentage of rubella infected women occurs in first trimester[41]. These findings could be interpreted as related to change in the permeability of the placenta at different stages in the pregnancy.

Other finding was revealed that 7.5% of aborted females in the first trimester and none of the complicated cases occurs in second trimester had HCMV infection. In contrast to recent study[42] which indicated that one case with HCMV infection was associated with mid trimester abortion, others observed the same association[43,44].

The results also demonstrated that 43.75% of cases with first trimester abortion had HSV infection and 31.8% of cases associated with second trimester abortion (no significant association compared to control group) , this might due to small sample size used in this study.

In this study the results reveled a significant association between 20(50%) cases with history of habitual abortions and HSV infection, this finding supported by other workers[45,46]. This suggests an increase in HSV infection or reactivation during pregnancy, whereas an increase in the other TORCH infections was not obvious, on the contrary to previous findings, many investigators established the association between toxoplasmosis or HCMV infection with recurrent spontaneous abortion[13,25,47-49], others suggested that HCMV infection of gestational tissue is not a common direct cause of recurrent spontaneous abortion[50].

Back to table 1, rubella per se may be a factor of inducing premature labor in about 21% of cases which is significant. This result was first reported in Iraq. An increase in frequency of prematurity following rubella infection was also reported[51]. From this study, it is observed that rubella does exist in our country, and carries a high risk of preterm labor and stillbirth and in view of a wide spectrum of its teratogenic potential. Its prevention by Expanded Program of Immunization is important for maintaining a high coverage strong surveillance and aggressive control of outbreaks.

Intrauterine fetal death was significantly associated with toxoplasmosis (28.5%), this result also first reported in Iraq. A study by Hammouda and his coworkers in 1993[6], indicated that 80% of IUFD cases were associated with toxoplasmosis, because fetal involvement by T.gondii occurs only after placental development (mid trimester), hence IUFD and stillbirth are mostly noticed[52]. It has been shown that 20% of women with history of stillbirth were significantly proved to have rubella IgM antibodies. An increase in fetal death rate following rubella in pregnancy was also noticed[53], while abroad comparison to our results registered a lower percentage[54].

There is a highly significant association between HCMV infection and congenital defect (46.15%), which was in agreement to result from other study in Iraq[16]. Many observers have incriminated this virus as a cause of congenital defect[7,38]. The congenitally HCMV infected infants present sever sequel at birth or during pregnancy[55,56]. A compromise solution might foresee the screening of women in at risk groups, such as health professionals and those working with small children, to be tested in the early stages of their pregnancies.

It is important to search for other causes of perinatal and intrauterine infections which may be a preventable such as parvovirus B19. Further studies include large sample size of cases are needed to reveal specific link between infection with TORCH agents and the complications that occur during pregnancy , using more reliable and sensitive methods as based on molecular biology.

For many years, most of complicated cases were investigated for single agent only missing combined agents infection; therefore, these observations strengthen the need for TORCH screen in complicated pregnancies[57].

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PREDICTIVE VALUE OF NUCLEOLAR ORGANIZER REGIONS IN PROSTATIC TUMORS IN IRAQ

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Abstract
Nucleolar organizer regions (NORs) which are important for regulation protein synthesis were identified in 100 sections of prostatic tumors by means of silver staining technique. A significant difference was found between the AgNOR counts in 30 benign prostatic hyperplasia (mean 2.07) and 70 malignant prostatic lesions (mean 6.54). The size, morphology, and distribution of AgNORs within the nucleus were also different in the two study groups. Overall, these findings suggest that prostatic carcinoma with multiple irregulars and widely dispersed AgNORs tend to be of high-grade malignancy.

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Introduction

NORs are loops of DNA that are responsible for ribosomal RNA "rRNA" transcription[1]. They are localized in the nucleoli of cells in chromosomes 13, 14, 15, 21, and 22 in association with protein[2]. As rRNA molecule are the main sites of protein synthesis it follows that the number of NORs in each cell nucleus reflect cellular activity[3]. NORs can be readily identified in paraffin wax sections by a silver staining technique. The latter produces silver binding to sulphydrel groups present on NOR-associated proteins. These were thought to include protein B23, C23, subunits of RNA polymerase I, probably other phosphoproteins[4-6]. These regions may partly reflect ploidy though an increase in ploidy doesn't necessarily lead to an increase in NORs in human tumor[7,8]. It has been speculated that large numbers of NORs within nucleus of hyperplastic or malignant cells might reflect increased cells synthetic or metabolic activity compared with normal tissue[8-10]. In this study we investigated the usefulness of the AgNOR technique in assessing the aggressiveness of prostatic tumors and the possibility that the silver-binding NORs could provide kinetic information in histological sections of benign or malignant prostatic tumor.

Materials & Methods

Sections from 70 patients with prostatic carcinoma and 30 with benign prostate hyperplasia were coded and stained for NORs. Three groups of malignant patients were studied, group 1 (n=23) had highly differentiated carcinoma, group 2 (n=38) had poorly differentiated glandular carcinoma and both groups with no metastasis at presentation. Group 3 (n=9) had poorly differentiated carcinoma with metastasis at presentation. For benign hyperplastic prostate two groups were studied (typical hyperplasia (n=25)), and atypical hyperplasia (n=5). All specimens have been fixed in 10% formaline and processed routinely through absolute alcohol and xylene before embedding in paraffin wax. Silver NORs were demonstrated according to the method of Crooker *et al*[11]. Counting was performed blindly and independently by two observers using a standard procedure[12]. In this clusters of black dots within nucleoli are counted as one AgNOR, black dots dispersed throughout the nucleus are counted as discrete AgNORs. The mean numbers of AgNORs per cell nucleus were determined for each case after counting 100 nuclei, on tissue section using an X100 oil immersion lens.

Results

The AgNOR counts for the 30 cases of benign hyperplasia ranged from 0.9-4.00 with a mean of 2.07, median 1.95 (SD=0.6) (Table 1). There were no significant differences in AgNOR counts between the two types of benign lesions (typical and atypical hyperplasia of the prostate) (Table 1). The mean AgNOR count for all malignant neoplasm was 6.54 per nucleus. The median count was 6.93 (SD=1.82) with a range

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of 2.9-10.7 (Table 1), this significantly exceeded the AgNOR counts in benign hyperplastic lesions (P<0.01). There were significant differences between different grades of the prostatic carcinoma. Thus well-differentiated adenocarcinoma without metastasis contained an average 2.9-10.5 AgNOR per cell nucleus (mean 5.13, median 4.78, SD=1.34), While poorly differentiated carcinoma with metastasis contained 5.1-10.7 AgNOR per cell nucleus (mean 7.89 median 7.80, SD=0.97) (Table 1).

Table 1: AgNORs/Cell in benign and malignant prostate lesions

Lesion	Mean±SD	Median	Range
Benign prostate hyperplasia			
Typical (n=25)	1.97±0.58	1.89	0.90-3.50
Atypical (n=5)	2.57±0.63	2.98	0.90-4.00
Total (n=30)	2.07±0.60	1.95	0.90-4.00
Prostate carcinoma			
Group 1(n=23) well-differentiated carcinoma with no metastasis	5.13±1.34	4.78	2.90-10.50
Group 2 (n=38) Poorly differentiated carcinoma with no metastases	6.30±1.22	5.78	3.80-10.50
Group 3 (n=9) Trabicular/solid Prostatic carcinoma with metastases	7.89±0.97	7.80	5.10-10.70
Total (n=70)	6.54±1.82	6.93	2.90-10.70

The difference between the first group prostate carcinoma versus the third group was significant (P<0.05). AgNORs in malignant cases were often dispersed throughout the nucleus, and showed a greater variability in size, morphology and staining characteristics when compared with benign cells (Figures 1 & 2).

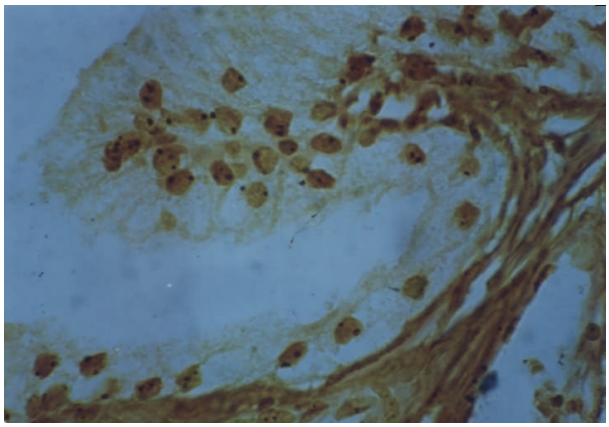

Figure 1: Benign prostatic hyperplasia demonstrates intranuclear black dots of AgNOR. (AgNOR stain X100).

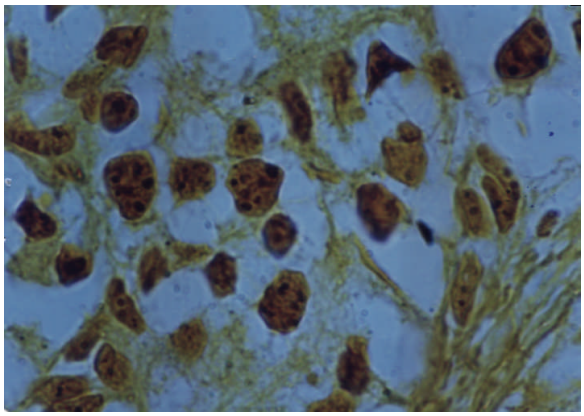

Figure 2: Well-differentiated prostate carcinoma with a mean AgNOR of 5.13. (AgNOR stain X660).

Discussion

The silver binding NORs protein is a simple, highly specific technique to mirror cellular proliferative capacity, has been applied to paraffin sections of lymphoma, cutaneous tumors, melanoma, breast tissue, small cell tumor of childhood, and other tissue[12-14]. Ploton *et al* (1986) and Gillen *et al* (1988) applied this technique to prostatic tumors and showed that the number of AgNOR dots within the nuclei was much greater in high grade malignancies than benign ones, also they found that the method may help in distinguishing between low and high grade malignancies[4,15]. Our results agree with the findings reported by above studies, although we found a wide scatter of AgNOR counts in carcinoma (range from 2.9-10.7), there was a clear distinction between the mean counts in benign and malignant prostatic lesions (2.07 & 6.54 respectively). In this study we have found that the higher the number and the more bizarre the morphology of AgNORs in the tumor, the higher the grade of malignancies. The reason for this tendency is obscure but may be related to increased nuclear activities. An increase in the mean AgNOR counts result of cell biopsy increase this result in a real increase of AgNOR bearing chromosomes[16]. Also the increase in transcription activity results in prominence of otherwise inconspicuous AgNORs[17]. The AgNOR technique has some limitations that have been previously detailed. A variable degree of overlap in AgNOR counts was noted between low or high grade malignant lesions prohibiting an absolute distinction based on these counts. Other problems are counting is tedious and time consuming. Variation in section thickness and possibly methods of fixation may

influence counts. Interobserver variability. These problems tend to detract from the value of AgNOR in diagnostic pathology but we believe that estimation of AgNORs provides us with a mean, albeit an indirect one of evaluating cell kinetic activity in routine paraffin sections.

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ADENOSINE DEAMINASE ACTIVITY IN THE SERUM OF PATIENTS WITH SCHISTOSOMA HAEMATOBIUM AND THOSE WITH BLADDER CARCINOMA .

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Abstract

Aims: To measure the level of adenosine deaminase (ADA)enzyme in the serum of patients with acute schistosomiasis, chronic schistosomiasis, chronic schistosomiasis with bladder carcinoma and bladder carcinoma in comparison to the healthy controls.

Materials & Methods: Two-hundred individuals were included in this study; 56 with acute schistosomiasis, 18 with chronic schistosomiasis, 20 with chronic schistosomiasis with bladder carcinoma, 50 with bladder carcinoma and 56 healthy individuals. Blood was collected from each individual. The level of ADA was measured in the serum according to the method of Giusti (1981).

Results: The ADA activity was significantly lower in all patient groups when compared to the healthy controls. The level was lowest in patients with chronic schistosomiasis with bladder carcinoma and bladder carcinoma.

Discussion: The reduction of ADA could be related to the immunosuppression state associated with schistosomiasis and bladder carcinoma.

Conclusions: ADA has a relatively decreased activity during *Schistosoma haematobium* infection and bladder carcinoma. The decrease in activity is correlated with the immunosuppression state associated with both diseases.

Key words: Schistosoma haematobium, Trematodes, Adenosine deaminase

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Introduction

Adenosine deaminase, ADA, (adenosine aminohydrolase, EC 3.5.4.4), is the enzyme that irreversibly catalyzes the hydrolytic deamination of adenosine and deoxyadenosine to inosine and deoxyinosine respectively and ammonia[1]. A unit of activity of ADA is defined as the amount of enzyme that deaminates one micromole of substrate per minute, under specified steady assay conditions. The normal values of ADA in human serum range from 2-17 U/L[2]. Studies have suggested a critical role for ADA activity in the normal development of the immune system[3,4]. These studies indicate that a deficiency in this enzyme in humans results in an autosomal recessive, X- linked form of severe combined immunodeficiency disease (SCID), which is characterized by the loss of both T- and B-cell functions[5,6]. The SCID locus has been mapped and the genetic defect identified as a mutation of the γ chain of the IL-2 receptor, which has been cloned and renamed the common γ (γ c) chain because of its association with cytokine receptors for IL-4, 7, 9 and 15. Thus, the early lymphoid progenitor cells in patients with SCID are unable to respond to cytokine signals that are crucial for the normal development of T-cells and later B-cells[7].

Studies concerning the correlation between ADA and parasites have been accumulating. Growth of *Trypanosoma musculi* in the murine host was limited by the availability of host purine. A portion of the spleen cells of infected mice displayed high levels of ADA, probably as a compensatory response to extra-cellular purine deficiency. The deficiency of ADA, by 2-deoxycoforomycin treatment, increased the parasite growth. The apparent competition between parasites and host cells for available purines suggested that depletion of extra-cellular purines should be considered as an approach to treating extra-cellular trypanosome infections[8]. *Plasmodium falciparum* growth in human erythrocytes *in vitro* seemed to be unaffected by the ADA level, and ADA was not essential for plasmodial growth[9]. Sheep experimentally infected with *Fasciola gigantica* were found to have decreased levels of ADA in

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their RBC's[10], which may suggest that the defective cellular immune function associated with fascioliasis, may be a result of ADA level reduction. In addition, schistosomiasis patients were also found to have decreased levels of ADA. After treatment, the ADA levels seemed to return to normal[11]. Mice, experimentally infected with secondary hydatid disease, also had decreased levels of ADA in their erythrocytes[12].

Schistosomiasis is an ancient human disease, representing today a major public health problem. It is caused by the different species of the genus *Schistosoma.* It is endemic in 76 countries with an estimated total population of 200 million people. Still there are about 600 million people at risk[13,14].

In Iraq, schistosomiasis is considered to be endemic, especially in the southern governorates, where *S.haematobium* is the prevalent species. The population at risk was estimated to be above 4 million individuals[13]. According to the annual reports of the Institute of Endemic Diseases, Baghdad (1997), schistosomiasis was found to be endemic in more than 12 governorates, with the highest prevalence rates being in Diyala, Anbar and Dhiqar respectively. In Dhiqar, it was found that 33% of the examined population was infected[15].

The observation that the relatively large organisms of *S.haematobium* can exist in the blood stream of the human host for up to 3 decades has intrigued immunologists and parasitologists for some time. Several mechanisms have been proposed for how the schistosome manage to elude the immune response, and more recently, intriguing results from several studies suggest that the parasite may go a step further and actually exploit the immune response for its own replication and transmission[16]. In addition to the long survival of the parasite in humans, there is a universal correlation between the endemicity of *S.haematobium*, genitourinary schistosomiasis and the frequency of bladder carcinoma[17].

Because of the above, this study was conducted to record the relationship between the immune enzyme ADA and *S.haematobium* infection in humans.

Materials & Methods

Subject selection

The individuals studied were divided into 5 groups:

Group (1): Those with acute schistosomiasis haematobium (56 individuals). They were diagnosed as so by finding viable ova in their urine .Those individuals were inhabitants of Belad-Rouz in Diyala Governorate.

Group (2): Those with chronic schistosomiasis haematobium (18 individuals). They were diagnosed as so by finding calcified ova in the bladder wall during cystoscopic examination or in biopsy specimens during histopathological examination. Those individuals attended Al-Kadhimiya Teaching Hospital, Al-Karama Teaching Hospital and private clinics in Baghdad.

Group (3): Those with chronic schistosomiasis haematobium who had developed bladder carcinoma (20 individuals). They were diagnosed as so by finding the calcified ova in the bladder wall and the presence of the tumour during cystoscopic examination and histopathological examination of biopsies obtained by transurethral resection of bladder tumour (TUR-BT). Those individuals attended the attended Al-Kadhimiya Teaching Hospital, Al-Karama Teaching Hospital and private clinics in Baghdad.

Group (4): Those with bladder carcinoma (50 individuals). They were diagnosed as so by cystoscopic examination and the diagnosis being confirmed by the histopathological examination of tumour biopsies obtained by TUR-BT. Those individuals attended Al-Kadhimiya Teaching Hospital, Al-Karama Teaching Hospital and private clinics in Baghdad.

Group (5): Healthy controls. 56 healthy individuals were selected for this study, 28 being males and 28 females. Their ages ranged from 2-80 years. Any individual who is a smoker, alcohol consumer, under any kind of therapy and with any other disease(s) was excluded from the study.

Blood collection

2 ml of venous blood was collected from the individual after disinfecting the anti-cubital fossa with 70% ethanol (Riedel-de Haen). Venipuncture was carried out with a 2ml disposable syringe with 23- gauge needle, after applying a tourniquet. The blood was placed in a sterile disposable plastic

tube. Serum was obtained by centnfugation (KLB) at 2000rpm, 4°C for 10 minutes.

Adenosine deaminase activity assay

The activity was determined in the serum according to the method of Giusti(1981).

Statistical analysis

The data were statistically analyzed using student's t-test.

Results

The mean concentration of ADA of healthy controls was significantly higher (P<0.0001) than that of patients with acute schistosomiasis, chronic schistosomiasis, chronic schistosomiasis with bladder carcinoma and bladder carcinoma. The mean concentration of ADA of patients with acute schistosomiasis was significantly lower (P≤0.000l) than that of patients with chronic schistosomiasis, but significantly higher (P≤0.000l) than that of those with chronic schistosomiasis with bladder carcinoma and bladder carcinoma. The mean concentration of ADA of patients with chronic schistosomiasis was significantly higher (P<0.0001) than that of patients with chronic schistosomiasis with bladder carcinoma and bladder carcinoma. There was no significant difference in the mean concentration of ADA in patients with chronic schistosomiasis with bladder carcinoma and bladder carcinoma (Figure 1).

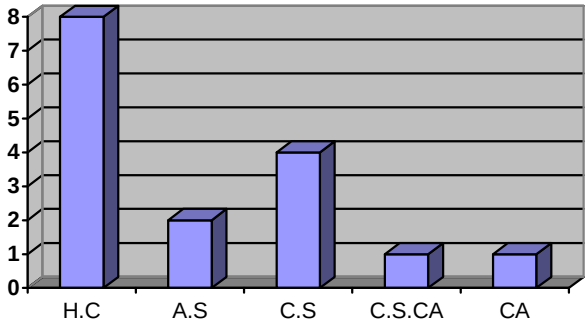

Figure 1: The mean concentration of adenosine deaminase in the serum of patients infected with Schistosoma haematobium and those who had developed bladder carcinoma , compared to the healthy controls
H.C. = Healthy controls, A.S. = Acute schistosomiasis, C.S. = Chronic schistosomiasis, C.S.CA.= Chronic schistosomiasis with bladder carcinoma, CA = Bladder carcinoma

The figures of ADA concentration of the healthy controls were all within normal range (2-17 U/L), whereas the figures of patients with acute schistosomiasis ranged from 1-4 U/L. The concentration of patients with chronic schistosomiasis was higher than those with acute schistosomiasis (range = 2-7 U/L). Patients with bladder carcinoma, with and without chronic schistosomiasis, had very low values of ADA (range =1-2 U/L) (Figure 2).

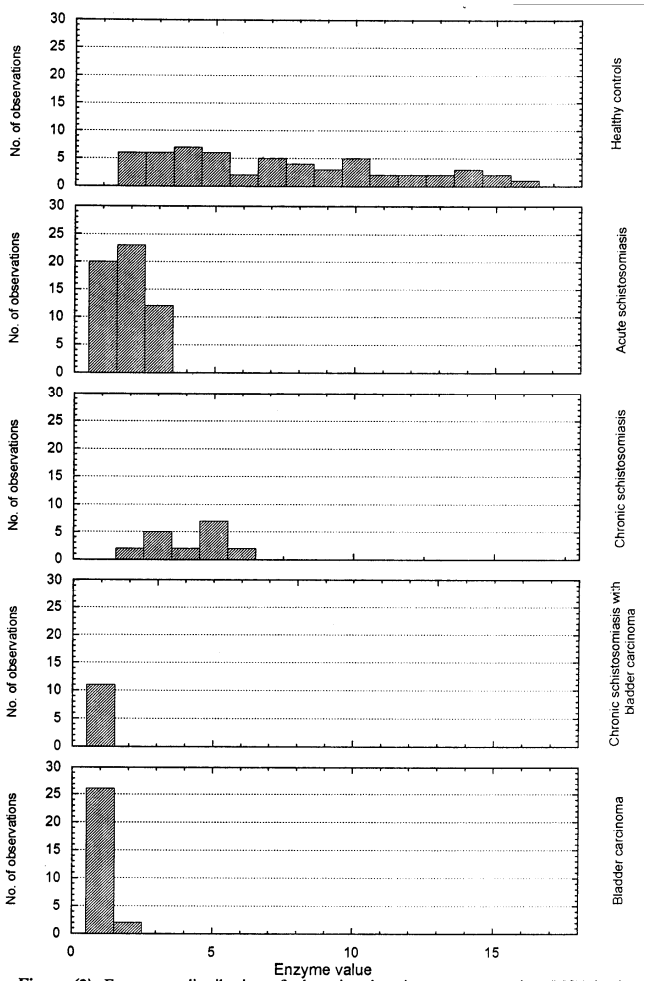

Figure 2: Frequency distribution of adenosine deaminase concentration (U/L) in the serum of patients infected with *Schistosoma haematobium* and those who had developed bladder carcinoma, compared to the healthy control

Discussion

The ADA activity results correlated strongly to the peripheral blood lymphocytes kinetics, where a decrease in ADA was accompanied by a decrease in the mitotic index (M.I.), replicative index (R.I.) and cell cycle progression (C.C.P.) and increase in sister chromatid exchanges (S.C.E.)[18]. This indicates the critical role of ADA in the normal development of the immune cells, as previously

reported[3,9,19]. B-cell dysfunction was also found to be associated with ADA deficiency. This was found to be due to the alteration in antigen receptors[20]. So a decrease in ADA activity could cause a state of immunosuppression. This is evident from the fact that severe combined immunodeficiency (SCID) patients have very few lymphocytes in their blood[9]. Improvement was noted after polyethylene glycol-modified ADA treatment[21] and somatic gene therapy[22]. Moreover, ADA deficiency causes an accumulation of dATP[9,23]. dATP was found to be an allosteric inhibitor of ribonucleoside reductase, arresting DNA synthesis and so cell replication[9,24]. Autopsies of patients with ADA deficient SCID showed a residual non-lymphoid architectural framework, corresponding to usual T-and B- cell zones, found in normal subjects[25].

The increase of S.C.E. frequencies that correlated to the decrease of ADA could be due to the fact that increased levels of dATP in lymphocytes have been shown to induce single strand breaks in DNA molecules, weakening in them the DNA-protein links[24].

The ADA activity in patients with *S.haematobium* infection was significantly lower than the healthy controls. ADA activity was also low in carcinoma patients, with and without schistosomiasis. Immunosuppression has been reported in all of these groups, as previously mentioned[9] and can be due to ADA deficiency. However, it was found that ADA activity was higher in chronic schistosomiasis patients than the other patient groups. This could mean that when the disease becomes chronic, antigen shedding is decreased, giving way for the enzyme and so immune cells to become reactivated. Nevertheless, when carcinoma develops, there is a decrease in the enzyme activity, which may lead to immunosuppression associated with carcinoma.

Similar results of decreased ADA activity in parasitic diseases were observed in schistosomiasis in humans and fascioliasis gigantica in sheep[11] and in mice experimentally infected with *Echinococcus granulosus*[12]. ADA was also found to be decreased in Hodgkin disease patients[26], chronic lymphocytic leukaemia and immunocytoma and Burkitt's lymphoma[27]. On the other hand, ADA was found to be elevated in Non-Hodgkin's lymphoma[28]. All these studies revealed that ADA was actually related to the proliferative activity and the differentiation of the neoplastic cells.

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ESTIMATION OF PLASMA ASCORBIC ACID IN ACUTE RESPIRATORY AND ACUTE DIARRHED DISEASES AND ACUTE FEBRILE ILLNESS IN IRAQI CHILDREN

Firyal H. Abdul-Jalil *B.Sc., Ph.D.*

Abstract

Plasma ascorbic acid (AA) levels were estimated in 20 healthy and 60 sick children hospitalized one-week duration from different Baghdad hospitals, department of pediatrics, in order to determine the changes in plasma AA level in different acute illness, 20 healthy and 60 children with acute illness were studied. 20/60 had acute gastroenteritis, 20 had acute respiratory illness and 20 had acute febrile illness that was suffering from acute respiratory and acute diarrhed diseases. The mean AA level in healthy children was 1.17±0.11 mg/dl. The levels were significantly lower in acute respiratory disease. Acute gastroenteritis children was 0.88±0.07 mg/dl, acute respiratory illness 0.98± 0.12 mg/dl and acute febrile illness 1.06±0.09 mg/dl. There was no significant correlation with malnutrition or anemia. Whether the addition of vitamin supplements would expedite recovery from acute respiratory and diarrhed diseases needs further evaluation.

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Introduction

Vitamin C is often used and more often misused in clinical practice. Apart from its proved value in the prevention and treatment of scurvy, some claim that it has efficacy in various disorders such as growth failure, anemia, bleeding disorders, infections[1]. Plasma AA increased significantly (0.63±0.24mg%, $p<0.01$) suggesting that a low based level was associated at least in part with acute phase of the disease. Supplementation with vitamin C and E suppresses neutrophil oxygen free radical production and lower the marker of lipid peroxidation in patient with MI[1].

Numerous studies have been done to determine plasma tissue ascorbic acid (AA) level in infections[2] and febrile illness[3], injury[4] surgical procedures[5], burns[6], cold exposure[7], malnutrition[8], experimental stress[9] and common cold[10].

Since children with acute illness constitute a large majority of patients, this study was conducted to examine a possible correlation between these diseases and plasma AA levels.

Patients & Method

This was conducted in 80. It included 20 healthy children (control group) and 60 hospitalized children. The duration of hospitalize was one week. 1-60 unhealthy children hospitalized one week duration from different Teaching Center Hospital for children, Al-Kadhimiya Pediatric Hospital, Hospitals department of pediatrics.

The children divided into five groups: Group I: healthy control 20 children. Group II: gastroenteritis 20 children, (Acute diarrhed). Group III: acute respiratory illness 20 children. A detailed history was obtained with special references to diet proceeding and physical examination was carried in Saddam center of pediatric Al-Kadhimyia hospitals in Baghdad and anthropometric measurements and necessary investigations were obtained in all children.

Plasma ascorbic acid level was estimated by the 2, 6-dichlorophenol indophenol visual titration method[1] within four hours of collection of venous blood samples in each case.

Result

Age distribution of the 80 children studied was as follows: 20 were below the age 1 year, children.

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30: one to 3 years children. 25: four to 6 years children. 5: seven to 10 years children. There were 40 boys and 40 girls in five classes according to their nutritional status.

Socio-economic status distribution was as follows: 10 children belong to class I, (malnutrition group), 40 children belong to class II, (high protein diet group), 20 children belong to class 111, (normal nutrition), 10 children belong to class IV, (low nutrition).

Diet preceding illness (estimated by the oral questionnaire method)[4] was adequate in 40 children and inadequate in 40 children. Assessment of nutritional status according to the standard criteria showed grade I malnutrition in 20 subjects, grade II in 9 subjects of high income group, grade III in one and normal nutrition in 53 subjects[3].

Hemoglobin levels were above 10.2 gm/dl in 40 children (normal), while 10 had mild anemia (7.0-9.9 mg/dl), 10 had moderate anemia (4.0-7.0 mg/dl) and 20 had severe anemia (4-4.8 mg/dl). The mean plasma AA level in healthy children was 1.17±0.12 with range of 0.90-1.30 mg/dl. Plasma AA levels were significantly lowers in children with acute infection illness (group II, III and IV) but not in control group ($p<0.05$).

Table 1: Comparison of Plasma AA Level in Different Groups

Group	Plasma ascorbic acid (mg/dl)	
	Range	Mean±SD
Healthy controls	0.97-1.18	1.17±0.12
Acute gastroenteritis	0.70-0.98	0.88±0.07
Acute respiratory illness	0.75--1.15	0.98±0.12
Acute febrile illness	0.82-1.20	1.06±0.09

Table 2: Relationship of ascorbic acid levels (mean S.D. mg/dl) to proceeding illness, protein energy malnutrition PEM and anemia

	Diet		Protein energy metabolism		Severe anemia	
	Adequate AA	Inadequat AA	Absent	Present	Absent	Present
I	1.08±0.11 13	0.98±0.06 7	1.07±0.12 15	1.02±0.10 5	1.07±0.12 20	-
II	0.88±0.08 11	0.76±0.08 3	0.98±0.08 3	0.79±0.07 12	0.85±0.06 8	0.78±0.07 12
III	1.02±0.09 12	0.93±0.09 8	1.43±0.09 13	0.91±0.08 7	1.02±0.09 12	0.94±0.21 8
IV	1.00±0.21 17	0.92±0.03 3	1.01±0.31 11	0.97±0.12 9	1.07±0.09 8	0.96±0.31 12
VR	9.50	9.78	7.05	8.57	6.25	10.82
DF	4/62	4/28	4/56	4/34	4/56	3/34
P	>0.005	0.005	0.005	0.005	0.005	0.005

Level of significance P<0.05, C=VR-variance ratio, d= DF-degree of freedom v1/v2, e-one-way analysis of variance, (ANOVA) applied level of significance P<0.05.

Discussion

Although the estimation of ascorbic acid in the buffy coat of blood (leukocytes and platelets) is a more valid index of tissue levels of vitamin C in the body in sub vitaminosis, ascorbic acid disappears more rapidly from the plasma than from buffy coat[19]. The latter does not begin to fall until the plasma level hills below about 0.4 mg/dl[20]. Estimation of plasma AA probably provides an earlier index of AA depletion from the body. Therefore the plasma AA has been estimated in this study rather than the buffy coat AA[2].

The mean plasma AA level in healthy children in this study was 1.17±0.12mg/dl, with range of 0.90-1.30 mg/dl. These are the studies of Vaishwanar[12] 0.93 mg/dl; Roe[13] 0.2-2.0 mg/dl. Gupta[14] 1.06 mg/dl and Baket and Framk[3] 0.8-1.5 mg/dl. However, Manchanda[15] and Hhalil[16] emphasized the wide prevalence of low plasma AA level below, and 0.8 mg/dl respectively in their study.

In group plasma AA levels were significantly lower. In group III the level of AA exceed group II AA. But less then normal level (0.75-1.15) mg/dl, which are suffered from acute respiratory system diseases[20].

The observations are comparable with those of Cupta[14] who reported a mean value 0.74+0.21mg/dl (control 1.06mg/dl in 8 children with gastroenteritis 0.80+0.16 mg/dl in 6 children with respiratory infection

Conclusion

The uses of vitamin C in acute diseases in large amounts of AA are used by the adrenal glands during illness in the synthesis of cortical hormones from cholesterol[18]. Observation of continued adrenal activity in patients with scurvy indicates that the adrenal cortex functions normally in the face of gross vitamin C deficiency.

The concept that AA constitutes a limiting factor in the synthesis of corticosteroids cannot be reconciled with the continued formation of these hormones in depleted animals.

There is some evidence that large doses of AA improve the utilization of steroids and prolong

their action by delaying break-down and excretion. Many uncertainties make it obvious those additional studies to determine the value of therapy with AA in acute respiratory and diarrhed disease in Iraqi children.

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IMPROVED DIRECT AGGLUTINATION TEST FOR VISCERAL LEISHMANIASIS BY USING HEAT-STABLE ANTIGEN TO BE APPLIED IN THE FIELD

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Abstract

Background: the direct agglutination test (DAT) has been proved to be convenient for use under field conditions. However, one of the major drawbacks of the DAT is the limited stability of the aqueous antigen (AQ).

Objective: to develop a DAT using an antigen that would stable at ambient temperature for prolonged period of time and to be used under field conditions.

Method: AQ antigen was prepared as described by other workers. For the production of FD antigen, we used three different procedures to find which one gives intact parasite after freeze-drying. The performance, stability and reproducibility of both antigens using DAT were tested.

Results: The production of FD antigen was obtained when the parasite antigen incubated with 30% (v/v) Dimethylformamide that resulted in ideal preservation of the structure as well as its antigenicity. The FD antigen remained fully active even after storage at 56˚C for the study period (6 months).

Conclusion: The major advantages of the FD antigen are that the production of a large batch of this antigen allows reproducible results in the DAT over a long period of time and that the FD antigen can be stored at ambient temperature.

Key words: Diagnosis, DAT, FD antigen, visceral leishmaniasis

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Introduction

Visceral leishmaniasis is a protozoal disease. It is found in five continents and is endemic in the tropical and sub-tropical regions of 88 countries. Globally there are 500000 new cases of VL per year[1]. In Iraq, it is usually a disease of children[2] but rarely occurs in adults[3], although some considered VL in Iraq as of infantile type[4]. In the last few years the number of reported cases increased by six-fold, this may be due to many factors as population movements, lack of chemotherapy and the destruction of health and vector control facilities during 1990-1991 war and the following sanication[5,6].

Diagnosis of VL is generally based on the clinical presentation and microscopic demonstration of the parasite in smear aspirates and/or culture. A parasitological proven diagnosis of *L. donovani* infection may be difficult to obtain[6]. A number of serological tests have been developed to the detection of anti-leishmanial antibodies in serum samples such as IFAT[7], ELISA, Immunoblot analysis[8], and the DAT. This latest test, making use of a suspension of stained *L. donovani* promastigotes, was developed originally by Allain and Kagan[9] and further modification was done by Harith et al[10,11]. The DAT is simple technique with a high sensitivity and specificity[23]. It has been proved to be convenient for use under field conditions[12]. However, one of the major drawbacks of the DAT is the limited stability of the aqueous antigen (AQ), especially when no cooling facilities are available, as often the case in the areas where VL is endemic[13] and Iraq is one of these endemic areas. Therefore, the availability of stable form of an antigen would facilitate the use of this particular technique (DAT) in the field.

Thus, the aim of this study is to develop a DAT using an antigen that would stable at ambient temperature for prolonged period of time and to be used under field conditions.

Materials & Methods

Preparation of the Antigen

AQ antigen was prepared essentially as described by Harith et al[11]. Briefly, mass production of the parasite was obtained by inoculating half liter bottles of the liquid medium of Al-Bashir[15] (1990) with rich promastigotes maintenance culture. After harvesting, the promastigotes were washed with lock solution

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and treated with 0.4% trypsin in lock solution at 37°C for 45 minutes, after which the promastigotes were fixed by treatment with 1% (w/v) formaldehyde in lock solution for 20 hr at 4°C. Following washing in cold citrate-saline containing 0.02% Coomassie Brilliant Blue, subsequently, the stained promastigotes were washed with citrate-saline. The number was adjusted at 6.5-7.5 X 10^7 parasite/ml in citrate-saline + 0.43 (w/v) formaldehyde as preservative.

The procedure for FD antigen production was developed in the Department of Medical Microbiology, College of Medicine and it was as follows: we used three different procedures to find which one gives intact parasite after freeze-drying. Part of the AQ antigen was incubated with [25% (w/v) dextran, 30% (v/v) glycerol or 30% (v/v) Dimethylformamide in citrate-saline] then frozen by dipping in liquid nitrogen for 1 hr. then transferred to the vacuum of the freeze-drier machine and left at least 6 hrs under freeze-drying.

Performance of DAT

The DAT was performed considering older modifications[11,12] and briefly: serum samples were diluted in a solution containing 0.9% (w/v) NaCl, 0.2% (w/v) gelatin, 0.78% (v/v) 2-Mercaptoethanol, and 0.03M urea. To discriminate between agglutination and non-agglutination, the use of V-shaped microwell plates was mandatory.

AQ antigen (50ul) was added for each well of the micro-well plates containing 50 ul of diluted serum. Prior to its use, aliquot of FD antigen was reconstituted in normal saline. Reconstituted antigen (50 ul) was added as in AQ antigen. We routinely employed an 18-hr incubation period at room temperature before reading the results.

Comparison of the performance of the DAT using AQ and FD antigens

All sera were tested with both FD and AQ antigen of the same batch to show if there is any titer difference.

Stability of the antigen

AQ antigen was stored at 4˚C and 20-30˚C. at various periods of time, the antigen was tested for its activity.

In order to be able to predict the stability of the FD antigen, we stored a number of aliqoutes at 4˚C, room temperatures and 56˚C. At various period of time, one of these aliquots was reconstituted and tested for its activity.

Reproducibility of the DAT

Three aliquots of FD antigen from the same batch were tested on 3 consecutive days, to show if there was any day-to-day variation in the reading.

Repeatability of the DAT

Three aliquots of FD antigen from 3 different batches were tested to show if there is any variation within-observer in readings, Kappa statistics was used for this purpose.

Results

Freeze-Dried Antigen

In order to obtain a whole parasite after freeze-drying, several methods have been tested. When freeze-drying done without any cryoprotectant, the parasite disintegrated or broken into particles of different sizes (Figure 1).

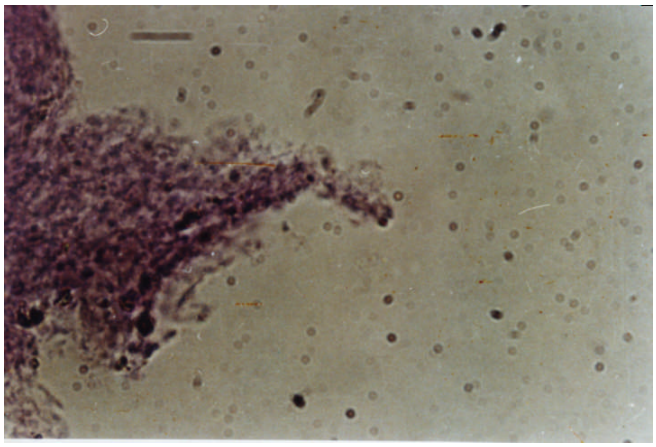

Figure 1: Trypsin-treated, formalin fixed, and Coomassie Brilliant Blue stained. *L.Donavani* Promastigotes after freez-drying without the use of cryopretectant

Positive sera were tested by DAT, all were negative, and when the antigen was reconstituted with saline, it never returns its homogenous state. Furthermore, the use of dextran did not offer a suitable cryprotection, even after long-term incubation. The results were similar to those when cryoprotectant agents were used. Also the use of the glycerol made the parasite extremely shrunken and after freeze-drying the parasites also destroyed and gave no results when used in DAT.

Incubation of the parasites in 30% Dimthylformamide (DMF) resulted in good structural preservation and excellent DAT results, so DMF used in the production of FD antigen (Figure 2).

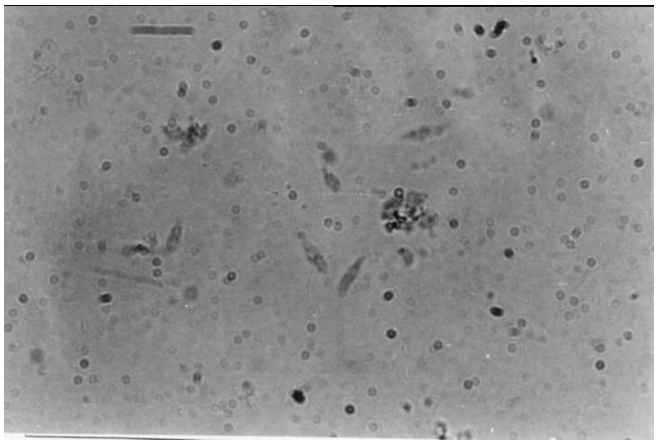

Figure 2: Trypsin-treated, formalin fixed, and Coomassie Brilliant Blue stained. *L.Donavani* Promastigotes after freez-drying with prior 30% (v/v) dimethylformamide

Stability of DAT antigen at various temperatures

In order to be able to study the stability of FD antigen using DAT, we stored a number of aliquots at 4˚C, room temperature, and 56˚C. The FD antigen remained fully stable when DAT was used and gave excellent results for the study period of 6 months. Microscopically, the whole parasite antigen preserved its integrity and it seems from the positive results of the DAT, its antigenicity was also preserved.

Stability of the AQ antigen at 4˚C and at room temperature

The AQ antigen stored at 4˚C gave perfect results for the first 2 weeks, but on the 3rd week the antigen started to deteriorate but still the results could be read. After 4 weeks, the AQ antigen deteriorated, so the reading became impossible because of autoagglutinations. When examined under microscope, the AQ antigen (stored at 4˚C for 3weeks) start to loose its Coomassie Brilliant blue stain and some parasites were lysed. After 4weeks storage, the AQ antigen appeared as clumps and lost the stain completely.

Comparison of the performance of DAT using the AQ and FD antigens

All sera of VL patients that were positive by IFAT/or BMA were tested with both AQ and FD antigens of the same batch. Titer comparison is shown in table 1.

Table 1: Shows the sensitivity and specificity of DAT using DF and AQ antigens

	Cutoff value	Sensitivity	Specificity
FD	1:800	100.0%	99.3%
	1:1600	96.3%	100.0%
AQ	1:1600	100.0%	100.0%

Statistical analysis (using Wilcoxon singed rank sum test) revealed that titers on the average 0.95 dilution step lower for FD antigen than AQ antigen ($p < 0.001$).

Sensitivity and specificity of DAT using AQ and FD antigens

Using the AQ antigen all serum samples of VL patients (107) gave titers of ≥ 1:1600. With cutoff value of 1:1600 for the DAT, all sera would be classified as positive representing a sensitivity of 100%. No serum sample from other groups of patients and controls gave a titer above 1:800, thus the specificity was 100%.

Using the FD antigen, 4 sera of 107 VL patients gave a titer of 1:800 and 103 gave titers that were ≥ 1:1600. With cutoff value of 1:1600 there was only 103 out of 107 VL patients would be classified as positive, representing a sensitivity of 96.3%. If the cutoff value was 1:800, all sera would be classified as positive, representing a sensitivity of 100%. One serum sample of a patient with toxoplasmosis and one serum sample from endemic controls gave a titer of 1: 800; all other sera (103) gave titers of ≤ 1:400. If the cutoff value stated 1:1600, the specificity will be 100%.

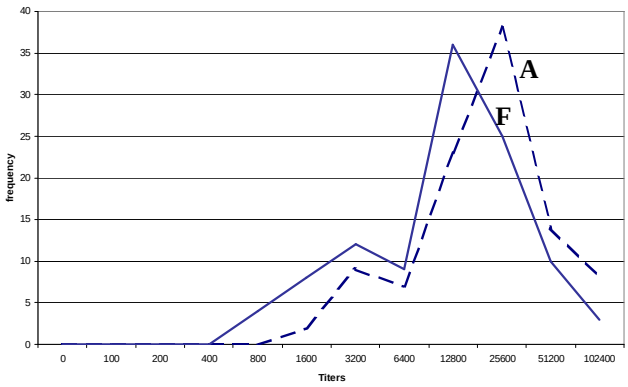

Figure 3: Titer comparison of DAT using FD and AQ antigens of 107 VL patients

Reproducibility of the DAT

Three aliquots of the FD antigen from the same batch, which had been stored at room temperature, were tested by DAT on three consecutive days with 50 positive sera of VL. Statistical analysis showed no systemic day-to-day variation in the results of the test.

Repeatability of the DAT

Three aliquots of the FD antigen, from three different batches, were tested by DAT on three consecutive weeks with 50 positive sera of VL,

Kappa statistics revealed excellent repeatability {high kappa value (range 0.86-0.97)}.

Discussion

A limited number of the available serological methods for provisional diagnosis of VL and for epidemiological studies are suitable for field application[8]. Among the factors limiting the use of these methods is the instability of the reagents especially the antigens and the need for sophisticated equipments and specialized skills. The DAT has been proved convenient for use under field conditions[13,16]. It has been reported that the major drawback of the DAT is the limited stability of the aqueous antigen[14].

One of the main aims of the present study was to develop a procedure for the production of heat-stable freeze-dried antigen as the production of such antigen could increase the application potential of the DAT in both reference and peripheral laboratories. In early trial of this study, newly produced AQ antigen for DAT was freeze-dried directly, but the antigen was destroyed and failed to give results in the DAT. This agreed with the fact that freeze-drying causes destruction of the cells because of the formation of ice crystals in the water of the cell[17].

It appeared that the use of cryoprotectant is possibly the solution for this problem. For this purpose, two cryoprotectant were used (dextran and glycerol). Dextran did not offer suitable cryoprotection, even after long- term incubation. This may be due to the high molecular weight of dextran that makes cell penetration is slow or does not penetrate at all. Glycerol made the parasites extremely shrunken and after freeze-drying, the antigen destroyed almost completely. After the failure of the common cryoprotectants in solving the problem, we decided to search for another cryoprotectant that meets the criterions of the ideal cryoprotectant. The ideal cryoprotectant should penetrate the cell in a short time to avoid the extraction of cell materials (should have structure similar to water), not exert osmotic effect (i.e. membrane should not hinder the passage of the cryoprotectant), not influence the cell structure, does not disturb the effect of fixatives, making solution of the cryoprotectant in water should have a pH close to the pH of the antigen, and it has no effect on Coomassie Brilliant Blue stain.

Dimethylformamide (DMF) was used before in light microscopy[18] and also used in electron microscopy for dehydration and cleaning of freeze-fracture replica, may be an interesting agent to be used as a cryoprotectant. DMF is an inorganic solvent, having dipolar structure similar to water, and has a low freezing point (-61). A 0.5M solution of DMF in water has a pH value of 6.7, which is close to the pH value of the antigen. Thus, concerning the physical properties of DMF, it would appear to be a useful agent for cryoprotection. We found that incubation of parasite antigens in 30% DMF (v/v) prior to freeze-drying gave an ideal structural preservation and did not affect the fixative or the stain.

After the success in obtaining freeze-dried intact parasite antigens, the antigens were tested by DAT to evaluate the preservation of the antigenicity after freeze-drying. The results were compared with those obtained with DAT using AQ antigen and analyzed using Wilcoxon singed rank sum test[19]. The results clearly indicate that the FD antigen generally gave a titer that almost one dilution step lower than the titer obtained with AQ antigen. However, for interpretation of the test results, there is no problem when the cutoff value is changed accordingly.

With cutoff value of 1:800 using FD antigen, the sensitivity was 100% and the specificity was 99.3%, while with a cutoff value of 1:1600, the sensitivity was 96.3%, and specificity 100%. But when the cutoff value of DAT using AQ antigen was stated at1: 1600 it gave a sensitivity and specificity of 100% (Figure 2). Our results about sensitivity agree with the results obtained by the previous workers[12,22].

The specificity of this was higher than that reported by other workers[14,23] and no cross-reactivity was observed with serum samples from patients suffering from, toxoplasmosis, tuberculosis, amoebiasis, giardiasis, hydatosis, schistosomiasis, brucellosis, typhoid fever, and cutaneous leishmaniasis and healthy controls and controls from an endemic area.

The high estimate of specificity in this study may be due to the absence of Chaga's disease, and African trypanosomiasis. This is possibly explaining the difference between the two studies, because of the cross-reaction of these diseases with Kala-azar and they are considered to be the main cross-reacting diseases.

These results were very encouraging for further investigations. The second line of investigations was the stability of both AQ and FD antigen at different temperatures. The temperature chosen for assessing the stability of these antigens were representative of what temperatures that may apply on those antigens i.e. 4˚C represent the temperature of the refrigeration, 20-30˚C represent temperatures of central laboratories, and 56˚C represent the highest temperature that might present in peripheral laboratories or any where, when no cooling facilities available which is the case in most endemic areas with VL.

AQ antigen remained stable at 4˚C for one month and for only two weeks at room temperature this is in agreement with the previous findings. In contrast, the FD antigen remained fully stable using DAT along the study period (6 months) at 4˚C room temperature (20-30˚C) and even56˚C. These results indicate that the use of FD antigen in the DAT is feasible and the problem of limited stability which has been reported before is solved.

In the evaluation of reproducibility and repeatability of the DAT using FD antigen, the DAT was found reproducible when no day-to-day variation in the reading and excellent repeatability indicated by high kappa values* (Range 0.86-0.97). Therefore we recommend this test to be used in both central labs and the field.

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ULTRASTRUCTURAL VASCULAR CHANGES OF THE HUMAN UMBLICAL CORD OF NEW-BORN BABIES FROM DIABETIC MOTHERS

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Abstract
The umbilical cord was chosen as a model for evaluating vascular and tissue injuries provoked by maternal hyperglycemia. For this purpose, 20 cords were collected from newborn babies of diabetic mothers and other 20 from non-diabetics (control group) and prepared for electron microscopy. The main electron microscopic findings are hazy (opaque), edematous endothelial cells with hazy (opaque) nucleus and nearly absent nucleolus compared to the control group. There is also hazy (opaque) and giant myocytes with relatively large nucleus compared to the control group.

Kew words: Diabetics, Umbilical cord, Newborn, Mother.

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Introduction

Diabetes has a major socio-economic impact, it is the fifth commonest cause of morbidity and mortality in Western countries and it's public health significance is enormous in almost all sociaties[1,2]. Diabetes in pregnant women may aggravate complications such as hypertension, retinopathy, urinary tract infection and hydramnious, in addition the fetus is at increased risk of congenital malformation[3]. It is well known that gestational diabetes is associated with increased risk of fetal macrosomia[4-7].

In 1989, Nordlander et al[5] reported that new born diabetic mother has a higher incidence to develop respiratory distress, congenital anomalies, hyperbilirubinemia with a weight of about 200 gm more than that of the normal weight for their gestational age. Furthermore it has long been known that a high perinatal morbidity is found in the off springs of diabetic mother[8], and it seems likely that their characteristic obesity is due to their own excess production of insulin stimulated by the maternal hyperglycemia[9]. The acute interruption of maternal glucose transfer to the fetus at delivery imposes an immediate need to mobilize glucose which results in neonatal distress[10].

The reasons for increased risk of congenital malformations in diabetic pregnant were unclear[11], probably diabetic embryopathy is multifactorial and many of the congenital malformations occur early in pregnancy before the pregnant woman may realize that she is pregnant[12], the resistance in the umbilical artery of diabetics as measured by Doppler velocimetry was significantly lower than that of the non diabetics[13].

Diabetic research has demonstrated that strict control of blood glucose level can improve pregnancy outcome and/or reduce the incidence of congenital malformations in infants of diabetic mothers[14], despite advances in therapy for maternal diabetes, the embryos of diabetic women remain at an increased risk of spontaneous abortion or delivery of an infant with major malformation[15].

Since the umbilical cord is considered as an important structure for the intrauterine development of the fetus, and since no reports were available to the authors about the changes which occur in the structure of the diabetic umbilical cords; the present study was planned to investigate the main ultrastructural changes in the full term human umbilical cords of new born delivered to diabetic mothers.

Materials & Methods

Twenty cords were collected from new born babies of diabetic mothers and other twenty from non-diabetics (control) from Mosul Teaching Gynecological Hospital from January 1995 to February 1996.

Four small pieces were chosen from each cord and fixed in mixed aldehyde fixation (FGA) of 1% formaldehyde + 2.5% glutraldehyde in M sodium cacodyle buffered at pH 7.4 for 6 hours[16]. Then post fixed in 1% osmium tetroxide for 2 hours and then dehydrated in ascending concentration of alcohol. Then cleared with xylene for 15 minutes and finally were

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embedded in Durcupan Acm and the capsules were polymerized in a Richert micro-oven at 65°C for 2 days.
Ultrathin sections were cut by a diamond knife. The sections were collected and stained with uranyl acetate followed by lead acetate and finally were examined by electron microscope (Zeiss EM9S-2). Micrographs were taken for some areas at a magnifications ranging between 1999x to 4880x.

Results

The control group (non-diabetics):

a. The endothelial cells of the umbilical artery had well defined crenated nucleus with a well developed nucleolus inside it (figure 1).

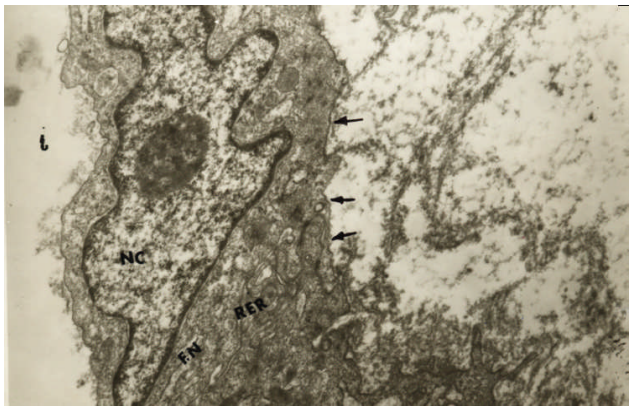

Figure 1: Electrom micrograph of normal umbilical artery showing: Part of the lumen (L), endothelial cells (E) with crenated nucleus (Nc) with a well defined nucleolus, Rough endoplasmic reticulum (RER) and well defined basement membrane (arrows). x 7220

b. The cytoplasm of the endothelial cells had rich endoplasmic reticulum of the rough type and dispersed pinocytotic vescicles especially near the cell surface (Figure 1).
c. The tunical media of the artery showed myocytes with a small nucleus (Figure 2).

The diabetic group:

a. The endothelial cells looked hazy, edematous with a hazy nucleus having an ill-defined nuclear boundries and poorly developed (not clear) nucleolus compared to the control group (Figure 3).
b. The tunica media showed large size myocytes (giant myocytes) which was hazy and edematous having relatively large nucleolus compared to the control group, with increased amount of collagen fibers in between the myocytes (Figure 4).
c. Characteristic electron translucent areas suggesting edema and increased collagen fibers

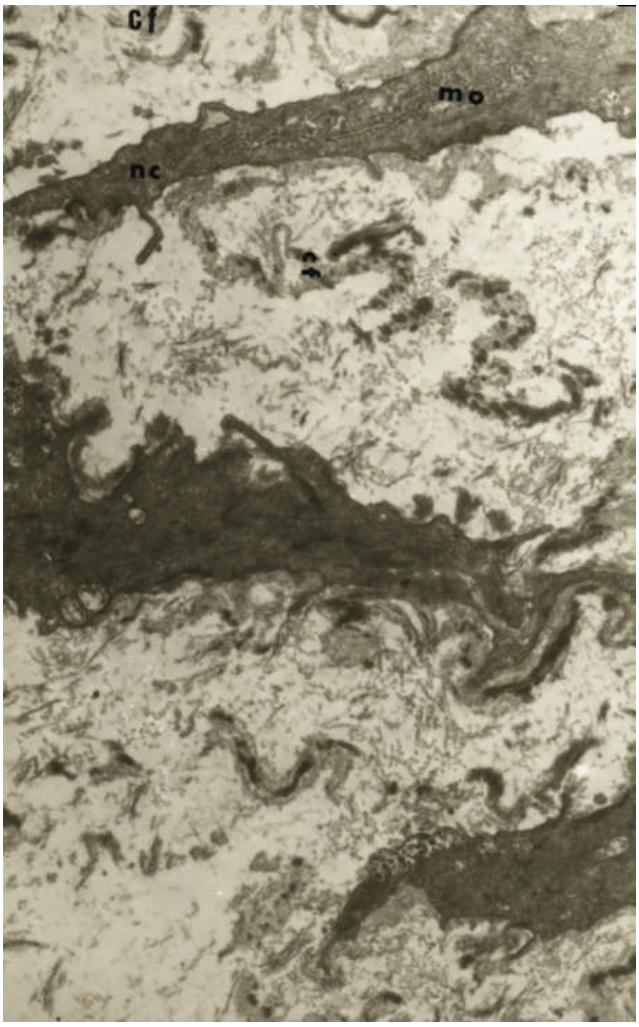

Figure 2: Electron micrograph through the tunica media of a normal umbilical artery showing myocyte cell (mo) having small nucleus (nc), and little masses of collagen fibers (cf). x 16320

in the subendothelial layer and tunica media (Figure 3).

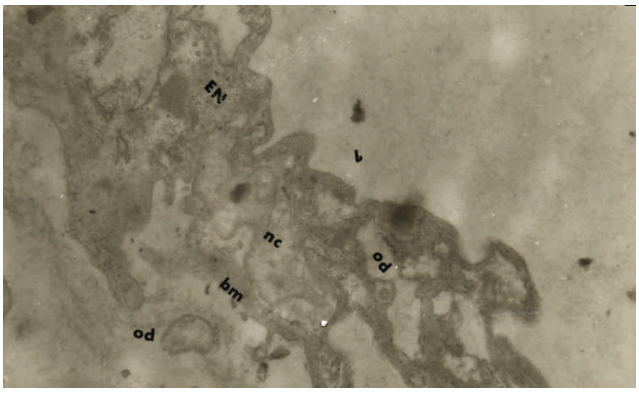

Figure 3: Electron micrograph of umbilical artery from a diabetic group showing: Part of the lumen (L), endothelial cells (En) with its nucleus (Nc), thickening and folding of the plasma membrane (Bm), subendothelial and intracellular oedema (od), and pseudopodia like projection to the lumen (P). x 7220

d. An increase in the amount of collagen and elastic fibers compared to the control group (Figures 3 & 4).

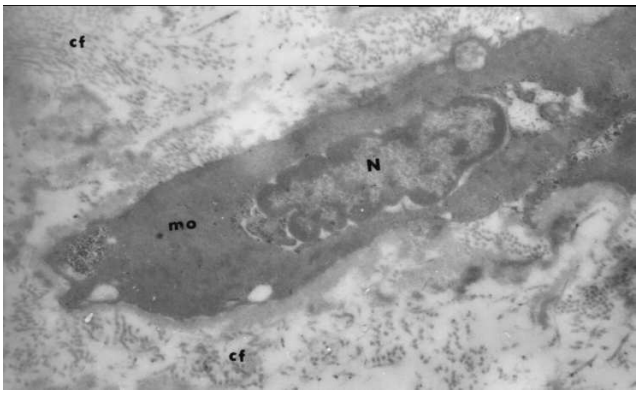

Figure 4: Electron micrograph through the tunica media of umbilical artery from a diabetic group showing: presence of giant myocyte (mo) with relatively large and hazy nucleus (N) , and collection of masses of collagen fibers (cf). x 16320

Discussion

The ultrastructural findings in the umbilical arteries of the control group were nearly similar to those reported before on human umbilical vesseles[17]; they were in agreement with those reported on sheep umbilical vessels[18].

The ultrastructural changes in the umbilical arteries of the diabetic group in the present study were thickening of the basement membrane which reflected vascular response to injury (diabetes), as in the presence of the hypoxia due to hyperglycemic acidosis. Death of some endothelial cells lining the artery will take place with intimal cellular turn over. This means that the endothelial cells will be replaced by migrating myocytes from the tunica media of the artery. A similar explanation was suggested by previous researchers[19,20] when they reported thickening of the basement membrane in skeletal muscle capillaries of diabetic patients.

The endothelial cells looked to be swollen, hazy and edematous with ill-defined nuclear develop compared to the healthy endothelial cells of the control group (which also show very clear nucleus with prominent nucleolus inside). Furthermore, the luminal surface of endothelial cells (of diabetic group) seems as if it send some projections to the lumen like pseudopodia, with characteristic finding of electron translucent areas in the subendothelial region suggesting the presence of edema which results from creation of very minute gaps between the adjacent endothelial cells (reflects a sign of cellular death)[20]. These gaps form temporarily when migrating myocytes from the tunica media will replace some dead endothelial cells. To best of our knowledge this finding has not been reported by any previous worker.

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HEMATOLOGICAL PARAMETERS IN HEALTHY NEONATES DELIVERED BY VAGINAL ROUTE AND CESAREAN SECTION

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Abstract

This prospective study was done on 120 healthy full term Iraqi neonates delivered at Al-Kadhimiya Teaching Hospital between February and September 1997. The aim of the study is to measure the haematological values for neonates delivered by the natural route or Cesarean section.

Medical history for neonates, sex, weight and Apgar scores were determined and standard haematological methods were applied at time of their delivery. The mean values finally obtained were: hematocrit 52.0% (±4.3), reticulocytes 4.0% (±1.5), nucleated red blood cells $0.350x10^9$ /l (2/100 white cells), platelets 206x109/l (±55), total leucocyte count $19.083x10^9$ /l (±3.38). The mean differential leucocyte count and percent was: polymorphonuclear neutrophil $11.474x10^9$ /l (±2.86) with 59.9%, band form $0.993x10^9$ /l (±0.301) with 5.2%, lymphocyte $5.145x10^9$ /l (±1.13) with 27.5%, monocyte $0.9x19^9$ /l (± 0.28) with 4.7% and eosinophil $0.385x10^9$ /l with 2.6%.

These results are comparable with others from Mediterranean and Asian regions, but appear lower than North American and European countries. However, vaginal delivered neonates had significantly higher total leucocyte count, absolute neutrophils and band forms than those delivered by elective cesarean section. ($P<0.001$), thus reflecting the influence of the mode of delivery on cell kinetics. On the other hand, there was no significant difference between the two groups with regard to hematocrit, platelets, and absolute number of lymphocytes, monocytes and eosinophils ($P > 0.05$).

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Introduction

In many instances, the haemotological values are frequently determined in the new born for diagnostic purpose in suspected infection (sepsis). bleeding, and hemolytic states[1,2]. However, sepsis seems to be the commonest objective to search for these determinants.

The early symptoms and signs of neonatal sepsis are often subtle; they may differ at various gestational ages, and are common to various illnesses, rendering diagnosis of sepsis difficult[3,4]. The total white blood cell count (WBC) alone had been of little and limited clinical use as a screening tool in the diagnosis of neonatal sepsis, because of the wide variations and overlaps in values between normal and abnormal infants[3,5].

These variations particularly the first few days of life arise from several factors[5,6]. However, many studies had defined normal range of white cells in the newborn and identified non-infectious factors that influence the whites and their differential count[3]. One of these factors is the mode of delivery whether vaginal (Vg D) or by Cesarean Section (CS)[3,7].

The interpretation of values obtained in an individual baby depends on knowledge of the range of normal values for the respective locality and factors influencing this range[2,5]. Data collected on normal haematological values in our local neonates is scanty.

The objective of this prospective study is to provide an initial data about some basic haemotological values in our local healthy neonates and to compare these values in infants delivered by VgD and those delivered by CS so that these will serve as baseline values to evaluate neonates believed to have sepsis.

Subjects & Methods

The subjects were 120 healthy, full term neonates delivered at Al-Kadhimiya Teaching Hospital of College of Medicine between February and September 1997. Only full term neonates (37- 41 weeks of gestation by last menstrual period, confirmed by ultrasound if applicable and physical examination at birth) whose weight was appropriate for gestational age with no maternal history of any illness were included.

Clinical information for each neonate was obtained including maternal age, gravidity, parity, gestational age, mode of delivery, baby's

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sex, birth weight, and Apgar scores at 1 and 5 minutes.

Haemotoligical tests that were performed include: haematocrit (HCT), reticulocytes (Retics) count, nucleated red cells count (NRBCs), platelets count (PLT), white blood cell count (WBC) and differential leucocyte count. Standard techniques were followed for parameters determination[8].

Results

The demographic data of 120 neonates included in this study are shown in table 1, and their haematological values are summarized in table 2.

Table 1: Demographic data of 120 neonates

Features	Range	Mean
Maternal age (years)	17-42	26.4
Gestational age (weeks)	37-41	38.2
Birth weight (kilograms)	2.7-4.2	3.27
Apgar score I minute 5 minutes	 7-9 8-10	 8.1 9.3
Multiple pregnancies Singleton Twin		 120 (100) 0
Sex Male Female		 65 (54.16 %) 55 (45.84 %)

Table 2: Hematological values of 120 neonates

Investigation	Mean±SD	SEM	Range	Mean %
Haematocrit (%)	52.01±4.3	0.39	42.0-62.0	
Reticulocyte count (%)	4.0±1.5	0.137	1.0-8.0	
Nucleated RBC Count ($x10^9$/l) per 100 leucocytes	0.350 2		0.0-1.0 0-9	
Platelet count ($x10^9$/l	206±55	5.05	90-350	
Total leucocyte count ($x10^9$/l)	19.083±3.83	0.35	9.0-28.0	
Neutrophils				
PMN	11.474±2.86	0.24	4.6-21.84	59.9
Band	0.993±0.301	0.027	0.32-1.84	5.2
Metmyelocyte	0.076		0.0-0.8	0.36
Myelocyte	0.06		0.0-0.72	0.26
IT ratio	0.1± 0.032	0.003	0.027-0.22	
Lymphocyte	5.145±1.13	0.1	1.92-8.97	27.5
Monocyte	0.9±0.28	0.025	0.19-1.68	4.7
Eosinophil	0.385*		0.09-1.15	2.6
Basophil	0.016		0.0-0.48	0.075

Range: the lowest observed value to the highest observed value.
* DS: not calculated because of skewed distribution and the mean is logarithmic.

Demographic data in relation to the mode of delivery {80 neonates (66.6%) were vaginally delivered and 40 (33.3%) were by CS}as in table 3.

Table 3: Demographic data in relation to mode of delivery

	Vaginal delivery		Cesarean Section		
Features	**Mean**	**SEM**	**Mean**	**SEM**	**P**
Maternal age (yr)	25.9	0.64	27.3	0.97	0.2
Gestational age (wk)	38.25	0.12	38.15	0.13	0.6
Birth weight(kg)	3.21	0.03 6	3.39	0.09 5	0.0 8
Apgar **I minute** **5 minutes**	 8.2 9.4	 0.06 0.06	 8.1 9.3	 0.09 0.09	 0.4 0.4
Mult. pregnancies **Singleton** **Twin**	 80 (100 %) 0		 40 (100 %) 0		
Sex **Male** **Female**	 44 (55 %) 36 (45 %)		 21 (52.5 %) 19 (47.5 %)		

***Two tailed t- test.**

Haematological values in relation to mode of delivery (VgD Vs. CS), are summarized in table 4.

Table 4: Hematological values in relation to mode of delivery

Investigation	Delivery	Mean±SD	Range *	Mean %
Haematocrit (%)	VgD CS	52.3±4.8 51.4±3.1	42-62 44-58	
Platelets ($x10^9$/l)	VgD CS	207±57.2 205±51.8	90-350 100-320	
Total WBC ($x10^9$/l)	VgD CS	19.975±3.5 17.36±3.72	11.0-28.0 9.0-24.0	
Differential count ($x10^9$/l) **Neutrophils** **PMN**	 VgD CS	 12.147±2.85 10.128±2.37	 6.0-21.84 4.6-14.24	 60.6 58.5
Band	VgD CS	1.07±0.28 0.383±0.289	0.36-1.84 0.32-1.44	5.5 4.9
Lymphocyte	VgD CS	5.203±1.05 5.03±1.28	2.68-8.97 1.92-7.92	26.7 29.2
Monocyte	VgD CS	0.94±0.21 0.90±0.26	0.19-1.68 0.27-1.60	4.5 5
Eosinophil	VgD CS	0.425±0.172 0.4±0.155	0.12-1.15 0.09-1.05	2.5 2.4

Range: The lowest observed value to the highest observed value

There was statistically no significant differences between VgD and CS neonates in the HCT and PLT means (P>0.05), while the mean total WBC of VgD neonates was significantly higher than that of CS neonates (P<0.001). Likewise, the VgD neonates had significantly higher absolute polymorphonuclear neutrophils (PMNN) and band forms than their CS counterpart (P< 0.001) as shown in table 5. The difference in the absolute lymphocytes, monocytes, and eosinophils between VgD and CS neonates was

statistically not significant (P>0.05) as shown in table 5.

Table 5: Relationship between mode of delivery and hematological values

	Cesarean Section		Vaginal delivery		
Investigation	**Mean**	**SEM**	**Mean**	**SEM**	**P**
HCT (%)	52.3%	0.54	51.4 x10^9/l	0.4	0.2
Platelet	207 x10^9/l	6.4	205 x10^9/l	8.2	0.8
Total WBC	19.975 x10^9/l	0.4	17.3 x10^9/l	0.58	<0.001
PMN	12.147 x10^9/l	0.31	10.128 x10^9/l	0.37	<0.001
Band Form	1.07 x10^9/l	0.03	0.838 x10^9/l	0.045	<0.001
Lymphocyte	5.203 x10^9/l	0.117	5.02 x10^9/l	0.2	0.5
Monocyte	0.94x10^9/l	0.023	0.9 x10^9/l	0.041	0.4
Eosinophile	0.425 x10^9/l	0.019	0.4 x10^9/l	0.024	0.5

* tow-tailed *t* test.

Discussion

There is no doubt about the existence of differences in the ethnic groups, environmental conditions and health statues between Iraqi infants and others in developed and developing countries, and the haematiological values reported in this study provide an initial effort to define a haematological reference range for our infants. Since there are no significant differences between males and females in hemograms during the neonatal period as reported by previous studies[2,3,5,10]. Our values for both sexes were combined for analysis.

The mean HCT value was 52.0±4.3%, it is lower than that of Europe and North America (61.0±7.4%)[1,11,12]. Yet, it is similar to the HCT mean (52.2%) reported by Sasankul *et al* of South East Asia in 1993[13]. On the other hand, it is higher than HCT mean of two African studies (45.0±6.5%) by Scott-Emuakpor *et al* in 1985[6], and (47.0±6.0%) by Mukibi *et al* in 1995[10]. The Retics and NRBCs values were not different from those reported for other neonates[11,12]. Increased number of retics and NRBC in peripheral circulation of the newborn are indications that the bone marrow is compensating for an anaemic state. Since the retics and NRBCs were not raised in this study, the low mean HCT values may be attributed to intrinsic (genetic) factors; However, it is essential to have HB, RBC, MCV, MCH and MCHC values to confirm this explanation. Other explanations for differences in HCT in the first few days of neonatal life among various studies is the site of samples since capillary blood has higher HCT than simultaneous venous or cord blood[8,11], that is in addition to the time of umbilical cord clamping since late clamping (30-60 seconds) after delivery with the baby held about 20 centimeters below the introitus has higher HCT than early clamping (<20 seconds)[11,14].

The mean platelet count of 206±55x10^9 /l (±SD) in our study is within normal limit; yet it is lower than that of Caucasians 290x10^9 /L[12] and that of Thailand 280±69x10^9 /L[13], while it is variable with Nigerian neonates (207±72x10^9 /L[15] of Nigeria, 269±57.5x10^9 /L of Malawian[10]) and 173±38x10^9 /L of North Nigeria[2].

Thrombocytopenia is generally defined as platelets count of less than 150x10^9 /L[8,11,12,16], 14 out of 120 babies in this study have platelet count less than 150x10^9 /L, and among them two babies had platelet count less than 100x10^9 /L. As all babies were healthy and full terms, the low platelet count could be due to racial differences as in Mediterranean races, where platelet counts as low as 80x10^9 /L has been reported in normal individuals[18]. This thrombocytopenia is probably non genuine and might be attributed to technical errors and or from the method of blood collection[1,8,19].

The mean total WBC count of 19.083x10^9 /L (range 9.0-28.0x10^9 /L) is lower than 24.06x10^9 /L (range 16.2-31.5x10^9 /L) that was found by Schelonka *et al*, 1994[20]. It is comparable with Thailand mean figure of 18.482x10^9 /L found by Sasankul *et al*, 1993[13]. Yet, it is higher than African means of 9.253x10^9 /L (range 3.0-22.0x10^9 /L) reported by Abdurrahman *et al*, 1983[2] and 12.3x10^9 /L (range 5.5-35.3x10^9 /L) found by Mukibi *et al*, 1995[10].

In the current study, a wide variation in the differential leucocyte count was found. The mean total PMN count was 11.4x10^9 /L with a mean percent 59% which are both higher than 9.4x10^9 /L and 52% reported by Altman *et al*, 1961[10]. To the contrary, they reported a high mean absolute bands and differential percent than in this study (1.6x10^9 /L vs. 0.993x10^9 /L and 9% vs. 5.2% respectively). The minimum PMN count observed in this study was 4.6x10^9 /L and a maximum was 21.84x10^9 /L. Manero *et al*, 1979 reported a peak PMN between 12-14 hours of age, with a minimum of 7.8x10^9 /L, and a maximum of 14.5x10^9 /L[5]. Some babies showed metamyelocytes and myelocytes in their peripheral blood. The maximum observed count was 0.8x10^9 /L and 0.72x10 ^{9}/L respectively. Clearly none of them exceeds the maximum counts reported by Xanthou in 1970 (2.0x10^9 /L

for metamyelocytes and $0.75x10^9$/L for myelocytes)[21].

The mean calculate of Immature to Total neutrophil (I:T) ratio was 0.1 with a maximum ratio found was 0.22. Schelonka *et al*, 1994, reported a mean ratio of 0.16 with maximum ratio of 0.27[20]. Manroe *et al*, 1979 found a maximum ratio for the first 24 hours of 0.16[5]. Sasankul *et al*, 1993 gave a ratio at 1-2 hours of 0.07[13]. The variation in the total and differential WBC counts between this study and others may be attributed to the followings: (1) differences in the time of blood collection, since there is a marked and rapid increase in the neurtrophil count during first 24 after birth which fully accounts for the increase in total WBC[2,21]. (2) different sites of blood samples, since the total leucocyte, absolute neutrophil and lymphocyte counts are higher from capillary blood than simultaneously obtained arterial and venous blood[22]. (3) the method of cells counting whether manual or automated and the number of cells counted for cell differentiation, since a 200 cell count can provide a more accurate estimate[8], and (4) subjective identification of mature neutrophils and bands in the blood smear. Scholonka *et al*, 1995, evaluated the degree of inter-reader variability in the identification of segmented and band neutrophils. He observed wide differences of band neutrophil identification and the immature to total neutrophil ratio[23].

Full term healthy neonates delivered by VgD had significantly higher total leucocyte, absolute neutrophil, and band counts than those delivered by CS. These results agree with those of Hasan *et al*, 1992[3] and Degaldo *et al*, 1994[24]. It is well known that during crying following heel puncture or chest physiotherapy in infants and with moderately severe exercise in adults there will be a transient neutrophilia. This is due to demargination of intravascular neutrophils to the circulating granulocyte pool without a leftward shift. Whereas following circumcision in infants and more violent exercise in adults there is a transient increase in band form in addition to neutrophilia. This occurs as a result of both demargination of intravascular neutrophils to the circulating granulocyte pool without a leftward shift. This occurs as a results of both demargination and increased flow of marrow storage pool of granulocytes to the peripheral circulation with a leftward shift[22,25-27]. Maternal labor, thus is considered as a combination of severe stress and physical stimulus, and their effects are also transmitted to the baby in the form of periodic physical forces and intermittent episodes both in mother and infant, which in turn, lead to an increase in neutrophil leucocytes and, if strong enough a leftward shift. However, babies delivered by elective CS would not be under such magnitude of stress and, in turn, would not necessarily show such haematological changes.

There was no differences in absolute lymphocyte, monocyte and eosinophil counts between VgD and CS babies, similar to Hasan *et al*, 1992[3]. However, Degaldo *et al*, 1994[24], showed that following spontaneous delivery there was a drastic decrease in the percentage and the absolute number of lymphocytes in venous blood simultaneously with the increase in the PMN cells and band forms. Also they found that following elective CS no leucocytosis was found; however, the percentage and absolute number of lymphocytes was also deceased, although not as pronounced as after spontaneous delivery[24]. Pittard and associates have demonstrated that babies delivered by VgD had decreased CD_2+, CD_3+ and CD_4+, lymphocyte subpopulations compared with those delivered by CS, probably as a result of increased catecholamines and cortisol in the former[24,28]. Also it is worthy mentioning that Herson *et al*, 1992, showed that VgD group had evidence of complement activation (increased C_3a) compared with elective CS groups. Yet, no differences were noted between the two groups in measurement of PMN motility (Chemokinesis or chemotaxis) or PMN degranulation[7].

There were no differences in the hematocrit and platelets between VgD and CS babies, similar to Hasan *et al*, who found no difference in hemoglobin and hematocrit levels between the two groups, but a higher platelets in VgD babies[3]. As mentioned earlier 14 false thrombocytopenia can be attributed to the methods of blood collection and platelets counting.

Conclusions

1. The neonates in this study have haematological values comparable with those of Mediterranean and Asian localities but lower

than white of North American and European countries.

2. The mode of delivery has an influence on neutrophil kinetics, and neonates delivered vaginally have significantly higher total leucocyte count, absolute neutrophils and band forms than those delivered by elective Cesarean Section ($P > 0.001$)

3. There is no statically significant difference in hematocrit, platelet, absolute lymphocyte, monocyte and eosinphil count between vaginal and Cesarean Section delivered neonates ($P>0.05$).

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MALE INFERTILITY AND THE PHYSIOLOGICAL ROLE OF ZINC

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Abstract

Background: Zinc may contribute to fertility through its direct or indirect effect on spermatogenesis.

Aim: To examine the relationships between concentrations of zinc in serum and seminal plasma and semen quality among infertile and fertile men, and on the other hand, clarification of the possible impact of zinc in male reproductive system.

Patients & Methods: The study included 58 males (infertile group) partners of couples who were undergoing investigations for infertility and 37 men (fertile group) whose wives were pregnant and have normal sex life.Seminal fluid and the reproductive hormones analysis were determined for both groups. The subject's serum and seminal plasma concentration of zinc were determined by colorimetric analysis.

Results: All the semen properties (count, motility, morphology) for the infertile men were lower than those for the fertile men. Except for serum testosterone hormone, all the other reproductive hormones (Luteinizing hormones LH, Follicle stimulating hormone FSH) for infertile men did not differ from those for the fertile men. It was found that the means of serum and seminal plasma zinc concentrations were lower in the infertile men compared with those in the fertile men. An attempt to correlate serum zinc concentration with seminal plasma zinc concentration in both group failed as no correlation could be found. Also, no significant correlation was found between zinc concentrations in serum and seminal plasma with semen properties.

Conclusion: Further studies to elucidate the significance of zinc, are suggested. Such studies may give hints to new ways of regulating male fertility.

Key words: Male Infertility, Zinc, Serum, Semen, Fertility, Spermatogenesis.

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Introduction

Zinc plays a critical role in many biochemical functions, including protein synthesis and nucleic acid metabolism. It serves as a catalytic component of over 200 enzymes and as structural component of various proteins, hormones, and nucleotides[1]. The first discovery of human zinc deficiency was in the Middle East in the early 1960s, and symptoms included growth retardation male hypogonadism, anemias and hepato-splenomegaly[2].

Zinc is a component of semen and it is though that at least 1 mg of zinc is excreted by on ejaculum. Zinc plays an important role in the processes of fertility, reproduction and sexual maturation[3]. At a biochemical level, zinc's primary role is a component of zinc metalloenzymes, many enzymes of the cell nucleus involved with genetic information transfer and cellular replication are metallonezymes of zinc. Zinc also participates in RNA metabolism, prostatic fluid and ocular tissues contain the highest levels of zinc in the body[4].

The present study aimed at clarification of the interrelationship of serum and semen zinc levels, in men with a history of infertility and men with no history of infertility. Also, investigation of the possible role of seminal zinc in the regulation of human spermatozoa functions.

Materials & Methods

Subject selection

Iraq men in the age range of 20 to 50 years were no apparent chronic or acute disease were selected for the study, 37 men of know fertility and 58 infertile men were studied.

The infertile men unable to father children for at least 1 year, their wives were considered to be fertile based on extensive gynecologic evaluations. At the first interview for infertile men, a complete history was obtained, especially with respect to any history of sexual dysfunction. Also, physical examination was performed to exclude patient with chromosomal abnormalities. None of the subjects were on drug treatment or on especial diet and none of the subjects used vitamin supplements.

Procedures

* Semen collection: semen analysis were performed on three separate specimens for each subject, samples were collected after 2-3 days of

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sexual abstinence by masturbation into polyethylene containers.

* Serum collection: Blood was drawn into sterile, disposable plastic syringes. After allowing 30 minutes for blood clotting, the serum was separated from blood cells by centrifugation at 900 g for 5 min. at room temperature. The serum was decanted and stored in a metal-free polypropylene tube at -20^{o}C until required.

* Semen Analysis: Samples were evaluated within 1 hour of collection using the methodology outline in (WHO) laboratory manual for the examination of human semen at 300 g for 10 min. at room temperature. The seminal plasma was decanted and stored in a metal- free polypropylene tube at -20^{o}C until required.

* Hormonal Assay: Basic endocrine measurements includes serum LH and FSH will testosterone by radio immunoassay method (RIA)[5] from (CIS bio international, groups ORIS, B.P. 32-91192. GIF-SUR-YVETTE CEDEX-FRANCE).

* Zinc analysis: Zinc analysis was done by Jenway 6100 spectrophotometer (model 6100 serial No. 3000; frequency 50/60 Hz, UK. England) according to the methods described by Shibata, S., that said the certain pyridylazo compounds of phenol derivatives are sensitive chromogenic reagents for the analysis of zinc and many other methods[6].

An aliquot of 50µL of serum was mixed with 1ml of the reagent and 10µL of seminal plasma was mixed with 1ml of the same reagent.

All tubes were mixed and incubated for 10min at 25^{o}C. Then measured against blank at 560nm using (CAT: No. 0033, GIESSE Diagnostics, C.F. 03084750581, P. IVAO 11572610077, Reg. Soc. N. 1103178. Trib- Roma).

Statistics

The results are presented as (mean ± standard deviation) for better comparison with relevant data in literature. The results within groups are also presented as range, and the significance of difference between groups was calculated using student's t-test two-tailed. The Pearson's correlations (r, p) and regression equation were calculated between each of the measured parameters to assess the shape of relationship based on the highest (r) value obtained.

Results

The mean ± standard deviation and range of semen quality (counts, motility, and morphology), serum reproductive hormones (LH, FSH, Testosterone) and serum zinc and semen zinc are listed in table 1.

Table 1: Parameters of semen quality, reproductive hormones, and Zinc concentrations in fertile and infertile men groups

Item	Fertile men group	Infertile men group	P value
	Mean±SD (range	Mean±SD (range	
Count (10^6/ml)	96.6±28.3 (57-154)	31.28±30.0 (0-98)	S
Motility (%)	75.1±11.7 (55-95)	15.0±12.3 (0-60)	S
Morphology %	84.3±5.5 (70-90)	56.9±31.8 (0-90)	S
LH (mIu/ml)	3.5±1.0 (15-50)	4.7±3.9 (0.9-23)	Ns
FSH (mIu/ml)	6.0±1.7 (2.8-9.8)	6.4±6.0 (0.9-34.5)	Ns
Testosterone (nmol/L)	22.5±4.5 (15.8-33)	18.0±8.2 (7-44)	S
Serum Zn (mg/dl)	118.7±16.8 (90.6-162)	97.5±26.9 (36-147.4)	S
Seminal plasma Zn (mmol/L)	3.1±0.4 (2.5-3.8)	2.1±0.6 (0.39-2.7)	S

Values between brackets represent the range
S = significant, ns = non significant

The parameters of semen quality were significantly lower in the infertile men group than in the fertile men group (P<0.0001). No significant differences were found in the mean concentrations of LH and FSH in serum, when fertile men group were compared with infertile men group, but the mean serum testosterone concentration was significantly lower in the infertile men group than in the fertile men group (P<0.005).

The results revealed that serum zinc levels in infertile men group are lower than in the fertile men group (P<0.0001). Also, seminal plasma zinc levels were lower in the infertile men group than in the fertile men group (P<0.0001).

From table 2, there was no significant correlation between serum zinc and the parameters of semen quality in both groups.

Table 2: Values of simple correlation coefficient (r) between Zinc concentration and parameters of semen quality for both groups

Item	Fertile group n =37		Infertile men group n =58	
	S. Zn	Seminal plasma Zn	S. Zn	Seminal plasma Zn
Count	-0.098	0.058	-0.006	-0.041
Motility	-0.285	0.12	-0.025	-0.187
Morphology	-0.071	-0.368	-0.179	0.099

Moreover, no significant correlation between semen zinc and the parameters of semen quality in both groups. No correlation was found between semen zinc and serum zinc level in the fertile men group (r=0.075) or in the infertile men group (r=0.120).

Discussion

Our data are in agreement with those of Bonde *et al*[7], who reported that not sperm concentration but sperm quality determines fertilizing capacity of spermatozoa.

Although, the most cases of male infertility are nonendocrine in origin. However, routine evaluation of hormonal parameter is not warranted unless sperm density is extremely low or there is clinical suspicion of an endocrinopathy. A scrotal varicocele is the most common causative finding in infertile men[8], and to explain the abnormalities in spermatogenesis with varicocele, the most point have been proposed was the abnormal blood flow can interfere with testosterone production, which in turn can interfere with sperm production and this in agreement with our results that about 25% of infertile men had varicocele.

We did not find any difference in the our data and in those presently published in the literature for that the serum zinc and semen zinc levels were significantly lower in infertile patients than fertile males[9], in contrast to other reports, that unable to find a significant difference in serum and semen zinc levels between fertile and infertile men[10, 11].

The lack of correlation between zinc concentration and semen quality found in our study suggests that biochemical complexity of seminal fluid attempts to perform such simple correlations between seminal plasma component and andrological parameters are likely to produce inconsistent results.

These effects include no significant correlation between the total amount of zinc per ejaculate and sperm quality[12]. With no statistically significant correlation between zinc concentration and the motile Sperm concentration[13]. However our results are in contrast of other studies that showed Zn-related decrease in human semen quality[14,15].

Most previous results of colorimetric methods and the present method found that the results obtained using the proposed method were not statistically different from those obtained by atomic absorption spectrophoto-metry[16,17].

The high level of zinc found in semen is due primarily to the secretions of the prostate gland and reflects prostatic stores. Serum zinc may be a reasonable indicator of zinc status. The lack of correlation between serum zinc and semen zinc found in our study suggests that mild zinc deficiency may lower serum zinc while the larger prostate zinc stores remain unaffected. However, we obtained 25% had varicocele, which are enlargement of the internal spermatic veins that drain the testes. The significant decrease of the zinc in seminal plasma in such patients indicated an impairment of the prostate secretion due to decreases the availability of oxygen and nutrient required for sperm live. Citrate is part of the circular chain of cellular respiration, known as the Krebs's cycle.

The Krebs's cycle is the process in which a sequence of enzymatic reactions involving the metabolism of carbon chains of sugars, fatty acids, and amino acids to yield carbon dioxide, water, and high energy phosphate bonds. The Krebs's cycle provides a major source of adenosine triphosphate energy and produce molecules that are starting point for a number of vital metabolic pathways for the cell, citrate that been chelated with zinc and their evidence that zinc required for oxygen consumption by sperm. Varicocele decreases the concentration of zinc and decreases the availability of oxygen for live sperm.

Conclusion

Further studies to elucidate the significance of zinc and other factors present in seminal plasma in different types of causes of male infertility for the functional properties of human spermatozoa appear to be of importance since such studies may give hints to new ways of regulating male fertility.

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THE FREQUENCY OF FIBROMYALGIA IN PATIENTS WITH IRRITABLE BOWEL SYNDROME

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Abstract

Background: Patients with irritable bowel syndrome (IBS) frequently complain of diffuse aches and pain which may be due fibromyalgia (FM). This study was conducted to assess the frequency of FM in patients with IBS, seen in the outpatient clinic at Ibn Seena Hospital in Mosul, over a period of 6 months.

Material & Methods: Fifty six patients with IBS, 27 men (median age 30 yr, range 20-50 yr) and 29 women (median age 38 yr, range 18-63 yr) were included in this study. For comparison, 51age and sex matched subjects who lack any history of gastrointestinal or rheumatological disorders were also studied as controls for the presence of F.M. All patients met the Rome II criteria for the diagnosis of IBS. The American College of Rheumatology (ACR) criteria were used for the diagnosis of FM.

Results: Fibromyalgia was found in 26 (46.4%) patients with IBS, compared to 7 (13.7%) of the control, the difference was highly significant (P< 0.0001). Of those patients, 17 (65%) were women and 7 (35%) were men (P< 0. 001). It was noted that these patients were older with their mean ± SD of age was 40.8 ± 10.57 years which was significantly higher than the FM-negative patients who were 32.96 ± 10.15 years (P< 0.007).

Conclusion: These results suggest that fibromyalgia is frequently found in patients with irritable bowel syndrome particularly women. This overlap between these functional disorders may give new insight into their pathophysiological basis.

Keywords: Fibromyalgia, irritable bowel syndrome, Rome II criteria

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Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by recurrent abdominal pain or discomfort associated with altered stool frequency or form, altered stool passage, passage of mucous and abdominal distension[1,2]. Fibromyalgia (FM) is a syndrome of chronic widespread musculoskeletal pain associated with multiple tender spots[3]. It is know considered to be the most common cause of generalized musculoskeletal pain in women between the age of 20 and 55 years[4].

These two conditions, IBS and FM, share many features. Both are common disorders, more prevalent in women with almost similar age distribution and moreover, both are considered syndromes of altered visceral and somatic perception, psychogenic or psychosomatic in nature. These similarities might suggest common pathogenic mechanisms for both[5].

Patients with IBS frequently complain of extra intestinal symptoms, including diffuse and bilateral aches and pains which can very well be due to FM. The prevalence of FM in patients with IBS has not been widely studied. Veale et al suggested a figure of 65%[6]. However, a recent study by Bart et al found a weak association and had criticized Veale et al study for using older classification systems[7]. The study was done, depending on the most updated diagnostic criteria for both disorders, to assess whether there is a significant overlap between these 2 functional disorders.

Patients & Methods

The study group included 56 patients with IBS 27 men (median age, 30 yr, range, 20-50 yr) and 29 women (median age 38 yr, range 18-63 yr). All patients were seen as outpatients at Ibn Seena hospital in Mosul over a period of 6 months with abdominal symptoms suggestive of IBS. They all met the recently revised and updated Rome 11 criteria for the diagnosis of IBS[8] (Table 1).

Table 1: Rome II diagnostic criteria of irritable bowel syndrome
(Two of the following three features are required for diagnosis).

	Abdominal discomfort or pain
1	Relieved with defecation; and/or
2	Onset associated with a change in frequency of stool; and/or
3	Onset associated with a change in stool form (appearance)
	For at least 12 weeks, which needs not be consecutive, in the preceding 12 months?

Fifty one age and sex matched subjects who lack any history of gastrointestinal or rheumatological disorders were also studied as controls for the presence of FM. The American College of Rheumatology (ACR) criteria were used for the diagnosis of FM[3,4]. All patients and the control group were examined by a rheumatologist who had no clinical details (unaware of whether a person had IBS or not). The detection of tender

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points was done by applying pressure equivalent to 4 kg/ cm to selected anatomic locations (Figure 1).

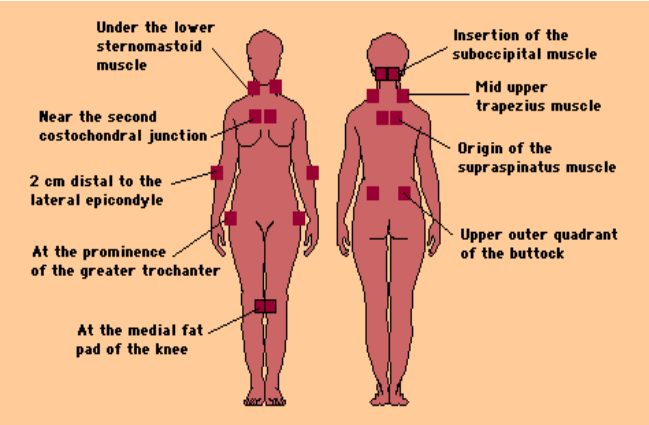

Figure 1: Tender points

The applied pressure has to whiten the examiner's fingernail, and the pressure should be applied gradually over a few seconds and to both right and left side of the body. Control points such as mid-forehead and the anterior thigh were also examined at the same time and should not be as tender as the predefined tender points. These areas may be useful in distinguishing FM from conversion reaction referred to as psychogenic rheumatism. A general musculoskeletal and neurological examination had also been performed on all patients which showed no evidence of arthritis, connective tissue disorder or neurological disease. The following laboratory tests including complete blood count (CBC), erythrocyte sedimentation rate (ESR) and creatine phosphokinse (CPK) were performed and were within the reference ranges.

Tender points in fibromyalgia: The nine "tender points" important for the diagnosis of fibromyalgia. Each is bilateral and tenderness on palpation of at least 11 in a patient with at least a three month history of diffuse musculoskeletal pain is recommended as a diagnostic standard for fibromyalgia. (Adpated from Goldenderg, DL, Hosp Pract. (Off Ed) 1989; 24:39)

Statistical Analysis[9]: The statistical methods used included simple statistical analysis (mean, median, SD). Chi- square test, unpaired t-test, and Z-test were used for comparison of the data. All values are significant at P<0.05.

Symptoms that cumulatively support the diagnosis of IBS:

(1) Abnormal stool frequency; > 3 per day and < 3 per week. (2) Abnormal stool form lumpy / hard or loose / watery stool. (3) Abnormal stool passage; straining, urgency, or feeling of incomplete evacuation. (4) Passage of mucous. (5) Bloating or feeling of abdominal distention.

Results

The frequency of FM in the 56 patients with IBS and in the control group is shown in Table 2.

Table 2: Frequency of FM in patients with IBS and control subjects

Group	FM	x	P value
Patients	26 (46.4%)	18.73	< 0.0001
Control	7 (13.7%)		

Of the 26 patients with FM, 17 (65 %) were women and 9 (35 %) were men, where (Z= 4.44, P < 0.001). As far as age is concerned, it was found that FM was associated with higher mean age in the IBS group. The mean ±SD of age was 40.84 ± 10.57 (range 23-63) years in the FM-positive patients which was significantly higher (P< 0.007) than the FM-negative subjects whose mean ±SD was 32.96-10.15 (range 18-53) years (Table 3).

Table 3: Sex and age distribution of FM-positive and FM-negative patients

Group	Male	Female	Age (years)	
			Mean±SD	Range
FM positive	9	17	40.84 ± 10.57	23 – 63
FM negative	12	18	32.96 ± 10.15	18-53

P value < 0.007

When the duration of IBS symptoms was considered, it was found that most (61 %) FM-positive patients had IBS symptoms for 2 or more years compared to 39 % of patients who had IBS symptoms for less than 2 years, the difference was highly significant (Z= 2.95, P= 0.0016).

Discussion

This study indicates that, compared with healthy controls, the patients with IBS particularly women have a significantly higher frequency of FM (46.4 % versus 13.7%, P< 0.0001). This association between these functional disorders may give new insight into their pathophysiology. The exact cause of IBS remains uncertain; many factors including gastrointestinal motility,

psychological dysfunction and emotional stress have been studied as possible factors. Despite intensive investigations, the results have often been conflicting, yielding no specific abnormalities[10]. Recent studies have focused on visceral hypersensitivity in the gut as a possible biologic marker for IBS[11]. Many patients with IBS have lower tolerance for rectal distension with a ballon than control[12]. Visceral and somatic hyperalgesia have also been reported in FM[13-15]. The strong association between IBS and FM may lead to the speculation that visceral hypersensitivity with altered perception which is centrally mediated may play a major role in the pathogenesis of these functional disorders. This observation support the theory that alterations in central nervous system processing of visceral afferent impulses, mediated by certain transmitters such as serotonin, bradykinins and neurotrophins, rather than mediated by local gastrointestinal nervous system, may be pathogenitically important in IBS and FM[16]. This can have therapeutic implications and can be a possible target for new treatments intended to relieve pain or modify altered perceptions in these patients by using antagonists to these mediators.

Currently there is no satisfactory treatment for IBS, largely due to the lack of understanding of the pathogenesis of this common condition The concept of visceral hyperalgesia as a proposed underlying mechanism, offers new hope for more scientific therapeutic interventions using the new class of drugs which reverse visceral hyperalgesia. It can be recommended to perform further studies to assess the usefulness of these new medications which are currently available in the treatment of IBS patients particularly in the subset of patients who also have FM[16].

In conclusion, irritable bowel syndrome and fibromyalgia frequently coexist particularly in women with longer duration of disease. This overlap might suggest a common pathogenetic mechanism for both, probably visceral hypersesitivity that is centrally mediated.

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CONDROMALACIA PATELLAE: AN OPEN LATERAL RELEASE IN 21 PATIENTS

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Abstract

Background: Twenty one patients (22 knees) were reviewed at Al-Kadhimiya Teaching Hospital. All patients had chondromalacia pattelae, which were symptomatic for at least six months. The average follow up after the operation was 14 months.

Follow up: At the follow up, 10 patients (11 knees) had unrestricted activity with complete pain relief, 5 patients had some aching pain after heavy activity, 4 patients had moderate restriction of activity on account of pain, and 2 patients remained symptomatic with severe restriction of activity.

Results: Indicate that 73% of our follow up patients had satisfactory results (46% excellent, 27% good). Unsatisfactory results were present in 27% of patients. Only those where an advanced articular damage was present, had the unsatisfactory result.

Conclusion: We feel that our experience suggests that one should limit this type of surgery to groups one and two stages of pattelae articular cartilage changes as found by arthroscopy.

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Introduction

The precise etiology of chondromalacia pattelae is not known. The origin of symptoms and the pathological changes found in the articular surface were described in several studies[1,2,3]. The introduction of arthroscopic examination[4] to establish the diagnosis and to stage the degree of articular damage has helped also to exclude any other concomitant pathology.

The operation of open lateral release was described first by Merchand in 1974[5,6]. Later arthroscopic release was described by Metcalf in 1982[7].

In over two thirds of patients a satisfactory result is obtained in most series whether the operation is a closed or an open one[8,9].

In this study we looked in to the different factors that influence the success of our operations apart from staging, age, sex, degree of activity, etc ….

Materials & Methods

Between March 1994 and June 1996, 31 patients (32 knees) fitted the criteria of this study. Only 21 patients (22 knees) were available at follow up. Table 1 show the age and sex distribution.

Table 1: Age and sex distribution

Age (years)	No. of knees	Sex	
		Female	Male
Over 20	9	7	2
Under 20	13	9	4
Total	22	16	6

Tables 2 & 3 show the pre and post operation clinical findings.

Table 2: Summary of patients treated by open lateral retinacular release

HI = History of Injury, P = pain, S = swelling, GA = giving away, CG = clinical group, SS = stage sign, G = grade.

No.	Age	Sex	HI	Preoperative				Postoperative				Comments	
				p	s	GA	CG	p	S	GA	CG	SS	G
1	16	F	N	3+	1+	1*	D	0	0	0*	A	+	I
2	18	F	Y	2+	0	0*	C	0	0	0*	A	+	I
3	17	F	N	3+	0	1*	D	0	0	0*	A	+	II
4	40	F	Y	3+	2+	2*	D	3+	3+	2*	D	-	IV
5	28	M	N	3+	1+	0*	D	0	0	0*	A	+	II
6	38	F	Y	3+	2+	1*	D	3+	3+	1*	D	-	II
7	28	F	N	2+	1+	0*	C	1+	0	0*	B	+	I
8	16	F	Y	2+	0	0*	C	0	0	0*	A	+	II
9	17	F	N	3+	1+	0*	D	0	0	0*	A	+	II
10	36	F	Y	2+	1+	2*	C	2+	2+	2*	C	-	III
11	31	F	Y	3+	1+	1*	D	0	0	0*	A	+	II
12	18	M	N	3+	0	1*	D	1+	0	0*	B	+	II
13	19	F	N	3+	0	1*	D	1+	0	0*	B	+	II
14	19	F	N	3+	0	0*	D	1+	0	0*	B	+	I
15	19	M	Y	3+	2+	0*	C	2+	2+	0*	C	-	I
16	30	F	N	3+	1+	0*	D	1+	0	0*	B	+	I
17	19	M	Y	2+	1+	0*	C	2+	2+	1*	C	-	II
18	18	F	Y	2+	0	0*	D	0	0	0*	A	+	I
19	19	F	N	2+	0	0*	D	0	0	0*	A	+	II
20	28	F	N	2+	1+	1*	C	2+	2+	1*	C	-	III
21	16	M	N	2+	0	0*	C	0	0	0*	A	+	I
22	35	M	Y	2+	0	1*	C	1+	0	1*	B	+	II

0 = none, 1+ = mild, 2+ = moderate, 3+ = severe, 0* = none, 1* = occasional, 3* = frequent, F = female, M = male, Stage sign (50) it indicate a tight lateral retinaculum performed with patient in a supine position and the relaxed knee flexed to 20° medical patellar extrusion of less than 1 quarter of the greatest pattelar width means positive sign

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Table 3: Preoperative findings

Finding	No of patients
Retropatellar pain	All knees
Swelling	12
Giving away	10
Apprehension test	3
Crepitus	19
Quadriceps wasting (> 2 cm)	3
Stage sign (evidence of tight lateral retinaculum)	16
Q-angle	22 with normal range (< 20 degree)
Skyline view	All were inconclusive

Using the outerbridge[10] classification of arthroscopic findings, our patients were graded preoperatively (Table 4).

Table 4: Arthroscopic findings by using outerbridge classification

Grade	No. of patients
Grade I	8
Grade II	10
Grade III	3
Grade IV	1

An initial period of conservative management of three months included reduced activity, non steroidal anti-inflammatory drugs and an intensive course of quadriceps strengthening exercise (isometric). The clinical assessment of these patients is shown in table 5.

Table 5: Clinical assessment system

Sign	Excellent	Good	Fair	Poor
Retropatellar pain	None 0	Mild 1+	Moderate 2+	Severe 3+
Giving away	None 0*	None 0*	Occasional 1*	Frequent 2*
Joint swelling	None 0	Mild 1+	Moderate 2+	Gross 3+
Activity tolerance	A	B	C	D

Our operative technique is done under general anesthesia with the knee fully extended. A 8-10 cm incision is made, 2 cm lateral to the outer border of the patella.

The superficial and deep retinacular fibers running between the outer border of the patella and the lateral femoral condyle are divided. The synovium is not opened.

A complete release is obtained when the patella can be turned on its side freely. A pressure bandage is applied after closure of the skin and subcutaneous tissue.

Static quadriceps exercise is begun the following day after surgery. Knee flexion is allowed up to 90^{o}. The stitches are removed after 12 days and the exercises are continued till full quadriceps power is obtained.

Results

Patients who had satisfactory results fitted group A and B Bentley classification[11,12]. The six unsatisfactory results were in group C and D. Thus, the degree of patellar articular damage determined the result of this operation (Table 6).

Table 6: Articular grading in relation to the results

Articular grade		No. of Knees	Results	
			Satisfactory	**Unsatisfactory**
GI 8 K **GII 10 K** **GIII 3 K** **GIV 1 K**	A B	18 4	16 GI 8 K GII 8 K 0	2 GII 2 K 4 GIII 3 K GIV 1 K
Total		22	16	6

K = knees

Age, sex and degree of activity did not influence the results significantly (partly because of the small number of patients). Young active males fared badly compared to females of the same group (Table 7).

Table 7: Age and sex distribution in relation to the results

Age and sex	No. of knees	Results	
		Satisfactory	**Unsatisfactory**
Females < 20	9	9	0
Male < 20	45	2	2
Female > 20	7	3	4
Male > 20	2	2	0
Total	22	16	6

The progress in clinical ratings of our patients is shown in table 8.

Table 8: Clinical rating system and results

	Preoperative				Postoperative			
					Satisfactory		Unsatisfactory	
					Excellent	Good	Fair	Poor
	None	Mild	Moderate	severe	None	Mild	Moderate	severe
Pain	0	0	10	12	10	6	4	(2)
Swell.	10	9	3	0	16	0	(3)1	2
GA	12		8	2	16		(4)	(2)
A	A	B	C	D	A	B	C	D
T	0	0	10	11	10	5	(4)	(2)
%					45.45%	27.27 %	18.18 %	9.01%

Swell. = swelling, GA = Giving away, A = activity, T = Tolerance, () = unchanged

None of our patients had any significant complication; only 2 of them had minor wound problems.

Discussion

This is a simple operation that should be done early before significant patellar articular cartilage damage occurs to get satisfactory results as shown in our study.

The results of our study compare well with the published results elsewhere (Table 9).

Table 9: Results of lateral release for patellar pain or pain and disability

1ry indication for LR	Study	No. of knees	Release type	FU	SR (%)
Pain	Larson et al 1978	45	Open	18.3	93
	Ceder & Larsom 1979	64	Open	14.7	81
	Micheli & Stanstski 1981	30	Open	18	77
	Ogilvie-Harris & Jackson 1984	56	Arthro.	60	66
	Lankenner et al 1986				
	Bray et al 1987	34	Arthro.	25.6	64.7
	Kackson et al 1991	50	Arthro	28	58
		39	Arthro	72	56
Pain & instability	Merchant & Mercer 1974	20	Open	12	85
	McGinty & McCarthy 1981	39	Arthro.	17	82
	Metcalf 1982	93	Arthro.	48.7	74
	Bigos & McBride 1984	102	Open	14.5	84
	Simpson & Barntee 1984	55	Arthro.	15	84
	Henry et al 1986	100	Arthro	34	88
	Schreiber 1988	53	Arthro.	20	75
	Aglietti et al 1989	45	Arthro.	48	68.5
	Dzioba 1990	78	Open	49	83

LR = lateral release, FU = follow up (months), SR = satisfactory results, arthro. = arthroscopy

No patellar instability resulted because of this operation in any of our patients. The extensor mechanism is not interfered with by this operation and in no patient was there any significant joint stiffness.

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THE DETECTION AND MANAGEMENT OF EARLY GASTRIC CANCER IN NORTHERN IRAQ: TWENTY YEARS EXPERIENCE

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Abstract

Background: Early gastric cancer (EGC) is a distinct form of gastric cancer that has an excellent prognosis, compared to the poor prognosis of gastric cancer; but it is rarely diagnosed. The present study presents our efforts in the diagnosis and management of (EGC), and ways of improving the diagnosis of this form of cancer.

Patients and Methods: Between 1982-2002 (20 Years), 224 patients with gastric cancer were diagnosed, 11 of them had (EGC) diagnosed by endoscopy and biopsy. All were studied and operated on. Data collected regarding: previous treatment and endoscopy, clinical features, investigations, types of surgery, operative findings, histopathology, and follow up.

Results: Eleven cases of (EGC) diagnosed from 224 cases of gastric cancers during the period of 20 years: 4.9%. Dyspepsia was the most common symptom present in 100% of patients, followed by nausea and vomiting in 36% of patients. 72.7% of (EGC) were located distally in the stomach, and 63.6% were of the depressed type (type III). 45.5% were intramucosal, 54.5 were submucosal, and lymph node infiltration was presents in 18.2%. Two patients had segmental gastric resection (RS), or pylorus preserving gastrectomy (PPG). Five-year survival was 88.9%.

Conclusions: (EGC) does exist in Iraq, and is the same as in other parts of the World. The incidence of the diagnosis is 4.9% which is low like the rest of the World, except Japan. It has an excellent prognosis. High index of suspicion and the frequent use of endoscopy and biopsy are important factors to help improve the diagnosis.

Key words: Stomach-Neoplasms-Surgery-Pathology. Gastroscopy.

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Introduction

Gastric cancer (GC), the second most common cancer in the world[1], with the second highest mortality rate of cancers worldwide, kills about one million people a year[2]. Although it has collective crude 5-year survival rate of less than 15%[3-5], there is a subset of patients with excellent prognosis; patients with early gastric cancer (EGC) have a survival rate equivalent to that of healthy, age-matched controls[1,6-8].

The current definition of (EGC) dates from the 1962 publication of the Japanese Society of Gastroenterological Endoscopy[9], which specified gastric adenocarcinomas confined to the mucosa or submucosa, irrespective of lymph node involvement[10-13]. Whether it represents the first phase of (GC)[14] or a separate clinical entity; it was established as a distinct form of (GC), with an excellent prognosis[6,7,8,15,16]. Because Japan has the highest incidence of (GC)[3,17] which is the most common form of malignancy there, mass screening programmes for (GC) were instituted and resulted in a dramatic increase in the prevalence of (EGC) from 1.3% of (GC) in 1946, to 36% in 1965[18], to around 50% in 1999, or even up to 70% as shown by many clinical reports of (EGC)[5,8,10]. Anyhow these results were not paralleled in other parts of the world e.g. in China which have a very high incidence of (GC), only 3% of (GC) cases were diagnosed as (EGC)[2]. In U.S.A and Europe, the percentage is 4-10% (EGC of GC), and though the diagnosis of (EGC) increasing but still the diagnosis and experience with (EGC) is limited[7,14,19,20].

In Mosul, Iraq, we diagnosed the first case of (EGC) in 1982, and to our knowledge this is the first report of (EGC) in Iraq. Iraqi Cancer Registry[21] does not mention this form of (GC), we think that it is certainly included in the (GC), but not as separate clinical entities because treating doctors have not recognized it as a separate diagnosis.

The aim of this paper is to:

1. Draw the attention to this form of (GC), and to help familiarise surgeons and endoscopists with this diagnosis.

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2. Discuss the causes of very low incidence of diagnosing (EGC) even by surgeons who are familiar with it.
3. Present our experience with diagnosis, clinical picture, pathology, surgical treatment, and prognosis of (EGC), with comparison to other studies.
4. Recommendations for improving the percentage of diagnosing (EGC) to improve the very low 5-year survival of this fatal disease (GC).

Patients & Methods

Between 1982-2001 (20 years); 224 patients with (GC) were diagnosed from patients who consulted or referred to the author, who runs an open access endoscopy and gastric surgery service both privately and at hospital (Mosul Teaching Hospital). Since the diagnosis of the first confirmed case of (EGC) in 1982, the author looked actively for (EGC) while performing gastroscopies. All gastroscopies were performed by the author. Eleven cases of (EGC) were diagnosed and treated during the study period, and all eleven patients were operated on. Data were collected from these eleven patients regarding: clinical features, diagnosis, previous treatment and gastroscopies, associated diseases, findings at operation (lymph node involvement and extent), type of surgery, postoperative complications, and follow up. Follow up was done 6 monthly both clinically and by gastroscopy, and liver ultrasonography.

Results

Eleven cases of (EGC) were diagnosed out of 224 cases of (GC) during the study period (20 years); a percentage of 4.9. Seven patients were males, and four were females (1.75:1). Age range was (47-70) years, with a mean of 58 years.

Diagnosis was made by gastroscopy and biopsy in all patients. Four patients were diagnosed at the first gastroscopy. Four patients were diagnosed at the second gastroscopy. Three patients were diagnosed at the third gastroscopy. Four patients were treated by antisecretory drugs for periods between 2-6 months prior to gastroscopy (36.4%) of the total. Two patients had associated diseases, one had duodenal ulcer, the other had erosive duodenitis, and both were also on antisecretory treatment.

Symptoms: upper GIT dyspepsia was the commonest presenting symptom, other symptoms and signs were: epigastric pain or dyspepsia present in 11/11 (100%), nausea and vomiting present in 4/11 (36%), anorexia present in 3/11 (27%), bleeding present in 3/11 (27%), and loss of weight present in 1/11 (9%).

Location in the stomach: 8 distal (72.7%), 2 middle (18.2%), 1 upper (9.1%).

Types: macroscopically: 7 depressed (excavated) type III (63.6%), 3 protruded types I (27.3%), 1 flat type II (9.1%).

Microscopically: 5 intramucosal (45.5%), 6 submucosal (54.5%), and 2 of them with lymph nodes infiltration (33.3%) of the submucosal; and 18.2% of the total number of (EGC) cases.

Types of surgical operations: 5 had Billroth II, 3 had Billroth I, 1 had subtotal gastrectomy and 2 had segmental resection (SR), or called pylorus preserving gastrectomy (PPG).

Follow up: Range, 2 to 20 years: One patients (operated on 1982), is still alive and well after 20 years. One patients (operated on 1987), is still alive and well after 15 years. Nine patients were followed up for 5 years; one patient died of recurrence of cancer after 3 years from surgery: 5-year survival 8/9 = 88.9%. Six patients were followed up for 5-10 years; two patients died of recurrence at 6 and 7 years after surgery; one patient died of heart disease after 7 years of surgery. Ten year survival (3/5) = 60%.

Discussion

Early gastric cancer (EGC) was not established as a distinct form of gastric carcinoma until the eighties, before that, terms like “superficial spreading carcinoma”, or “carcinoma in situ”, were used to describe it, or it was simply called gastric cancer[20,22-24].

Because Japan has the highest incidence of gastric cancer[3], and with the application of mass screening programmes, there have been many clinical reports of (EGC) from Japan, as early as the sixties and seventies. But not until the eighties that numerous experiences were also published from Europe, South America, Australia and North America, but although that this form of (GC) has a universally favorable prognosis in most countries, it still accounts for only a small fraction of gastric carcinomas[4,8,25-27].

When we diagnosed the first case of (EGC) in 1982 the pathologist reported it as "carcinoma in situ"; and the term (EGC) was not used, and little or not known. Later, as more was known about this condition, the author had a high index of suspicion for it while performing gastroscopies, but still only 11 cases out of 224 (GC) were detected in 20 years, (4.9%). Although this is very low compared to reports from Japan, it is similar, little more or less, compared to reports from Europe, America, and China. Table (1) summarizes some of these reports during the eighties and nineties.

Table 1: Reports on EGC from different countries for comparison

Series	Period	No. of ECG out of total no. of GC	%
Tachibana et al., Japan, 1999.[8]	1986-1996 10 Years	100/197	50.8
Yokota et al., Japan, 1999.[10]	1985-1995 10 Years	34/923	21
De-Leo et al., Italy, 1990.[28]	1963-1988 25 Years	99/1140	8.7
Arsene et al., France, 1998.[4]	1978-1990 13 Years	100/1160	8.6
White et al., U.S.A., 1985.[23]	1965-1977 1978-1983 10 Years	12/147 7/118	8.2 6
Traynor et al., Ireland, 1987.[29]	1972-1985 14 Years	11 /157	7
Longo et al., U.S.A, 1987.[30]	1982-2001 20 Years	17/302	6
Al-Atrakchi. Iraq, 2002.[*]	14 Years	11/224	4.9
Carmalt et al., Australia, 1990.[16]	1974-1981 7 Years	18/514 27/872	3.5 3.1
Shi et al., China, 1985.[24]			

[*] Present study. (EGC) Early gastric cancer.

The high percentage of Japan is due to screening programs, which are used for asymptomatic patients, i.e. detecting the (EGC) before it produces symptoms. The low figures in the rest of the world including Iraq are due to late presentation of (GC) i.e. when the patient is symptomatic, added to that the time taken to diagnosis by repeated gastroscopy and biopsy, the cancer would be advanced.

There are, in our view, other reasons for not diagnosing (EGC); one of them is the use of Ba-meal x-ray for investigating patients with upper GIT symptoms and not endoscopy; several clinical reports have documented the low sensitivity of upper tract radiography for superficial gastric mucosal abnormalities[31-34]. With visual inspection alone, endoscopists correctly diagnose (EGC) only 50% of the time[32,35], but with multiple directed and random biopsies, gastroscopy is highly sensitive and specific for (EGC)[36,37]. Moreover the practice of not taking a biopsy unless a suspected lesion is seen should be changed to a policy of taking multiple random biopsies in symptomatic patients, even if no visual abnormalities are apparent. Longo *et al*[37] and others[38], diagnosed (EGC) in approximately 10% of symptomatic patients using random biopsy technique in patients with no obvious lesions seen at endoscopy.

Another reason for not diagnosing (EGC) is the treatment of dyspeptic symptoms with acid suppression prior to gastroscopy, this masks and delays the detection of gastric adenocarcinoma[39]. Many of our patients in Iraq are usually treated in this manner. The treating doctor prescribes antisecretory drugs for long periods, (as in four out of 11 with (EGC) in this series); the patient becomes asymptomatic, even though he might have an (EGC). Also patients even if they are referred for endoscopy, the endoscopist may fail to identify the lesion (healed by antiscretory drugs). In a study done in England (2000), Wayman *et al*[40] studied the healing effect of proton pump inhibitors on (EGC) in a series of 7 patients with (EGC) who were inadvertently treated with proton pump inhibitors; in each case the patient became asymptomatic; the endoscopic signs disappeared and the lesion could not be recognized even by an experienced endoscopist, and concluded that primary care physicians must resist the pressure to prescribe proton pump inhibitors before endoscopy, particularly in older patients. In another study by Bramble *et al*[39] in U.K. (2000), on 133 patient who died of (GC) who were treated by antisecretory therapy prior to gastroscopy, it was found that the treatment of dyspeptic symptoms with acid suppression prior to gastroscopy led to delays in the detection of gastric cancer in one third of the patients.

In most published reports of (EGC), men outnumber women by a 1.5:1 to 2:1 ratio, with the age range of (44-70)[4,5,10,16,18,23], which are very similar to our series: M:F (1.75:1), and age range (47-70).

Hundred percent of our patients complained of epigastric and/or dyspepsia that mimicked peptic ulcer disease. Other series had similar complaints in 84%[41]; 75%[27] and 51.7%[42] of patients. Symptoms of advanced cancer are not prominent, like loss of weight (9% in our series), not reported in the previous 3 series.

The location of (EGC) in our series which was distal in (72.7%), and the macroscopical appearance of the depressed type (7/11, 63.6%), is similar to other reports whether form Europe[42], U.S.A[30], or Japan[10].

Microscopically: we had five intramucosal (45.5%), six submucosal (54.5%); two of them had lymph node infiltration i.e. (18.2%) of the total number of 11 cases of (EGC). These results are nearly the same as a study done in Ireland[29] where the mucosal were 5/11 (45.5%), the submucosal 6/11 (54.5%); but lymph node metastasis was 0%. Similar results were reported in studies done in France[43] (mucosal 56%; submucosal 44%; lymph node metastasis 16%). In Spain[42] (intramucosal 44.8%, submucosal 55.2%, and lymph node metastasis 13.8%). Lymph node metastasis less than ours was reported, 12% (Germany)[44]; 10% (France)[25]; and 10% (Japan)[45].

Types of operations: Since 1995, whenever possible we tried to treat patients with (EGC) that are in the antrum or mid-stomach, by the operation of segmental resection (SR); or pylorus preserving gastrectomy (PPG); since the prognosis of patients with (EGC) is excellent and these patients show long term survival after surgery, a special attention must be directed to preserving gastric function in these patients, it is also important to decrease the postoperative chronic morbidity, which may follow partial or subtotal gastrectomy. Two of our patients with (EGC) at the antrum and distal body of the stomach underwent this operation (in 1995 and 1997). In this operation the distal part of the stomach is resected, but retaining a 1.5-2 cm. pyloric cuff, thus preserving the function of the pylorus and decreasing the postoperative complications. (PPG) was adopted in Japan during the second half of the nineties, but its standard procedure has not been established yet[46]. Steps like grade of lymph node dissection, and preservation of vagus nerve are still under study by some authors[47,48]; but all agree, that it can be performed safely, with low incidence of major complications. It has benefits in decreasing postoperative chronic morbidity like weight loss and dumping, and it has a better postoperative outcome than the conventional distal gastrectomies. It was also found to have good cancer curativity, and it is recommended for the treatment of (EGC)[46-49]. Although the number of (PPG) is only two in this study and it is not enough to draw conclusions from; but both of these patients are well and they had no chronic postoperative complications.

Follow up: there is a universal agreement on the excellent prognosis of (EGC), our results are in full agreement with others. Our 5-year survival of 88.9% is nearly the same as 88% in a study done in U.S.A[7], 86.8% (France)[4], 86.3% (France)[25], 86% (Japan)[5], 92% (England)[27], and 84.3% (Spain)[42]. Some reported higher 5-year survival; 100% (Chile)[26]; some reported lower figures: 70% (Germany)[44], and 65% (Australia)[20]. Our 10-year survival of 60% is also comparable to other studies; 68.6% (France)[43], 68% (Chile)[44], 76.6% (Japan)[5].

It is worth mentioning again that our first patient with (EGC) diagnosed 1982 is still alive after 20-years of surgery; another patient operated on in 1987 is still alive after 15-years of surgery. Both had their (EGC) limited to the mucosa only, and there was no lymph node metastasis. While our 3 patients who died of recurrence and metastasis (at 3, 6, and 7 years after surgery) had extension of the cancer into the submucosa and had lymph node metastasis at operation; indicating that the presence of these factors leads to a worse prognosis in (EGC). Reports from Japan[45,50], U.S.A.[7], and France[43,51], confirm the importance of submucosal invasion of (EGC), and lymph node metastasis as worse prognostic factors, than (EGC) limited to the mucosa, or without lymph node metastasis, which have excellent prognosis. They also agreed that lymph node metastasis was specifically related to (EGC) recurrence. Thus, lymph node dissection is indispensable for the treatment of (EGC).

Conclusion

1. EGC does exist in Iraq and it is not different from that reported in Japan and the Western World. The incidence is similar to the West and it has the same excellent prognosis in comparison to (GC).

2. Familiarity with this disease and high index of suspicion by both treating doctors and digestive endoscopists is essential to diagnose (EGC). By the increased use of endoscopy in patients with persistent non-specific GIT complaints, with random biopsies even if no lesion is seen, may increase the number of patients seen with (EGC).
3. Treating doctors should avoid treatment of dyspeptic symptoms with acid suppression prior to gastroscopy, as this mask and delays the detection of gastric cancer, especially in patients older than 45 years.
4. The use of the recent operation of segmental resection or pylorus preserving gastrectomy in the treatment of patients with (EGC) is safe, and probably with better results than the conventional gastric resection.

For the future, it is hoped that the use of endoscopic ultrasonography to diagnose the depth of invasion of (EGC)[52], endoscopic mucosal resection[17], and laparoscopic gastric resections[53], may be possible by gaining more experience coupled with acquiring the appropriate instruments in this field.

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TUBERCULOSIS IN DIABETIC PATIENTS

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Abstract
Three hundred patients with active pulmonary tuberculosis (positive sputum smear) were studied for presence of diabetes mellitus in one year period (May 1998) in the institute for TB control. Two hundred and four patients (68%) males and (96) patients (32%) were females. Sixty patients (20%) were diabetics, 18 of diabetics (30%) were on treatment with insulin while 42 patients (70%) are an oral hypoglylemic drugs and diet.
In diabetic the mean age of affected patients was 40-49 years compared to 20-29 years in non diabetics. Relatively equal groups of diabetic and non diabetic patients had minimal or moderate disease. Twelve diabetic patients (20%) require more than 4 months for conversion compared to 24 (10%) in non diabetic patients. At the end of the second month, (168) non diabetic (70%) have negative sputum compared to 27 diabetics (45%). Bilateral lower lobe involvement is seen more frequently in diabetics in (18) patients (30%) compared to 21 non diabetic patients (8.75%). This study shows the higher association of TB with diabetes, a typical location radiologically with a typical clinical presentation.

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Introduction

Diabetes is a common clinical problem where 4.5% of Middle East population affected[1], on the other hand, tuberculosis is emerging again as a major health problem and an estimated incidence in developing countries is 100-500 per 100.000/ per year[2]. Diabetes is an established risk factor for tuberculosis[3] and in the United States the association of diabetes and tuberculosis is similar to HIV infection[4] and tuberculosis is present in 1.2% of newly diagnosed diabetic in Uganda[5] where 52.8% of tuberculous diabetic patients use insulin. Mortality rate in tuberculous diabetes is three fold higher than in general population treated for tuberculosis[6] and this implies that tuberculosis co-existent with diabetes is a great clinical problem.
It has been stated but not adequately assessed that pulmonary tuberculosis in diabetic or immuno compromised patient often has a typical pattern radiologically and it involves the lower lobe predominently[7].
This study was conducted to estimate the relative risk of tuberculosis in our diabetic patients, the severity of the disease and its clinical and radiological pattern.

Patients & Methods

Sixty out of three hundred patients with active pulmonary TB had clinical and chemical diabetes (FBS) 140 mgm/dl) or 2 h. post prandial blood sugar > 200 mgm/dl)[8]. All patients had active pulmonary TB. (Positive sputum) and all attend the institute of TB control. All patients had full history physical examination, Drug history, Chest X-ray and FBS with Sputum examination direct smear and culture, follow up include chest x-ray and repeating sputum examination every month.
Every patient had at least 3 drugs on starting chemotherapy (Rifampicin, I.N.H., ETIBI, and/or (Streptomycin). Patients were followed up until they complete 9 month course of treatment (three months on 3 drugs Rifampicin. INH. ETIBI or Streptomycin) and 6 months on 2 drugs (Rifampicin + INH).
Diabetes was classified to Type 1 (insulin dependent diabetes I.D.M.M), usually younger than 30 years. Thin and had severe hyperglycemia.
Type II (non insulin dependent Diabetes usually over the age of 40 years. obese and on diet or oral hypoglycemic drugs).

Results

Table 1 show that 28 patients (30%) with active pulmonary TB their age ranged 40-49 years. While only 9 patients (15%) over the age of 50

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years. Male to female ratio is 2.1:1 in both diabetic and non diabetic tuberculos patients.

Table 1: Frequency distribution of age and sex of patients with active pulmonary Tuberculosis

	Male		Female	
Age (years)	**Diabetic**	**Non diabetic**	**Diabetic**	**Non diabetic**
0-9	0	0	0	0
10-19	3 (5%)	18 (7.5%)	0	3 (1.25%)
20-29	3 (5%)	51 (21.25%)	6 (10%)	30 (12.5%)
30-39	6 (10%)	8 (7.5%)	3 (5%)	6 (2.5%)
40-49	186 (30%)	8 (20%)	6 (10%)	15 (6.25%)
> 50	9 (15%)	33 (13.75%)	6 (10%)	18 (7.5%)
Total	39(65%)	168(70%)	21(35%)	72(30%)

Table 2 show that 18 (30%) non diabetic patients were on insulin therapy.

Table 2: Distribution of Diabetic patient according to the type of treatment in patients with active pulmonary Tuberculosis

Insulin Dependent Diabetic	18 (30%)
Non Insulin Dependent diabetic	42 (70%)

Table 3 shows that 168 (70%) non diabetic patients are converted to negative sputum within two months after starting chemotherapy compared to 27 (45%) diabetic patients.

Table 3: Time of Sputum (Conversion for cases with active pulmonary Tuberculosis)

Time of Conversion	Diabetics	Non-diabetics
End of Second month	27 (45%)	168 (70%)
3rd month	21 (35%)	39 (16.25%)
4th month	-	9 (3.75%)
> 4 months	12 (20%)	24 (10%)
Total	60	240

Table 4 shows that both minimal and moderate lung involvement is relatively equal in both diabetic and non diabetic tuberculos patients. 48 diabetic (80%) compared to 225 (93.75%) non diabetic patients.

Table 4: Distribution of cases according to the severity of the disease

Severity of the disease	Diabetic	Non-diabetic
Minimal	24 (40%)	147 (61.25%)
Moderate	24 (40%)	78 (32.5%)
Advanced	6 (10%)	12 (5%)
For advanced	6 (10%)	3 (1.25%)
Total	60 (100%)	240 (100%)

Table 5 shows that non diabetics had upper zone involvement more commonly than in diabetic patients. Lower zone involvement is more common in diabetic compared to non diabetic patients.

Table 5: Distribution of cases according to location of lesion

Site of the lesion	Unilateral		Bilateral	
	Diabetic	**Non-diabetic**	**Diabetic**	**Non-diabetic**
Upper Zone	6 (10%	87 (36.25%)	12 (20%)	15 (18.75%)
middle Zone	6 (10%)	39 (16.25%)	3 (5%)	15 (6.25%)
lower Zone	27(45%)	33 (13.75%)	6 (10%)	21 (8.75%)
Total	42(70%)	159 (66.25%)	18 (30%)	81 (33.75%)

Discussion

The risk of developing pulmonary tuberculosis of all types and bacteriologically confirmed cases were 3.47 times and 5.15 times higher in diabetics than in the control group[9]. In the United States, the association of tuberculosis and diabetes in Hispanics was (25%)[4] which is similar to our results where 20% of tuberculous patients had diabetes mellitus, it affect male > females and affect patients in their 40's and 50's years of age. In Uganda, a greater risk was observed in those at the age of 30-49 years than in those at the age of 50 years or more[5]. The severity of diabetes control or compensation and more advanced disease is correlated with high level of glycolysated hemoglobin and tuberculous patients with uncontrolled diabetes are prone to destruction, intoxication and they are more resistant to treatment, discharged bacteria more frequently[11]. Pulmonary tuberculosis in the presence of diabetes mellitus runs more unfavorably in less compensated patients. In our study, twenty one diabetic (30%) on insulin therapy which is associated with more severe diabetes and more uncompensation and its more difficult to control[8]. In this study 168 patients (70%) non diabetic responded within two months compared to 27 Diabetic patients (45%). In Japan (2.4%) of chronic excretory of TB Bacilli more than twelve months had diabetes mellitus.

Pulmonary tuberculosis is found predominantly in the lung apices[14], it has been suggested that tuberculosis tend to occur predominantly in the lower zone[7,15] and multiple lobe involvement was the predominant chest roentgenogrophic finding in both diabetic and non diabetic[15]. In this study Bilateral lobe involvement is seen in more frequently in diabetics. 18 patients (30%) compared to 21(8.75%) non-diabetics respectively.

Diabetics and immunocompromised patients have a higher prevalence of multiple cavities

within any given Lesion and by non segmental distribution than do patients without underlying disease[16]. Tuberculosis may progress rapidly and high index of suspicion is required, it remains a significant cause of morbidity and mortality among diabetic patients in developing countries[17].

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ASPIRIN AND NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN ACUTE UPPER GASTROINTESTINAL TRACT BLEEDING

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Abstract

Objective: Acute upper gastrointestinal tract bleeding (AUGITB) is the most common emergency in gastroenterology and still carries high mortality. It is not uncommonly precipitated by consumption of drugs. The aim of this study was to assess the association between this problem and the use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs).

Methods: One hundred and forty six patients who were presented with AUGITB were studied. They were all asked about recent consumption of aspirin and other NSAIDs, antecedent history of peptic ulcer or ulcer-like symptoms prior to the onset of bleeding. All patients were endoscoped within 48 hours of hospital admission to identify the source of bleeding and the findings between drug users and non-users were compared.

Results: It was noted that 39% of the patients were drug users, and aspirin was found to be the most commonly used agent (47.4 %). Antecedent history of peptic ulcer or ulcer-like symptoms was only obtained in 42.1% of the drug users as compared to 85.4% of the non-users ($p<0.01$). Acute gastric and duodenal erosions were the commonest endoscopic finding among the drug users, accounting for 40.4%, however, they were found in only 9% of the non-users. The group of drug users was older, had more women, needed more blood and had a higher mortality than the non-users group.

Conclusion: The use of aspirin and NSAIDs is significantly associated with AUGITB which is probably associated with high mortality. Thus over prescription of these drugs should be avoided. They should not be used for simple pain and should be used when really indicated, with caution in the elderly and in patients with dyspepsia.

Key words: NSAID's, Upper GI Bleeding

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Introduction

Upper gastrointestinal tract bleeding (UGITB) is one of the commonest gastroenterological emergencies in adults[1]. In Iraq it represents 7.5% of medical hospital admission[2,3]. The mortality in the developed countries has remained constant at 10% despite the increased availability of intensive care units, improved methods of diagnosis, advances in fibreoptic endoscopy and in modern surgical techniques[1,4].

It is widely accepted that aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) can cause gastric and duodenal mucosal injury and ulceration[5,6].

Recent findings also suggest an important role of aspirin and NSAIDs in producing peptic ulcer and upper gastrointestinal haemorrhage, particularly in older patients[7-14], however, other studies, have found no significant association[15-17].

Aspirin and NSAIDs are among the most widely prescribed drugs throughout the world[18]. Because of their frequent use, even relatively small risks may have major public health implications.

The exact way by which aspirin damages the gastric mucosa is not fully understood, however, many mechanisms have been put to cause this injury. These include impairment of mucosal defenses by penetrating the protective mucus and bicarbonate layers and damaging epithelial cells, so the gastric acid is poured through the breached defenses and further injures the cells. Other mechanisms are inhibition of mucosal prostaglandin synthesis, reduction of mucus and/or bicarbonate secretion, interference with cell turn over, as well as systemic effects such as platelet dysfunction[19].

The mechanism by which non-aspirin NSAIDs cause gastrointestinal damage is uncertain; all were known to inhibit prostaglandin synthesis, which could contribute to their toxicity[19-22].

We conducted this study to:

1. Evaluate the prevalence of aspirin and NSAIDs use among patients presented with AUGITB.
2. Draw out a comparison between drug users and non-users in relation to antecedent history of

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peptic ulcer or ulcer-like symptoms prior to the onset of bleeding, endoscopic findings, transfusion requirements and outcome between the two groups.

Patients & Methods

From September 1999 To March 2000, 146 patients (105 males, 41 females, mean age = 47y, SD = 15.5, range 16-82 years); admitted to Ibin-Sina Hospital in Mosul because of haematemesis or melena or both were considered for inclusion. Patients with comorbid illnesses like heart failure, renal failure, diabetes mellitus and stroke were not included in this study.

All had oesophagogastroduodenoscopy performed within 48 hours of admission to identify the source of bleeding. Patients were questioned by one of the authors about consumption of aspirin or other NSAIDs including type, dose, route and duration of treatment. Drug use was considered to be the drug used in the week before admission. Patients were also asked about past history of peptic ulcer or ulcer-like symptoms, alcohol or tobacco consumption.

For all cases, a record was also made of the blood transfusion requirement, the number of units of blood and the outcome (survival and death) on the study form. Patients were divided into groups; drug users (Aspirin and NSAIDs) (57 patients, 35 males and 22 females) and non-users (89 patients, 70 males and 19 females).

Statistical Analysis: The statistical method used include the unpaired t-test, with the data are presented as mean ± SD. Statistical significance is considered when p is < 0.05.

Results

All 146 patients proved to have AUGITB, the source of bleeding as identified by endoscopy was duodenal ulcer in 77 (52.7%), gastric erosions in 22 (15.1%), oesophageal varices in 14(9.6%), gastric ulcer in 12(8.2%), duodenal erosions in 9 (6.2%), Mallory-Weiss tear in 4 (2.7%), neoplasms in 3 (2%), and in 5 (3.4%) no definite cause was found (Figure 1).

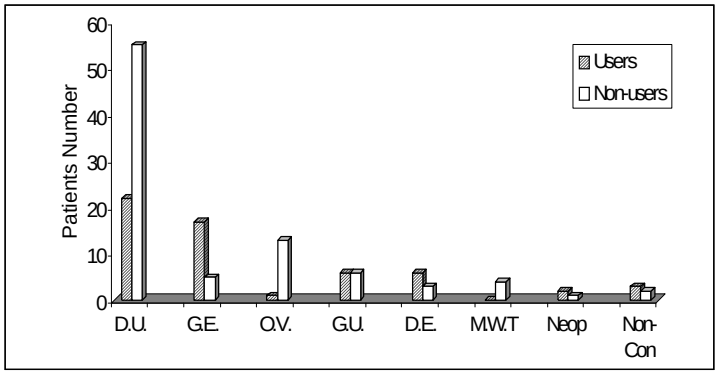

Figure1: Endoscopic findings in patients with upper gastrointestinal bleeding among users and non-users of NSAINDs

D.U.= duodenal ulcer, G.E.= gastric erosions, O.V.= oesophageal varices, G.U.= gastric ulcer, D.E.= duodenal erosions, M.W.T.= mallory weiss tear, Neop= neoplasia, Non-Con= non-conclusive.

Of the 146 patients, 57 (39%) were taking aspirin or other NSAIDs (drug users) before admission. Twenty two (53.7%) of the 41 female patients were drug users compared with 35 (33.3%) of the 105 male patients, the difference was significant (X^2 **cor**=4.13, $p < 0.05$). As far as age is concerned, it was found that the use of these drugs increases with increasing age, being highest for people aged 60 and above (Figure 2). However, there was no significant difference in the age between drug users whose mean age was 50 years (±SD 15.6) (range 16-82 years) and non-users, their mean age 44.9 years (±SD 15) (range 18-73 years).

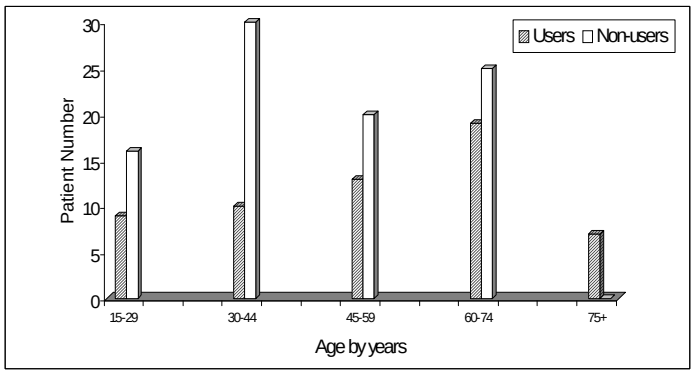

Figure 2: NSAID users by age among patients with upper gastrointestinal bleeding

There was a highly significant difference between both groups regarding the presence of antecedent peptic ulcer disease or dyspepsia. Seventy six (85.4%) patients of non-users had such history compared to only 24 (42.1%) patients of drug users. Among the group of drug

users, aspirin was the most commonly used (47.4%), followed by ibuprofen (31.6%), indomethacin (8.8%), mefenamic acid (1.8%), piroxicam (1.8%) and multiple drugs were used by 4 (7%) patients.

Endoscopic findings: Duodenal ulcer was found in 22 (38.6%) patients of users, but in non-users, it was found in 55 (61.8%) patients. Gastric erosions were found in 17 (29.8%) patients of users compared to 5 (5.6%) patients of non-users, also duodenal erosions were found in 6 (10.5%) patients of users compared to 3 (3.4%) patients of non-users. Gastric ulcer was found in 6 (10.5%) patients of users and 6 (6.7%) patients of non-users.

Oesophageal varices was found in 13 (14.6%) of non-users and 1 (1.7%) of users. Mallory-Weiss tear was found in 4 (4.5%) patients of non-users and in none of users. Neoplasms were found in 1 (1.1%) patients of non-users and in 2 (3.5%) patients of users (Figure 1 and Table 1).

Table 1: Endoscopic findings in each group of NSAID users

Endoscopy	As	Ib	Indo	MA	Di	Bi	Multiple
DU	9	10		1			2
GU	4	1					1
GE	10	1	3		1	1	1
DE	2	2	2				
Ose. Var.	-	1					
MWT	-	-					
Neop.	1	1					
Con non.	1	2					
Total	27	18	5	1	1	1	4

As = aspirin, Ib = ibobrufin, Indo = indomethacin, MA = mefanimic acid, Di = diclofenac, Bi = biroxicam, D.U=duodenal ulcer, G.U=gastric ulcer, G.E=gastric erosions, D.E= duodenal erosions, Oes.Var.=oesophageal arices, M.W.T=Mallory- Weiss tear, Neop.=neoplasia. Non.Con= non-conclusive.

In 5 patients (3 of users and 2 of non-users) the cause of bleeding could not be identified because of the severity of bleeding.

There was a significant difference between both groups in the blood transfusion requirements. Forty one (71.9%) of drug users required blood, compared to 43 (48.3%) of non-users ($p < 0.01$).

When the outcome between the two groups was compared, it was found that 5 (9.1%) patients of drug users died and 5 (5.6%) of non-users died, the statistical difference between the two groups was not significant ($p < 0.75$). However, in the group of non-users four of the dead patients had oesophageal varices due to advanced liver cirrhosis.

There was no significant difference between the two groups in the use of tobacco or alcohol. The daily dose, duration of intake of aspirinand NSAIDs and their indications are summarized in tables 2, 3, 4 and 5 which demonstrate that 17 (29.8%) patients gave only one day history of exposure to the drug prior to onset of bleeding and in 41 (71.9%) patients, the duration of intake was a week or less.

Table 2: Daily doses of NSAIDs and aspirin

Daily dose	As	Ib	Indo	MA	Di	Bi	Multiple
One/day	7	1	1	-	-	-	-
Two/day	11	6	1	-	-	1	-
Three/day	7	11	3	1	-	-	-
> three/day	2	-	-	-	1	-	4
No.	27	18	5	1	1	1	4

As = aspirin, Ib = ibobrufin, Indo = indomethacin, MA = mefanimic acid, Di = diclofenac, Bi = biroxicam

Table 3: Duration of intake of NSAIDs and aspirin

Duration	As	Ib	Indo	MA	Di	Bi	Multiple	Total
One day	12	2	-	-	1	-	2	17
2-7 days	10	9	1	1	-	1	2	24
> 1 week	-	1	1	-	-	-	-	2
> 1 month	4	5	-	-	-	-	-	9
> 1 year	1	1	1	3	-	-	-	5

As = aspirin, Ib = ibobrufin, Indo = indomethacin, MA = mefanimic acid, Di = diclofenac, Bi = biroxicam

Table 4: Endoscopic findings in relation to the duration of intake of NSAIDs and aspirin

Endoscopic findings	1 day	2-7 days	> 1 week	> 1 month	> 1 year
DU	1	11	1	7	2
GU	1	3	0	2	0
GE	10	5	0	0	2
DE	3	1	1	0	1
Ose. Var.	0	1	0	0	0
Neop.	1	1	0	0	0
Con non	1	2	0	0	0
Total	17	24	2	9	5

Table 5: Indications of intake of NSAIDs and aspirin

Indication	As	Ib	Indo	MA	Di	Bi	Multiple
Headache	19	1	1	-	-	1	-
Joint pain	-	15	3	-	1	-	3
Myalgia	1	2	-	-	-	-	-
Fever	2	-	-	-	-	-	-
Toothache	1	-	-	-	-	-	-
Antiplatelet	2	-	-	-	-	-	-
Abdominal pain	-	-	-	1	-	-	-
Chest pain	1	-	-	-	-	-	-
Suicidal	-	-	-	-	-	-	1
Eye problem	1	-	1	-	-	-	-
Total	27	18	5	1	1	1	4

As = aspirin, Ib = ibobrufin, Indo = indomethacin, MA = mefanimic acid, Di = diclofenac, Bi = biroxicam

Discussion

This study like others, confirms the highly significant association between AUGITB and the use of aspirin and NSAIDs[9,10,23-28]. This was observed in 39% of our patients who were drug users.

It is quite striking that this association is particularly demonstrable for short-term use, as

71.9% of the drug users had been exposed to the drugs for a week or less, and 29.8% of them had history of only 24 hours exposure prior to the onset of bleeding. This is quite different from the finding reported by Boston Collaborative Drug Surveillance which found no evidence of significant association between UGITB and less heavy use of aspirin[27,29,30].

However, other studies have demonstrated this association both for long term as well as short term use[3,29,31,32]. Unexpectedly, only two patients were taking aspirin as antiplatelets and the dose was higher than 100 mg which is recommended for prophylaxis. We also found that ibuprofen was the most commonly used NSAIDs taken by the patients. Although this agent is relatively less injurious to the gastroduodenal mucosa, however, it was overprescriped and overtaken by the patients because of its popularity as well as its availability in the market.

We found a significant association of drug use for women (53.7%) and for older patients; this can be explained by the fact that this group of patients consumes the largest number of these drugs. Moreover, most of non-drug users (85.4%) had history of peptic ulcer disease or ulcer-like symptoms prior to the onset of bleeding, this confirms the notion that symptoms of peptic ulcer disease are a risk factor for development of peptic ulcer complications in non-aspirin, non-NSAIDs users, this finding is consistent with other studies[23,33].

Nevertheless, among the 57 drug users, such history was lacking in more than half (57.9%) of them and bleeding was the first symptom. This finding may indicate that the lesions found in these patients are entirely caused by aspirin and NSAIDs rather than exacerbation by these drugs of an underlying peptic diathesis. This conclusion is supported by the fact that acute erosions (gastric and duodenal) were the main cause of bleeding among drug users, being responsible for 40.3% of cases which is significantly different from the 9% among non-users. This is in agreement with the experimental evidence that gastric erosions can be induced by aspirin and NSAIDs[7,34,35].

Duodenal ulcer was the commonest cause of bleeding among non-users, constituting 61.8% similar to other studies[2,3,36]. However, it was found in 38.6% of drug users, and in the absence of control series, it is difficult to conclude that duodenal ulcer are entirely caused by these drugs, and could only represent an exacerbation by aspirin and NSAIDs of pre-existing ulcer.

Oesophageal varices were the second common cause of bleeding among non-users, accounting for 14.6% which is comparable to the results of previous studies in Iraq[2,3]. This figure is higher than that reported from U.K., were oesophageal varices accounted for 1-6% of UGITB[36-38].

However, it is similar to that reported in the American Society for Gastrointestinal Endoscopy (ASGE) survey[30]. Among the group of drug-users, oesophageal varices have been found in only one patient (1.7%), a finding which may rule out the relation between varices and exposure to these drugs. This can also be true for Mallory-Weiss tear which was not found in any of the drug-users.

Our study revealed a significant difference in the transfusion requirements as 71.9% of drug-users needed blood compared to 48.3% of non-users, similar to other study[23]. In addition a study of the outcome revealed that the mortality rate among users was 9.1%, and although this is not statistically different from the 5.6% mortality rate among non-users, nevertheless 4 of the 5 non-users patients who died had variceal bleeding due to liver cirrhosis, a highly lethal condition that carries the highest mortality rate (30%) of any of the major causes of gastrointestinal bleeding[39].

The inclusion of these 4 patients with variceal bleeding in this group may have contributed to the statistical non-significance between the two groups. Accordingly, and taking this point into consideration, we may conclude that the mortality rate among drug users is higher than that of non-users.

This study did not show significant difference neither in the use of tobacco nor in the use of alcohol between the two groups, and most published case-control studies[9,10,32], have found that alcohol and tobacco were not significantly associated with UGITB.

Although our findings are difficult to place in context without control series, however, it can be concluded from this study that the use of aspirin and NSAIDs is significantly associated with AUGITB which is probably associated with high mortality. Thus, overprescription of these drugs should be avoided; they should not be used for simple pain and should be used if really

indicated, with caution in the elderly and in patients with dyspepsia.

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THE EFFECT OF PRAZIQUANTEL ON ABDOMINAL HYDATID CYST DISEASE

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Abstract

A prospective study of the effect of Praziquantel (PZQ) cysts was performed during a period of (22) months extending from November 1996-September 1998. Fifty-seven cases were diagnosed as abdominal hydatid cysts, 11 excluded from the study because samples of hydatid cysts not are obtained.

The remaining 46 patients including a total number of 104 cysts were randomly divided into groups, the first was the control group (15patients/25cysts), the second group was the treatment group which was subdivided into 2 groups, the PZQ group (22patients/61cysts) they received PZQ tables for 14 days pre-dominantly, and the PZQ+MBZ group (9patients/18cysts) received PZQ for 14 days and mebendazole (MBZ) for 1 month pre-operatively. All patients underwent surgery.

The viability of the Scolices from the cysts from the different groups had been checked immediately after surgery by Flame Cell activity and Eosin excluding tests and found as 81-100% in the control group, 21-40% in the PZQ group and 1-20% in the PZQ+MBZ group. So the combination (PZQ+MBZ) was significantly more effective than PZQ alone ($p<0.05$) and the latter compared to control was as well so effective ($p<0.05$). The effect of cyst site, size, daughter cysts and age was also studied.

So that Praziquantel in combination with mebendazole is more effective ($p<0.05$) in reducing viability of scolices than Praziquantel alon though the latter proved very effective ($p<0.05$) compared to the control.

Aim of the study: To study the possible role of Praziquantel of recurrence of hydatid cyst disease by studying its effects on cyst viability.

Key words: Abdominal hydatid cyst, Praziquantel

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Introduction

Hydatid cyst disease is a parasitic infection of the liver and other organs by the flatworm, echinococcus, E.grnulosus is the causative organism in classic hydatid; cyst, while infection with E.multilocularis result in alveolar hydatid disease a more aggressive, less localized affliction[1].

It is still a major health problem in infested areas of the world. It can involve any organ and mimic almost any pathologic condition[2]. In Iraq hydatid cyst disease is considered both more dangerous and more difficult to manage than cancer as the latter can be controlled in its early stages while it is difficult to eradicate the former[3].

Surgery remains the treatment of choice for the majority of individuals infested with E. granulosis advances in medical management of hydatidosis with newer antihelmenthic medications have been made and limited experience with percutaneous aspiration and drainage of H. cysts have been reported[1,4]. Presently the use of antihelmenthic medications complements surgical management but do not replace it.

Recurrence: In spite of the use local injection of scolicides during the operation and the various methods of closed aspiration, freezing cone and plastic sheath…etc, still recurrence is one of the best significant post operative complications in man occurring approximately in 10% of patients[1,3,6,7]. When recurrence occurs further surgery is associated with increasing morbidity and mortality[5].

Praziquantel: this isoquinoline has been found to be more effective scolicidal agent in *in vitro* cultures of E.granulosus and tat combinations of albendazole and Praziquantel are more effective than either alone[6,7]. The same facts were true in animal studies and in man. Since a 10 days preoperative treatment with PZQ resulted in more than 90% of the protoscolices in human hydatids being recorded as dead at surgery[8], an important role in preventing recurrence had been suggested for perioperative PZQ treatment. Its mechanism of action is unknown but may be by spastic paralysis of the parasite. After oral administration the drug is rapidly and efficiently absorbed from the intestine, with bioavailability of 80-100%[9].

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It is very well tolerated, with a rate of side effects of about 10-15%[9]. It is used for Bilharziasis and other Trematodes as well as Cestodes.

Patients & Methods

From November 1996 to September 1998, 57 cases of abdominal hydatid cysts had been admitted to the surgical wards of the Al-Kadhiymia Teaching Hospital, 11 cases had been excluded from the study because hydatid samples either could not be obtained or tested for viability.

The remaining 46 cases (30 females & 16 males) were randomly divided into groups; the control group (15 patients) was given no treatment and surgery done after diagnosis and the treated group (31 patients) which was further subdivided into 2 groups; the PZQ group, (22 patients) who received PZQ tablet in a dose of 50mg/kg/day for 14 days, & combination group (9 patients) who received the same dose of PZQ + mebendazole 40mg/kg/day for 1 month. Baseline investigations including LFTs & US were obtained and repeated in fortnight and 1month intervals.

Viability tests: Hydatid fluid was the material by which the viability of hydatid cysts tested, and this was recovered either from removed cysts, of splenectomy greater omentum, or resected liver, or from hepatic cysts by aspiration prior to scolecidal injection. H. fluid was immediately taken from theater to the lab and checked by 2 methods:

First: Flame cell activity: Multiple fluid samples had been taken from each one slides prepared on which a drop or two of hydatid fluid examined under light microscopic under 40X, 100X, & oil emersion power to detect this flame cell activity which is a flickering movement exhibited by the scolex and it is a sign of viability, the scolex is dead if no flickering is exhibited.

Second: The ability for exclusion of biological stain: A drop or two of eosin 0.1% was put on the fluid drop(s) in the slides prepared above; dead scolices will take the stain viable ones will since they have the ability to exclude the stain.

$$\% \text{ of viability} = \frac{\text{No of viable scolices/HPF} \times 100}{\text{Total No of scolices (viable + dead)/HPF}}$$

$$\text{Mean \% of viability} = \frac{\text{\% of viable of cyst 1 + \% of viability of cyst 2 + … x100}}{\text{Number of cysts}}$$

Results

The clinical manifestations are illustrated in table 1.

Table 1: clinical manifestations of hydatid liver disease

Clinical Manifestations	% Hydatid Cyst
A symptomatic	75%
Symptomatic	25%
Abdominal pain	79%
Dyspesia	50%
Fever and chills	30%
Juandice	25%
Arthritis	5%
Signs	
RT upper quadrant	70%
RT upper quadrant tenderness	20%
Laboratory	
Eosinophilia	35%
Bilirubin >2mg/dl	20%
WBC>10000/mm^2	10%

In this study the maximum age incidence was in the age group (31-40), it was more common in females (about 65%), and more prevalent among inhabitants of rural areas (63%). Ten patients presented with recurrent cysts; 7 of these were in the treated group and 3 in control. The liver was the organ most involved, 41 out of 46 cases (89.1%), alone in 30(23.9%) in association with other viscera. The spleen was the next organ (Table 2).

Table 2: Correlation between sites of involvement by hydatid cyst disease and no. of patients involved in the control group and the two treated subgroups

Site	Number of patients			
	Treated group		Control group	Total number & %
	PZQ	PZQ + Meben.		
Liver alone	14	5	11	(30) 65.217%
Liver & greater omentum	1	2	1	(4) 8.69%
Liver & spleen	2	1	1	(4) 8.69%
Spleen alone	1	1	1	(3) 6.521%
Liver & pelvis	1	0	1	(2) 4.347%
Liver & lung	1	0	0	(1) 2.173%
Abdomen	1	0	0	(1) 2.173%
Pelvis	1	0	0	(1) 2.173%
Total	22	9	15	(46)

PZQ = praziquantel, meben. = mebedazole

The right lobe was involved in 76% and the left in 24% of the 50 cysts found in the liver. The greater omentum and the spleen showed the next

higher involvement as far as the number of cysts (Table 3).

Table 3: Correlation between viscera involved and No. of cysts in the control group and treated subgroups

Site	Number of cysts						
	Treated groups				Control group		Total No. of cyst
	PZQ		PZQ + Meben.				
	Case	Cyst	Case	Cyst	Case	Cyst	
Liver	19	24	8	10	14	16	50
G. omentum	1	28	2	4	1	2	34
Spleen	3	4	2	4	2	6	14
Pelvis	2	4	0	0	1	1	5
Abdomen	1	1	0	0	0	0	1
Total	69		18		25		104

G. omentum = greater omentum, PZQ = praziquantel, meben. = mebedazole

The commonest presenting complaint was a right upper quadrant pain (Table 4).

Table 4: Clinical manifestation of hydatid cyst disease

Complaints	Number of patients	
	Treated group	Control group
Right upper quadrant pain	16	7
Mass	5	5
Ultrasonic examination	3	1
Jaundice & pain	2	1
Dyspepsia	2	1
Left upper quadrant pain	1	1
x-ray diagnosis	1	-
mass + pain	1	-
Total	31	15

Tolerance to either drug was very good with only mild side effects namely dizziness & headache, no treatment was stopped, and patients were only observed during the first few days (Table 5).

Table 5: The side effects of the drugs

Side effects	Total no. of patients PZQ group (22)	Total no. of patients PZQ + MBZ group(9)
Dizziness and headache	13	6
Nausea and vomiting	10	3
Abdominal	6	3
Increase transaminase	0	3
Urticarial rash	1	2
Agranulocytopenia	0	0
Nair loss	0	0

PZQ = praziquntel, MBZ = mebendazole

Viability: Table 6, 7, and 8 represent the viability order in the 3 groups of patients i.e. PZQ, PZQ+MBZ, and the control groups. They show that the highest number of cysts in the PZQ+MBZ group is in the viability order (1-20%) which is significantly lower than that of the PZQ alone group (21-40%) ($p<0.05$) and this in itself is significantly lower than that of the control group (81-100%) ($p<0.05$). In either group viability was higher in liver & spleen cysts than cysts of the momentum, pelvis and abdominal cavity ($p<0.05$). Figures 1 & 2 correlate between cysts size, daughter cysts with the mean % of viability in the treated & control groups, respectively.

Table 6: Percentage of viability of the cysts from patients in PZQ group

Site	No. cyst treated	% of viability					
		0 %	1-20%	21-40%	41-60%	61-80%	81-100%
Liver	24	2*	2	6	12	1	1
Spleen	4	1*	-	1	2	-	-
G. omentum	28	2*	5	16	3	2	-
Pelvis	4	-	1	2	1	-	-
Abdomen	1	-	-	1	-	-	-
Total	61	5	8	26	18	3	1

*Infected cysts

Table 7: Percentage of viability of the cysts from patients in PZQ+MBZ group

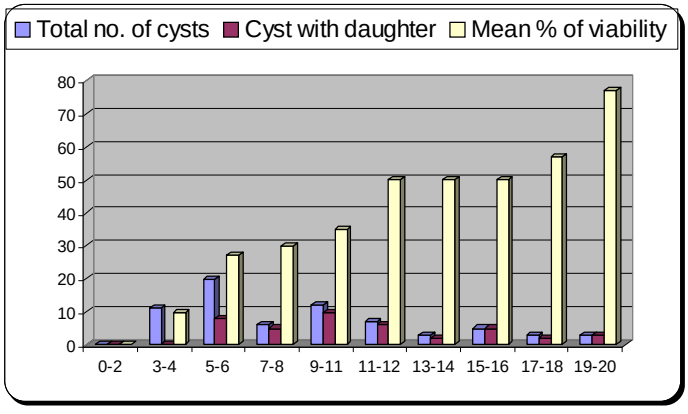
Site	No. cyst treated	% of viability					
		0 %	1-20%	21-40%	41-60%	61-80%	81-100%
Liver	10	3*	3	3	1	-	-
Spleen	4	-	1	2	1	-	-
G. omentum	4	1*	3	-	-	-	-
Pelvis	0	-	-	-	-	-	-
Abdomen	0	-	-	-	-	-	-
Total	18	4	7	5	2	-	-

*Infected cysts

Table 8: Percentage of viability in the control group

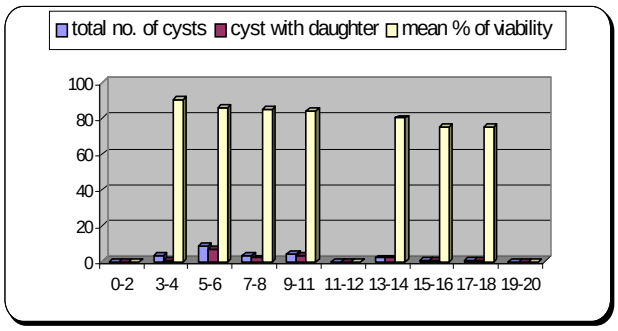
Site	No. cyst treated	% of viability					
		0 %	1-20%	21-40%	41-60%	61-80%	81-100%
Liver	16	2*	-	-	-	2	12
Spleen	6	-	-	-	-	2	4
G. omentum	2	-	-	-	-	-	2
Pelvis	1	-	-	-	-	1	-
Abdomen	-	-	-	-	-	-	-
Total	25	2	-	-	-	5	18

*Infected cysts



Cyst size (cm)	0-2	3-4	5-6	7-8	9-11	11-12	13-14	15-16	17-18	19-20
Total No. of cysts	0	11	20	6	12	7	3	5	3	3
Cysts with daughters	0	0	8	5	10	6	2	5	2	3
Mean % of viability	0	10	27	30	35	50	50	50	57	77

Figure 1: Correlation between cyst size, daughter cysts with the mean viability in the treated group



Cyst size (cm)	0-2	3-4	5-6	7-8	9-11	11-12	13-14	15-16	17-18	19-20
Total No. of cysts	0	3	9	3	4	0	2	1	1	0
Cysts with daughters	0	1	7	2	3	0	2	1	1	0
Mean % of viability	0	90.3	86.1	85	83.8	0	80	75	75	0

Figure 2: Correlation between cyst size, daughter cyst and mean % of viability in the control group

Discussion

The findings of this study regarding age distribution, rural prevalence, the higher involvement of the liver and mainly its Rt. Lobe, as well as the presenting complaint of Rt. upper quadrant pain & mass, are all in concordance with other studies[1,10]. But our findings of higher incidence among females is only so with local literature (Al-Janabi of Iraq)[11] while others showed equal male & female prevalence. In the evaluation of treatment response each cyst was regarded as a separate parasitic unit since not all cysts with the same localization responded equally to treatment. So chemotherapy results were analyzed in terms of cyst localization, size, age, number and structure, as well as drug factors.

Cyst factors

Cyst localization: The higher % of viability in the liver and spleen cysts may suggest that the well formed pericyst (pseudocyst) affects drug penetration & concentration inside the cyst.

Cyst size: Significant differences ($p<0.05$) in the viability of cyst of different sizes were noticed (Figure 10), and this again can be explained by a thicker pericyst, preventing penetration & concentration of the drugs in the treated groups, in the bigger cyst.

Cyst number: It is reported that the more number of cyst in one organ or patient the more susceptible it would be to chemotherapy[12,13]. In this study one case with 28 cysts in the greater omentum in which 16 of them showed viability of (21-40%).

Cyst structure: In the treated group (Figure 10), cysts with daughter cysts had higher viability than those without, possibly due to the added barrier of daughter cyst walls. In the control group cysts with daughter cysts had higher viability possibly due to nutritional need[12, 13].

Cyst age: With age there will be increase both in thickness of wall & number of daughter cysts and this increases viability.

Drug factors

Drug used: This study tested as a single drug only PZQ, which a large number of in vitro studies proved as being the best scolecidal[1,12] but little in vivo ones, and revealed a significant effect.

Drug plasma concentration[8]: A definite relation had been shown. Unfortunately we had not such a facility.

Drug combination: This study showed that PZQ+MBZ a significantly better effect than PZQ alone. It had been demonstrated that using eosin exclusion and flame cell activity tests for viability leads to over-estimation of parasite viability and under-estimation of drug efficacy and that electron microscopy, enzyme digestion, and injection to lab, animals make a better study[14,15].

Recommendation

We strongly recommend the use of Praziquantel alone in combinations for all patients with hydatid cyst disease both pre-operatively to kill the parasite and post-operatively to prevent the implantation of spilled viable scolices during surgery. More extended studies are needed.

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THENAR FLAP: EXCELLENT FINGERTIP CONTOUR BY LEAVING THE RECIPIENT FINGER TO HEAL BY SECONDARY INTENSION AFTER FLAP SEPARATION

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Abstract

Background: Injury to the fingertip can result in significant functional and aesthetic deficit. There are different treatment modalities in reconstruction of fingertip soft tissue defects. The proximally based thenar flap is a random pattern skin flap taken from the thenar area. It provides thick skin coverage with minimal donor site deficit.

Aim: Reconstruction of finger tip injuries by proximally based thenar flaps with new minor modifications to ensure regularly round fingertip with some elongation.

Patients and method: Finger tip injuries were reconstructed by the proximally based thenar flap. After flap division the raw areas in the recipient fingers were left to heal by secondary intention, the patients were evaluated for the final shape of the finger tip and the development of complications.

Results: The flap provided regularly round finger tip contour in 17 patients (94.4%) with elongation of the reconstructed fingertip. Complications included partial flap loss (one patient), stiffness (one patient) and thumb parasthesia (one patient).

Conclusion: Minor modifications in thenar flap reconstruction can provide excellent shape of the finger tip (regularly round contour) in addition to elongation. They include separation of the flap and leaving the recipient finger raw area to heal by secondary intention, making the flap wider than the flap width, and suturing the tip and the sides of the flap to two thirds the circumference of the defect. Oblique closure of the donor site can close the skin easily without the need for extensive undermining. Finally the study demonstrated certain measures that should be considered to decrease the risk of PI joint stiffness.

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Introduction

Each function of the hand, whether it is that of sensory discrimination or motor precision manipulation and grasp, is dependent on a normal fingertip[1]. The fingertip is one of the most specialized parts of the human body and virtually irreplaceable if lost. It consists of all structures distal to the distal interphalangeal crease, i.e. the perionychium (nailbed, nail and paronychium), volar pulp, and distal phalanx[2].

Fingertip injuries constitute one of the most common traumatic injuries, loss of or injury to this highly specialized skin can lead to significant dysfunction and long term morbidity[3,4].

Injuries of the fingertip and nail bed require treatment to minimize pain, speed healing, maintain length and shorten the time of functional impairement[3,4]. Many techniques of fingertip reconstruction have been described[5]. The most appropriate method of wound closure for a particular finger tip injury depends upon several factors. The type and extent of injury should be carefully evaluated prior to treatment. Other considerations include the patient's age, occupation, hand dominance and medical history[3].

Treatment modalities range from primary debridment and conservative dressings to the various methods of skin closure (suture, graft, local or distant flap) through to replantation and free tissue transfer[1,2,6-8,10].

There is a clear consensus that local and regional flaps are superior to other methods of treatment for major distal phalangeal amputations, they provide the quality of near normal tissues necessary to restore adequately the lost pulp[9,11].

The thenar flap is a satisfactory reconstructive technique for the treatment of finger tip injuries; it has the advantage of transferring thicker palmer skin from the thenar area to fingertip defects while avoiding a donor deficit on adjacent normal fingers. It can be based proximally, distally or

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even laterally and thus can be used for amputations of any orientation on the index, long or ring fingers[2,12]. On the other hand, thenar flap has been criticized for resulting in flexion contracture of the proximal interphalangeal (PI) joint and tenderness of the donor site[9,13-15].

In this study thenar flaps were used to reconstruct distal traumatic amputations in the index and middle fingers. The recipient fingers were not sutured after flap separation and the raw area healed by secondary intention (wound contraction and epithelialization).

Patients and Methods

The study included 18 patients with fingertip injuries affecting the index and middle fingers. In all of the cases the injury was a traumatic amputation at or distal to the distal interphalangeal crease with loss of the pulp and exposure of the bone. The extent of tissue loss and bony exposure precluded closure by simple wound approximation or local fingertip flap (Figure 1). There were 15 male and 3 female patients with their ages varying between 16 and 51 years. The index finger was involved in 11 cases and the middle finger in 7 cases.

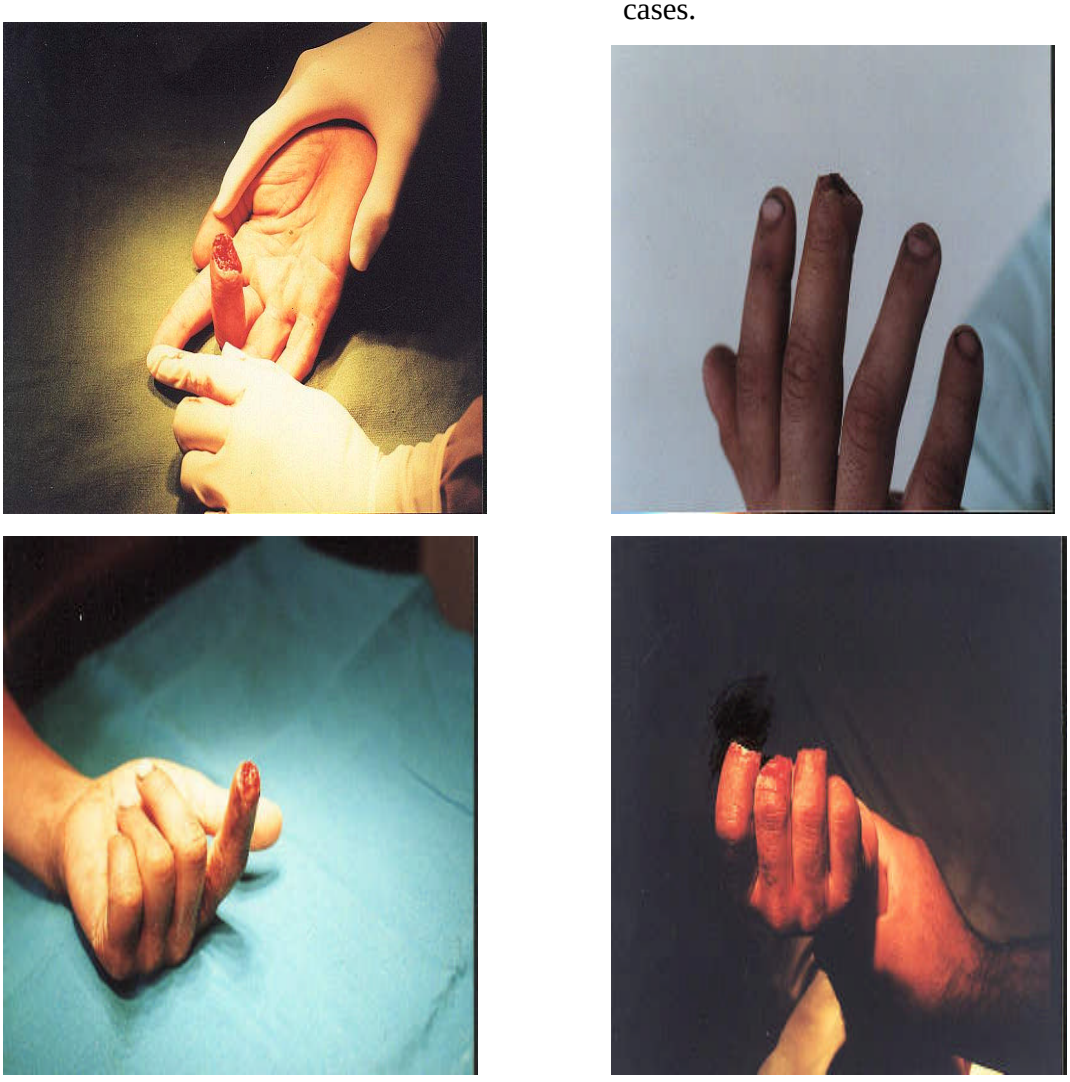


Figure 1: The study included injuries in the middle and index digits that cannot be closed directly or by a skin graft

All of them were managed surgically using proximally based thenar flaps to cover the soft tissue loss. After flap division the recipient wounds were left to heal by secondary intention and followed up for a period of 2-6 months.

Surgical technique:

The operations were done under general anesthesia with the aid of an arm tourniquet.

Marking: A pattern of the tissue defect was done on a paper and outlined on the lateral aspect of the thenar area just proximal to the skin crease of the thumb metacarpophalangeal joint (Figure 2). The flap is proximally based and the recipient finger flexed to establish the exact location of the flap base.

The flap is rectangular in shape with its length range of 1.5-2.5 cm (making it 3-7 mm longer than the diameter of the defect), and a width of 1-1.5 cm (2-3 mm wider than the width of the defect).

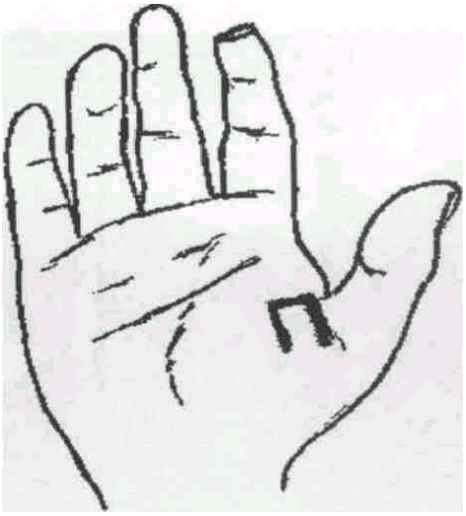


Figure 2: Proximally based thenar flap just proximal to the skin crease of the thumb metacarpophalangeal joint

Flap elevation: Elevation starts by incising the marked edges by a scalpel then the flap is raised off the thenar muscles by blunt dissection to include all the subcutaneous fat. Care should be taken to avoid the digital nerve to the radial side of the thumb which is superficially located and commonly seen during flap elevation. The tourniquet is removed and hemostasis is done using bipolar electrocautery.

Donor site closure: The donor area is closed directly in one layer after undermining of the wound edges. The direction of the closure is done in an oblique manner in which the lateral angle of the tip of the flap is approximated to the midpoint of the medial long limb (Figure 3).

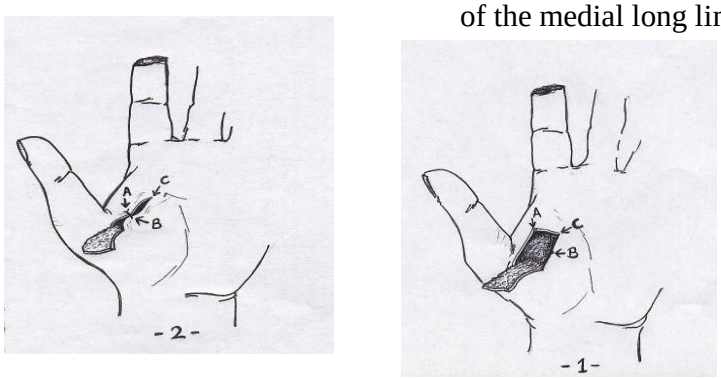


Figure 3: The best direction to close the thenar site with minimal tension is to approximate the lateral angle of the defect (point A) to the midpoint of the medial long limb of the defect (point B)

Flap inset: The recipient finger is flexed and the thumb is palmer-abducted to meet the finger halfway (Figure 4), the flap is attached using interrupted silk sutures to approximate the tip and the lateral walls of the flap to two thirds the circumference of the recipient finger (Figure 5).

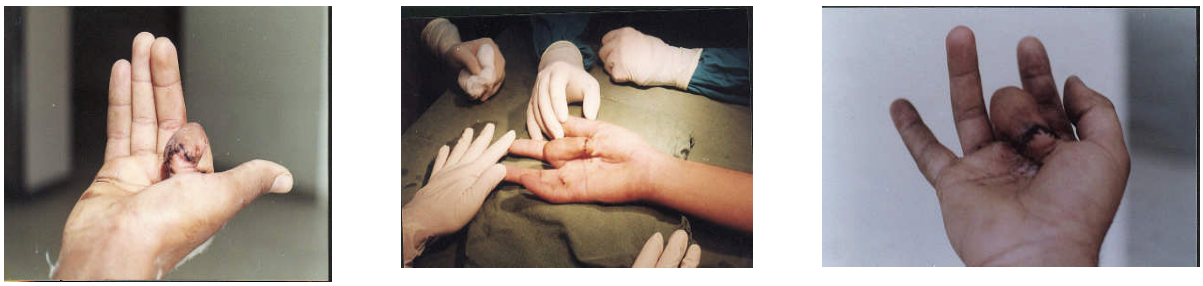


Figure 4: Flap inset

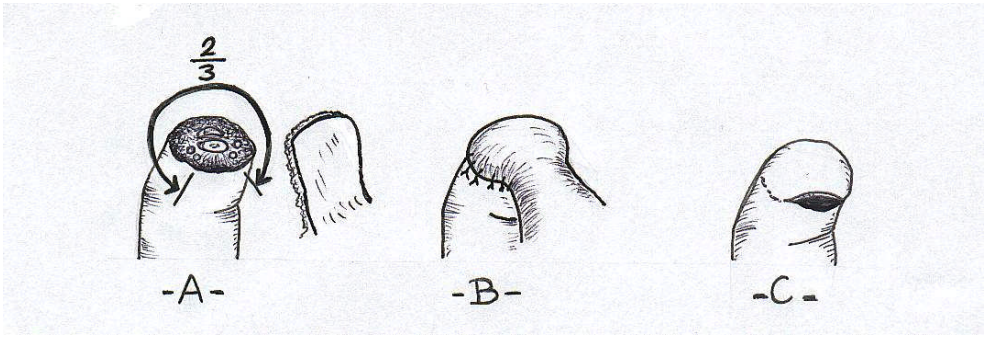


Figure 5: The tip and sides of the flap (which is few mm wider than the wound) are sutured to two thirds the circumference of the defects, this will create flap bunching to form a round tip with some elongation, in addition, the resulting wound after flap separation will be small and rapidly closed by secondary contraction and epithelialization

Splinting and dressing: Non adherent lubricated gauze is applied to the raw area in the flap base and the entire recipient finger is covered by dry gauze. Early in the study the recipient fingers were splinted by back slab to maintain the finger in the flexed position and prevent tension on the suture line, later we did not use splints and the finger was kept in flexion by dorsal adhesive tape attaching it to the wrist. Crepe bandage dressing was done leaving the rest of the fingers exposed.

Flap separation: The flaps were separated after 14-21 days; the operation was done either under local or general anesthesia, and frequently there are bleeding vessels in the donor site, after hemostasis the donor site closure is completed by silk. The recipient finger proximal interphalangeal joint is manipulated and extended under anesthesia and the raw area in the recipient finger resulting from flap separation is left open without suturing and covered by lubricated gauze.

Follow up: The patients were seen every 7 days in the first two months then monthly for a period of 2-6 months. Wound care and antibiotic ointment application were done for the open flap base in the recipient finger to facilitate closure of the wound by secondary intention {wound contraction and epitheliali-zation},(Figure 6).

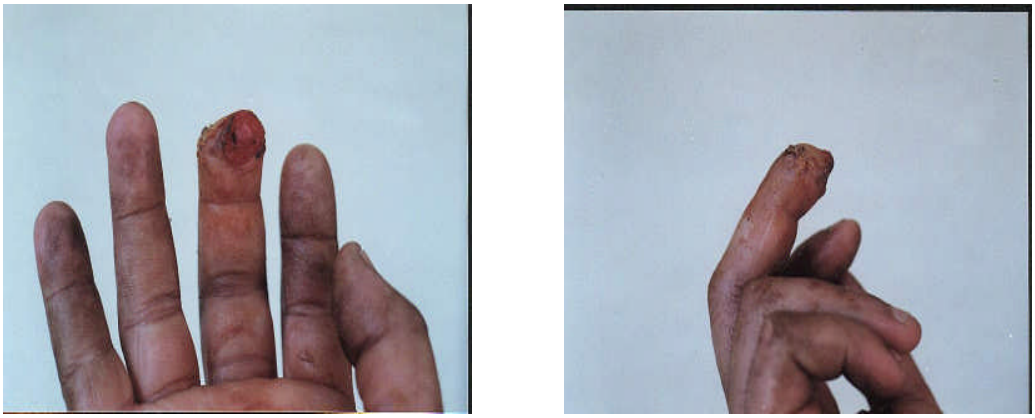


Figure 6: After separation the flap base in the recipient finger was left to close by secondary intension.

The patients were evaluated for:
1- Time needed for wound contraction and epithelialization.
2- Development of complications (In the donor and recipient sites).
3- Final shape of the reconstructed finger tip and patient satisfaction.

Results

In all of the 18 digits included in this study the recipient wounds were closed by secondary intention within a period of 14-21 days after flap separation. In 17 cases the rounded contour of a fingertip was restored as well as elongation of the amputated finger tip (Figure 7). Partial flap loss developed at the tip of one case resulting in some irregularity in the contour of the fingertip, and the cause of the loss was kinking of the flap base.

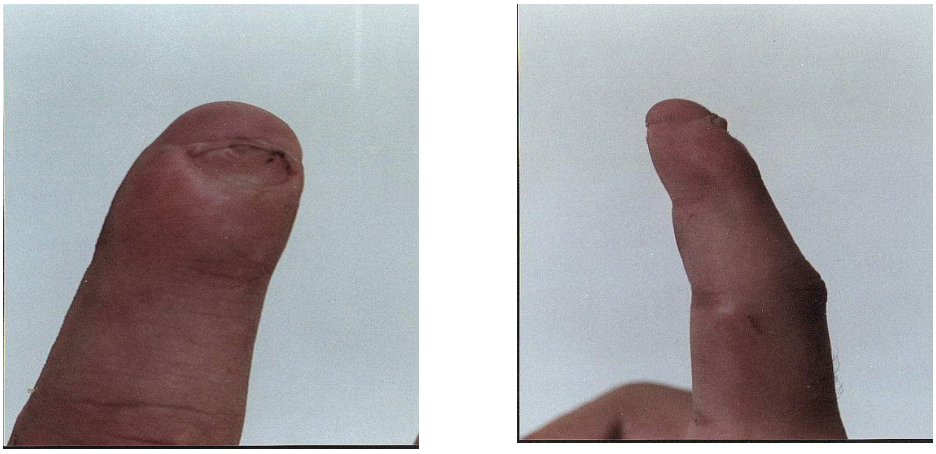


Figure 7: Excellent finger tip contour and 6-8 mm elongation, the photograph taken 28 days after flap separation.

Seventeen of the patients were satisfied with the final spherical shape of the finger tip and started to use their injured hands 4-8 weeks after operation. All the patients were hospitalized for one day at the first stage, and discharged in the same day after the second operation.

All the patients developed protective pain sensation in the flaps when examined six months after the operation. One case developed minor proximal interphalangeal joint stiffness (10 degrees) improved by physiotherapy, one case developed parasthesia in the ulnar aspect of the thumb and gradually within two months.

Donor site complications included granuloma at the suture line in one case, and maceration in the palmer skin creases due to continuous skin folding and wetness in 2 cases, there were no cases of donor site painful scar, scar hypertrophy or first web space contracture (Table 1).

Table 1: Complications

Complications	Number of patients
Partial flap loss	1
Joint stiffness	1
Thumb parasthesia	1
Donor site granuloma	1
Palm skin maceration	1

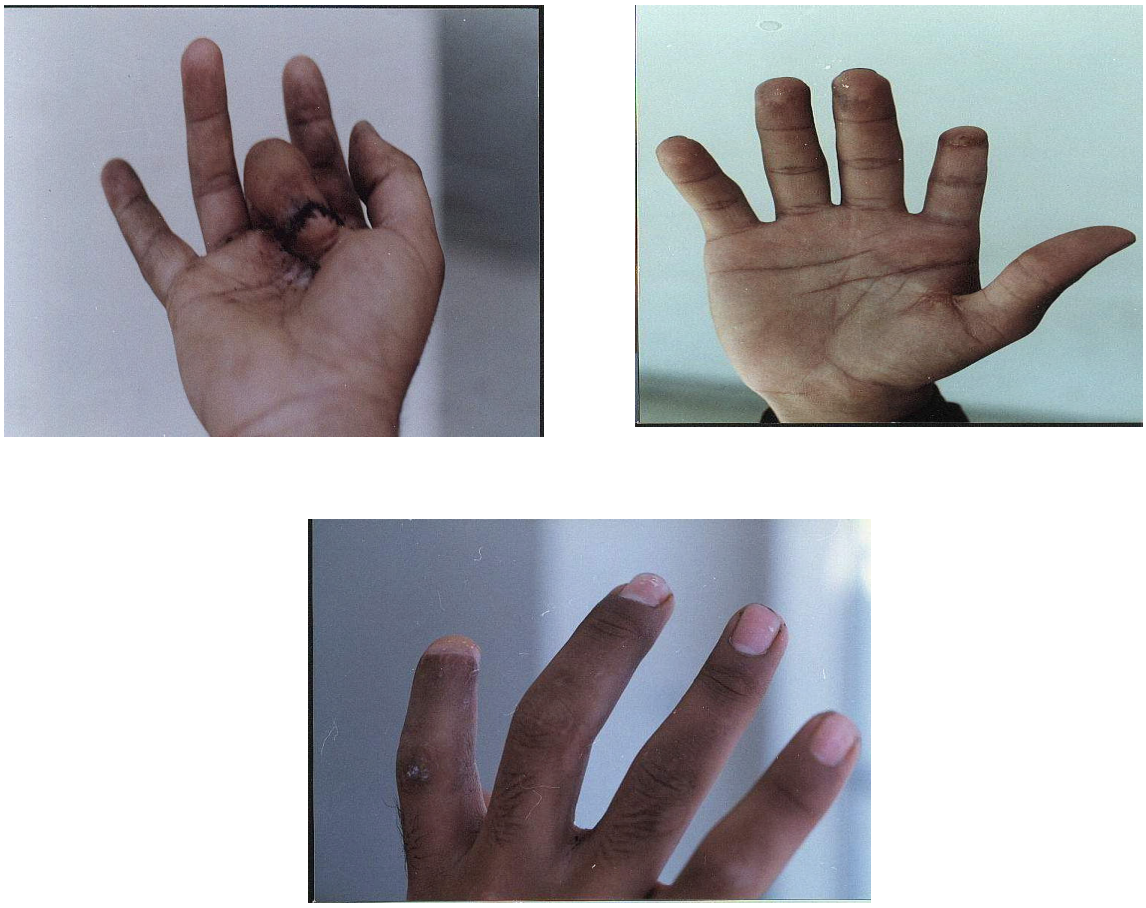


Figure 8: A 20 year old boy with index fingertip amputation at the distal interphalangeal joint level. Reconstruction resulted in round fingertip with 6-7 mm elongation.

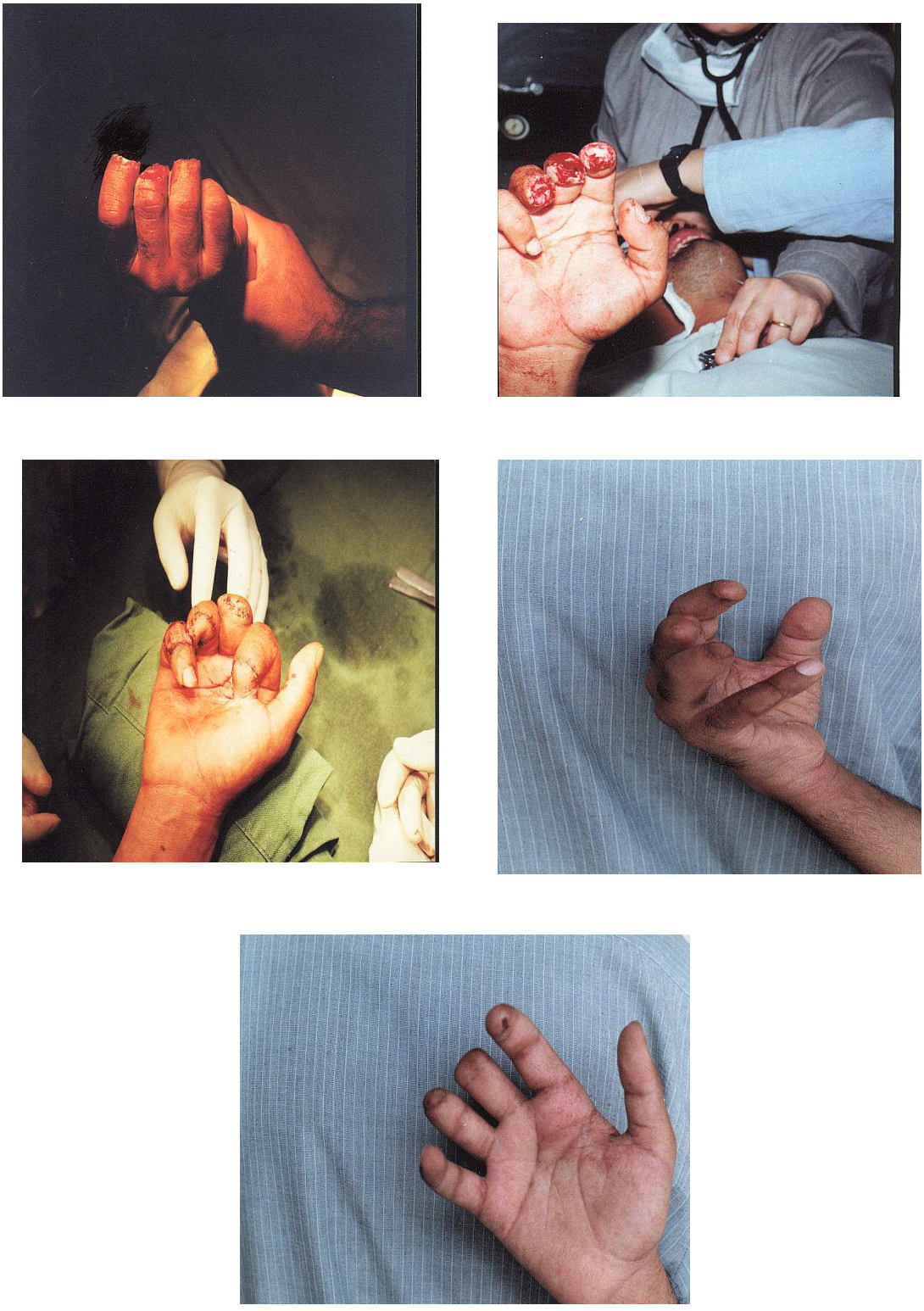


Figure 9: Amputation in the index, middle and ring fingers. The index finger reconstructed by thenar flap, the middle finger by direct skin closure and the ring finger by cross-finger flap from the little finger. Post operative photographs show more finger tip elongation and better finger contour in the thenar flap reconstructed finger (index finger).

Discussion

The hand, more than any other organ system, enable us to manipulate and control our environment and when hand injuries occur the quality of human life is altered. The fingertips are the terminal extensions of the hand and are the part most frequently injured[16].

In addition, it is a very visible and socially important structure. A deformity in the fingertip can result in significant psychological impact in some patients even when the functional deficit is minimal.

The normal round fingertip contour is usually lost after injury in addition to the shortening of the finger. Some reconstructive procedures can close the resulting wound easily and rapidly with minimal complications but without adding length or restoring the round contour of the tip (e.g grafting). There is also the problem that these common injuries mostly present in emergency departments and are treated initially by relatively inexperienced doctors[1].

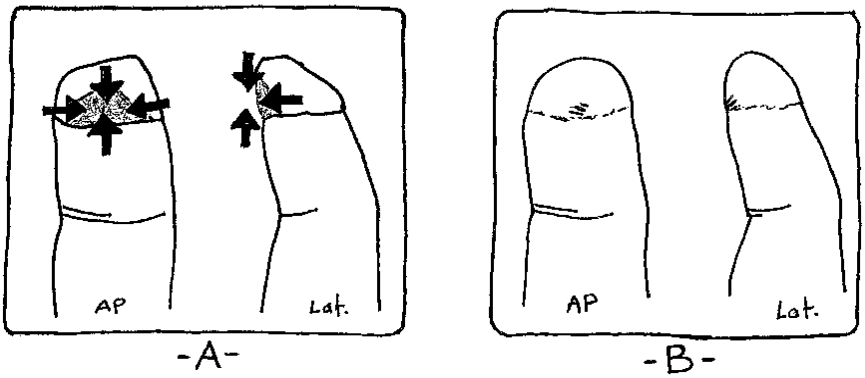
The use of skin flaps in fingertip reconstruction can restore some of the lost length. However, reconstruction of the round counter is not always possible at wound closure after flap separation.

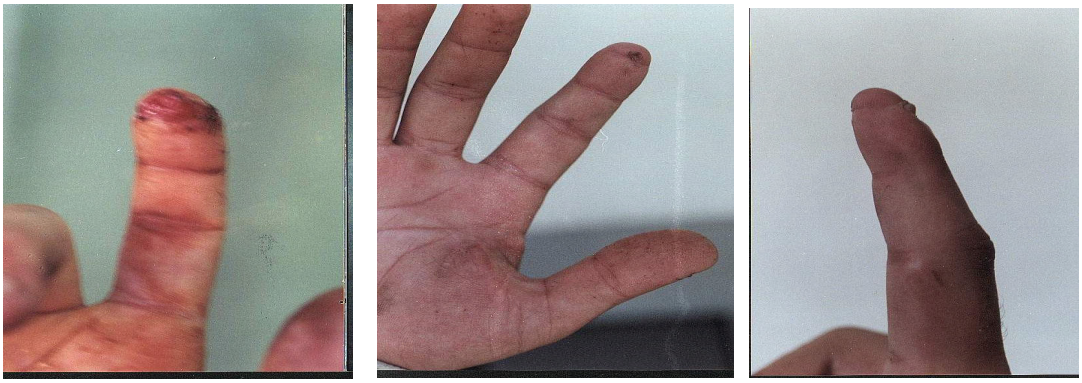
The present study showed that regularly round fingertip contour can be obtained after division of the base of the thenar flap by leaving the resulting wound in the recipient digit to heal by secondary intention (wound contraction and epithelialization), the forces of wound contraction acting on the edges of the wound resulted in complete spherical shape of the finger tip (Figure 11).

Suturing the wound primarily after separation of the flap pedicle requires some de-bulking of the flap to avoid tension at the suture line resulting in shortening in the reconstructed finger for few millimeters (Figure 12). Moreover, excessive tailoring of the flap to form a tapered tip may de-vascularize the flap.

Other measures that aid in the formation of a round tip and pulp tissue include:

1. Making the flap as thick as possible.
2. Making the flap wider than the defect width to create bunching of the skin after suture.
3. Suturing the tip and sides of the flap to two-thirds the circumference of the defect to make the wound that will heal by secondary contraction after flap separation as small as possible (Figure 5).





-C- **-D-** **-E-**

Figure 11: healing of the recipient wound after flap base separation by secondary intention. Wound contraction brings tissues from all directions towards the wound (A,C) to form round finger tip contour (B,D,E) with pinpoint scar in the tip (D).

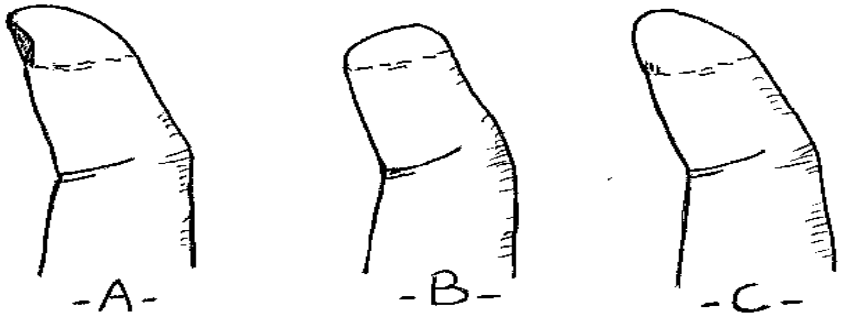


Figure 12:A, finger tip reconstructed by thenar flap after flap separation. B, when the resulting wound closed primarily the flap requires some debulking to facilitate closure without tension, resulting in shortening. C, if the wound is left to heal by secondary intention the result will be regularly round tip without significant loss in the length.

The use of thenar flaps has been criticized principally for resulting in unacceptably frequent flexion contractures of the proximal IP joint of the recipient finger and for persistent tenderness of the flap donor site[9]. In this study one case developed minor (10 degrees) flexion contracture, a 51-year-old man in whom the separation of the flap was delayed for 21 days. The rest of the patients did not developed stiffness and the main measures that prevent development of PIP joint stiffness include:

1- Proper selection of patient (elderly are more liable for stiffness).

2- Making the flap length longer than the finger defect to increase the angle of PI joint flexion.

3- Making the flap base proximal in the palmer area to increase the angle of the PI joint and decrease the angle of the MP joint (protective positions).

4- Separation of the flap after 14 days rather than 21 days.

5-Manipulate the joints under anesthesia during flap separation operation.

Donor site closure is usually done by direct approximation[9,13,14], although skin grafting can be used for larger flaps[13,14]. In this study, the direction of donor site closure was planned in a way that facilitates wound approximation without the need for extensive skin undermining which may lead to injury of the sensory and motor nerves in the area (Figure 3). Tender or unacceptable donor area scars were not recorded in this study. After flap separation, brisk bleeding is commonly seen from the base of the flap, care should be taken during electrocoagulation of this bleeding to avoid injuring the sensory digital nerve of the ulnar aspect of the thumb which is located just under the flap base. One of our patients developed

parasthesia of the ulnar aspect of the thumb for 2 months after that full recovery was obtained gradually.

Finally in the period between the first and second stages of the reconstruction (14-21 days), the hand should be dry and cleaned frequently because maceration of the palmer skin especially of the palmer skin creases may develop with eventual fissuring or infection.

Conclusion

The thenar flap is a satisfactory reconstructive technique for the treatment of fingertip injuries. Some modifications in the surgical technique can provide regularly round tip contour with few millimeters elongation. These modifications include:

1. Leaving the wound after flap separation to heal by secondary intention (wound contraction and epithelialization).
2. Making the flap wider than the defect width.
3. Suturing the tip and the sides of the flap to two-thirds the circumference of the defect.

The risk of PI joint stiffness can be decreased by:

1. Proper selection of patients.
2. Making the flap length longer than the finger defect.
3. Making the flap base proximal in the thenar area.
4. Separation of the flap as early as 14 days.
5. Manipulation of the joints under anesthesia during flap separation.

Donor site defect can be closed directly without excessive undermining by closing the defect obliquely utilizing the skin folds that develop during palmer abduction of the thumb.

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CHILDHOOD INTUSSUSCEPTION: A STUDY OF 32 CASES

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Abstract

Objectives: To find out the commonest presenting features and the relation between early or late diagnosis and the outcome and what the best mode of treatment is and what is the underlying pathology.

Design: Case study.

Setting: The study was conducted in Al-Khansa maternity and children's teaching hospital in Mosul over the period from the 1st March to the 31st December 2000.

Participants: Thirty two patients less than 4 years old with symptoms and signs consistent with intussusception admitted to that hospital during the study period.

Main outcome measures: Information taken from their mothers (age, sex, residence, feeding pattern, complaints). Plain abdominal X-ray and ultrasound were taken for them.

Results: Acute abdominal pain (screaming) and vomiting were the commonest symptoms (81.2%) and the sausage shape mass was felt in 37.5%. Most patients presented early in the first 24-48 hours (84.3%). Plain abdominal X-ray was not informative in 46.8% and ultrasound of the abdomen was positive in 43.3%. Pneumatic reduction was successful in 8 patients and the remainders underwent operative reduction. The mortality was 3.1% and intestinal lymphoma can be an underlying pathology found in 2 patients (6.25%).

Conclusions: Screaming attacks and vomiting are common features and sausage shaped mass is not always palpable, diagnosis is mainly clinical and early diagnosis has a better outcome. Pneumatic reduction can be tried first and is beneficial in suitable cases.

Key words: lntussusception.

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Introduction

Intussusception occurs when a portion of the alimentary tract is telescoped into a segment just caudad to it, it is the most common cause of intestinal obstruction between 3 months and 6 years of age, it is rare in neonates[1]. 60% of patients are younger than one year, this may be due to changes in bowel flora associated with the introduction of new food to the infants, and it is 3-4 times more common in male than female[2]. The incidence varies from 1-4/1000 live birth[1].

There is no specific etiology but rota virus and adenovirus have been blaimed[2,3], and has seasonal peak in spring and autumn[1,2]. There are 2 clinical types: primary (idiopathic) and secondary due to polyp, tumor and inverted meckles diverticulum account for 2-10%.

It is most, often ileo-colic and ileo-ileo-colic, less commonly ceco-colic and rarely exclusively ileal[1].

Diagnosis is mainly clinical and it has to be differentiated from gastroenteritis, enterocolitis, meckle's diverticulum and henoch-schonlein purpura[1,2]. Any child with intussusception requires clinical evaluation and assessment of the general condition. There are 3 methods of treatment:-

1. Air insufflation tried first when there is no evidence of peritonitis or perforation and in early cases 24-48 hours, in babies with good general condition and in the idiopathic type and in those babies who are 2 months-2 years .
2. Hydrostatic pressure reduction, it was the treatment of choice for childhood intestinal intussusception[4]. Instead of proceeding directly to open surgery after failed hydrostatic reduction, laprascopy is performed and reduction is successful in nearly half o the cases. The remainders are treated by conventional surgery[5].
3. Surgical treatment: A child who initially has prolonged symptoms bloody stools, severe abdominal distension and tenderness with signs of shock has gangrenous or at least severely compromised bowel require resuscitation (antibiotics, blood, plasma, fluid) and surgery[2].

Recurrent Intussusception: Intussusception may recur and its rate about 4% and mainly occur following barium enema reduction than following surgery[2]. The chance of recovery is directly related to the duration of intussusception before reduction[6]. The mortality rate with treatment is 1-2%. Mortality is very low in the

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first 24 hours, but is naturally high in the irreducible or gangrenous cases[7,8].

The Aim of Study

To find out the commonest symptoms and signs of the disease, the best mode of treatment, the relation between early or late diagnosis and the outcome, and to see whether there is an underlying pathology.

Patients & Methods

Thirty-two patients with signs and symptoms consistent with intussusception were studied prospectively in Al-Khansa rnaternity and children's teaching hospital during the period from the 1st March to the 31st December 2000.

The range of their age was from 2 months to 4 years, 19 of them were males and 13 were females. A full history was taken from their mothers including age, sex residence feeding pattern, complaints as (abdominal pain, vomiting irritability). Then full systematic examination including digital rectal examination was done.

Erect plain abdominal x-ray was done to all the patients and abdominal ultrasound was done to 30 patients of them because 2 patients were shocked and transferred immediately to surgery, barium enema was not done because of lack of facilities in our hospital and saline enema was not done also, because of fear of perforation without x-ray control.

All the patients were given intravenous fluid to correct their dehydration and they were prepared completely for proper treatment (air insufflation or laparotomy).

Results

Age: From table 1, we can see that the peak age was from 5-12 months. While only 9.4% of children were older than 2 years.

Table 1: Age distribution

Age	Number of patients	%
< 5 months	4	12.5
5-12 months	23	71.9
13-24 months	2	6.6
> 24 months	3	9.4

Sex: The disease is more common in males than in females with a male / female ratio of 1.5:1.

Residence: The majority of patients came from urban areas 78.125%, while only 21.87% patients were from rural societies.

Onset of symptoms: Most patients presented during the first 24-48 hours while only (15.62%) presented later than 48 hours which means a late presentation (Table 2).

Table 2: The onset of symptoms

Onset	Number of patients	%
< 12 hours	4	12.5
12-24 hours	15	46.8
24-48 hours	8	25
> 48 hours	5	15.62

Clinical manifestations: From table 3, we can see that abdominal pain (screaming attacks), vomiting and bloody stool are the main presenting symptoms.

Table 3: The clinical manifestations *

Clinical manifestation	No. of patients	%
Abdominal Pain [screaming]	26	81.25
Vomiting	26	81.25
Bloody stool	23	71.875
Fever	22	68.75
Abdominal pain	14	43.75
Lethargy	13	40.628
Abdominal mass (sausage shape)	12	37.5
Diarrhea	8	25
Perforation	2	6.25
Shock	2	6.25
Prolapse through anus	1	3.125

* Patients may have more than one feature.

Investigations: From table 4, it is clear that the plain abdominal x-ray and abdominal ultrasound were not conclusive in about half of cases.

Table 4: The findings of investigations

Investigation	Finding	No of patients	%
x-ray abdomen	Gaseous distension	10	31.25
	Air fluid level	7	21.8
	Inconclusive	15	46.8
US abdomen	Abdominal mass	13	43.33
	Inconclusive	17	56.6

Modes of treatment: The majority of patients 24 (75%) required surgical intervention and from those 2 patients had gangrenous segment which required resection and end to end anastamosis. Eight patients (25%) improved after pneumatic reduction.

Type of Intussusception: The most common type is ileocolic intussusception (62.5%), then ileoileocolic (16.6%), then colocolic (12.5%), and the least common type is ileoileal (8.3%).

Type of pathological lead point: From table 5, we can see that lymphorna is a pathological lead in causing secondary intussusception.

Table 5: The underlying pathology

	Underlying pathology	No. of patients	%
Secondary	Lymphoma	2	6.25
	Meckles	1	6.25
	Polyp (small bowel)	1	3.1
Primary		28	87.5

Outcome: All patients improved, only one patient died because of septicaemia post-operatively (3.1%).

Discussion

In all the patients this is their first attack. The peak age incidence of intussusceptions is between 5-I2months of life. It is less frequent below 2 months of age.

The male sex was more than the female sex with male to female ratio of 1.5:1, these findings are consistent with other studies done by Wyllie[1], Raffensperger[2], Garcia, Flores; Zuniga *et al*[4], Vanessa M. Wright[9].

Most of the patients presented between 24-48 hours (84.3 %), while only 5 patients (15.6 %) presented later than this, similar findings were also encountered by Mohammed[10].

The acute abdominal pain (screaming attack, irritability) and vomiting were the major presenting symptoms found in 26 patients (81.25 %) these results are nearly similar to that found by AL-Shahawani[3], Mohammed[10]. Korany-Champan-and Schenzer[11].

Bloody stool (Red current jelly stool) was found in 23 patients (71.87%) but AL-Shahawani[3] found that 58% of his patients were having red current jelly stool, probably because our series are smaller in number than his series and most of the patients presented lately.

Lethargy was a common sign found in 13 (40.62%) patients but Mohammed[10] found lethargy in 23.6 % of his patients, and lethargy which result from excessive vomiting and loss of fluids and blood indicates a late presentation.

Abdominal mass (sausage shape) was elicited in 12 (37.5 %) patients while AL-Shahawani[3] elicited this mass in 73% of his patients, because his series contained lot of early cases without the presence of abdominal distention which make the abdominal muscles more rigid and tense due to the presence of peritonitis, and all these make the palpation of the mass difficult.

Peritonitis and possible perforation with shock were present in 2 patients (6.2 %), due to delayed presentation after 48 hours.

Ultrasound of abdomen showed abdominal mass in only 13 patients (43.6%) but Wyllie[1], Hudson and Pomes[12] claimed that ultrasound of the abdomen is very sensitive in the diagnosis of intussusceptions. Because our ultrasonographers have less experience with paediatric problems and have a high false results.

Eight Patients (25%) underwent reduction by air insufflation, which is simple, safe, and reliable, and it was successful in all these patients, but Shehita[13] and Gorenstein *et al*[14] found that air enema was successful in 83% and 85% of their patients respectively. Air insufflation, was not applied to all the patients because during the period of the study many new pediatric surgeons joined the unit have no experience in air insufflation and they prefer laparotomy rather than air insufflation.

Operative reduction was done in 24 (75 %) patients, which is similar to that reported by Mohammed[10], while Al Shahawani[3]. did open reduction in (33%) of his patients. Because Mohammed in Baghdad used surgery as the main method of treating intussusceptions while Al-Shahawani in Mosul prefers air insufflation as the first choice of management, which is comparable to other series all over the world.

The site of intussusceptions was ileocolic in 62.5%, ileoileocolic in 16.66%, colocolic in I2.5% and finally ileoileal in 8.3 % of patients, these are similar to that found by Mohammed[10].

The underlying pathology was intestinal lymphoma in 2 patients (6.25%) and Meckle's in 1 patient, polyp in 1 patient (3.1%) while Mohammed[10] found Meckle's in 50% of his secondary cases and lymphoma in 33.3 %. Primary cases were found in children less than two years old except one baby who was ten month old who had Meckle's diverticulum, secondary cases were found in children more than two years old and the high incidence of lymphoma reflects the high incidence of the disease in our area where lymphoma considered the commonest solid tumor in children in northern Iraq[15].

One patient died forming 3.1 % mortality rate; also the mortality rate reported by Mohammed[10] was about 2.6%.

Conclusion

1. Intussusceptions are more common in boys than in girls.
2. Acute abdominal pain and vomiting were the commonest presenting symptoms and the characteristic sausage shape, mass is not always palpable.
3. Ultrasound of the abdomen is helpful in the diagnosis as it can show the typical kidney shape

shadow of intussusceptions if it is done by expert hand.

4. Early pre sentation has better prognosis than delayed presentation.
5. Pneumatic reduction is very helpful in early management but the underlying pathology is better revealed by open reduction.

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EFFECTIVENESS OF LOW DOSES OF CORTICOSTEROIDS IN ACUTE SEVERE ASTHMA: PROSPECTIVE STUDY

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Abstract
Thirty asthmatic patients (18 females and 12 males) were divided into 3 groups who received low doe (50 mg 6 hourly intravenously), medium dose (100 mg 6 hourly intravenously), and high dose (200 mg 6 hourly intravenously), and were evaluated by serial PEFR and a clinical score for their response to treatment over 12 days.
There was no significance difference (P>0.05) in the mean of their PEFR at 75% significant difference in the days at which they showed a maximum response.
There is no advantage of high dose corticosteroid, and low dose is as effective as high dose in the early treatment of acute severe asthma.

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Introduction

Bronchial asthma is a common problem in the emergency room, in spite of its prevalence there are few well-defined guidelines for the emergency room treatment of acute exacerbations of this disorder[1]. The use of corticosteroids in the setting of acute asthma has traditionally been reserved for patients without response to conventional emergency therapy and who require hospitalization[2], but the Corticosteroid does in the treatment of acute severe attack remains controversial.
Some authors have stated that steroids are needed early and should be used in all cases of hospitalized asthmatic patients[3,4], some studies have shown the effect of corticosteroids in acute asthma to be delayed at least 6 hours[5].
Other studies failed to show any benefit for early administration of corticosteroids in patients with acute asthma. Routine administration of corticosteroids on initial presentation in such patients may not be warranted[6]; they concluded that overall outcome for patients with acute airways obstruction is not improved by early administration of high-dose intravenous corticosteroids. Many patients responded to beta-adrenergic and theophylline therapy within 6-8 hours, regardless of previous steroid administration. These results suggest that the administration of corticosteroids to patients with acute asthma can be delayed at least several hours without influencing clinical outcome, but many patients with acute asthma who require emergency therapy subsequently continue to have respiratory symptoms, 25% of these patients return to an emergency facility within 10 days for repeated treatment, and up to 23% of them required hospitalization, and a short course of high dose corticosteroids would reduce the relapse rate following an acute asthmatic attack[7].
Our present study was conducted to determine the effectiveness of low dose of corticosteroids in acute asthma, the degree of airway obstruction and responsiveness to treatment were assessed by an objective measurement [serial peak flow rate (PFR) measurements] which is the more sensitive in detecting a steroid response than FEV_1, or FVC[8].

Patients & Methods

Thirty patients with severe asthma were evaluated-all patients were admitted to the teaching hospital Saddam of medicine. 18 were females and 12 were males, their age range from 15-40 years old.
Patients with chronic bronchitis, emphysema, other known lung diseases, heart failure, hypertension, diabetes mellitus, smoker or users of steroid medications were excluded in order to limit the study to uncomplicated cases of asthma.
The criteria that determined admission into the study [assessment of an acute severe asthma] were as shown in table 1.

Table 1: Features of acute severe asthma[9]

Any of the followings indicates acute severe asthma:
1. PEFR 100-200 L/min
2. Respiratory rate ≥ 25 breaths/min
3. Pulse rate ≥ 110 beats/min
4. Cannot complete sentence in one breath

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Those with silent chest, cyanosis, bradycardia, confusion or coma were not included in the study (life threatening attack).

Before any therapy, all patients were evaluated by history which includes the duration of asthma, present and past asthma medications. Physical examination included determinations of the sitting blood pressure, resting radial pulse, respiratory rate, pulsus paradoxus, accessory muscle use, dyspnea and wheezing. Pulsus paradoxus was measured with a sphygmomanometer and was quantitated as the difference in systolic blood pressure between inspiration and expiration, values greater than 10 mm Hg were considered to be positive[10]. Accessory muscle use was defined as visible contraction of the sternocleidomastoid muscles[11]. Dyspnea was defined as the patient's own assessment of breathlessness. Wheezing was defined as a musical sounds associated with airway narrowing[12]. The patients were admitted to the emergency room for a maximum period of twenty-four hour (24 hr.) in order to see the response to the casualty unit treatment according to the protocol shown in table 2.

Table 2: Treatment protocol

1st 24 hours[10] (emergency room	1. Oxygen 2. Aminophylline 5mg/kgm I.V. over 20 minutes followed by aminophylline 0.5mg/kgm/hour as continuous infusion 3. Hydrocortisone I.V. (low, medium or high dose)
1st-2nd day of admission	Either hydrocortisone 50mg x 4 I.V Or hydrocortisone 100mg x 4 I.V. Or hydrocortisone 200mg x 4 I.V.
3rd-12th day of admission	Either prednisolone 20mg (10mg x 2) orally Or prednisolone 40mg (20mg x 2) orally Or prednisolone 60mg (30mg x 2) orally)

Those who responded to emergency room treatment were excluded from the study (BEFR $\geq$ 50% of predicted value), and those who failed to responded to emergency room treatment were hospitalized for 12 days (BEFR < 50% of predicted value).

Although the need for corticosteroids in active severe asthma is well established, the appropriate dose is not known[13]. So the thirty patients were randomly divided in to 3 groups (groups 1, 2 and 3) who received intravenous hydrocortisone 50mg (low dose), 100mg (medium dose) and 200mg (high dose) administered every 6 hours for 48 hours which is started at causality unit in order delay in corticosteroids for those who require hospitalization) and followed by oral prednisolone 20 mg (10 mg x 2), 40 mg (20 mg x 2) and 60 mg (30 mg x 2)/ day respectively.

The peak expiratory flow rates (PEFR) was measured with mini peak flow meter twice daily (at morning and evening), and the highest of the three values was recorded.

The patients were followed up daily by a scoring of their illness as shown in table 3 to see the response to the therapy.

Table 3: Scoring system for acute asthma[14]

Sign & Symptom	Score 0	Score 1
1. Loss of exercise tolerance	No	Yes
2. Using accessory muscles (tracheal tug & intercostals recession	Absent	Present
3. Wheezing	Absent	Present
4. Respiratory rate/min	Under 25	Over 25
5. Pulse rate/min	Under 110	Over 110
6. Pulsus paradoxicus	Absent	Present
7. BEFR L/min	Over 200	Under 200

A score of 4 or more means the patient is ill (severe asthma)

The tapering of steroid was according to the reading of PEFR (risen above 75% of their predicted normal). The non-responding cases had been excluded from the study (those with persistent low or decreasing PEFR readings). The patients who received I.V. aminophylline in the ward were excluded from the study also in order to limit the evaluation of PEFR response to corticosteroids only.

Results

We were able to evaluate 30 patients; there was no significant difference between the three groups in age and the duration of asthma (Table 4).

Table 4: Age and sex difference

Data	Group 1 Low dose	Group 2 Medium dose	Group 3 High dose	P value
Number	10	10	10	
Sex	6 females & 4 males	5 females & 5 males	7 females & 3 males	
Age (years)	29.2±8.6	27.6±9.5	29.4±7.0	>0.05
Duration of asthma (yr.)	6.8±6.2	9.6±7.9	7.2±3.0	>0.05

The BEFR at morning and evening, with the day at which each patient reached 75% of predicted PEFR throughout 12 days follow up of the three groups are shown in tables 5, 6 and 7.

The T-test was used to compare group 1 (low dose) with group 2 (medium dose), and group 1 (low dose) with group 3 (high dose). There was no statistically significant difference in morning and evening mean PEFR readings over the 12 days between these groups ($P > 0.05$).

The mean days of 75% of predicted PEFR response for group 1 (low dose), group 2 (medium dose), group 3 (high dose) were 8.2±2.1, 6.9(2.3), 6.7±1.8 respectively, with no significant difference between them ($P > 0.05$).

The morning and evening mean PEFR readings at these mean days of response were compared by using t-test also with no significant difference ($P > 0.05$).

The mean days of response, morning and evening mean PEFR readings when 50% of predicted PEFR reached, and when 25% of predicted PEFR reached, were compared statistically with no significant difference (Table 5).

Table 5: Comparison of Data

Characteristic	Group1 Low dose	Group 2 Medium dose	Group 3 High dose
Morning mean BEFR over 12 days	314.1±106	364.8±119.6	354.2±118.9
Evening mean BEFR over 12 days	327.2±104.7	378.2±111.8	368.2±113.3
Mean day at which 75% of predicted BEFR reached	8.2±2.1	6.9±2.3	6.7±1.8
Morning mean BEFR at mean day of 75% response	358±70.5	410.5±96.6	399.5±93.9
Evening mean BEFR at mean day of 75% response	370±65	414.5±94	412.5±102.8
Mean day at which 50% of predicted BEFR reached	4.9	4.1	4
Morning mean BEFR at mean day of 50% response	277.5±79.3	297.5±105.9	277±65.7
Evening mean BEFR at mean day of 50% response	296.5±79.7	312.5±93.4	298±73.8
Mean day at which 25% of predicted BEFR reached	1.1	1.2	1.2
Morning mean BEFR at mean day of 25% response	147.5±27.4	146.5±27.7	146.5±21.9
Evening mean BEFR at mean day of 25% response	166±24.1	176.5±36.5	167.5±46.8

The scoring of each patient was improving with treatment over the 12 days as shown in table 6.

Table 6: Scoring of the patients of the 3 groups

Score	Group1 Low dose	Group 2 Medium dose	Group 3 High dose
Mean day of score 4	1.2	0.7	0.9
Mean day of score 2	2.1	1.9	1.6
Mean day of score 0	3.9	3.7	3.4
Mean day of 50% response	4.9	4.1	4

There was no significant record of side effects in these groups regarding blood pressure, blood sugar, and weight gain.

Discussion

The high dose corticosteroids (500 mg hydrocortisone IV/day, and 40-60 mg prednisolone orally/day) is well accepted in treatment of acute asthmatic patients in our medical practice[9,15].

Schneider *et al* showed a significant reduction in both the need for hospitalization and the number of return visits with the early use of large, intravenous dosages of steroids in patients with acute severe asthma[16].

Field *et al* stated that a short course of high dose corticosteroids in outpatients reduces the relapse rate and symptoms following an acute asthmatic attacks[2].

The high dose of corticosteroids is well known to have many side effects including water retention, hypertension, hyperglycemia, hypokalemia and muscle weakness[17].

In our patients, who received different doses of corticosteroids over 12 days, the mean days at which 75% of the predicted value reached were 8.2±2.1 for group 1, 6.9±2.3 for group 2, 6.7±1.8 for group 3 with the $P>0.05$ (no statistically significant difference), which mean that the low dose is effective as the high dose, and this was in agreement with Britton et al. who demonstrated that there is no advantage of high dose corticosteroids over conventional doses given intravenously for status asthmaticus[18], while the clinical improvement (illness scoring) was observed at 2^{nd}-4^{th} day of admission, and this can be explained by that when our patients became asymptomatic the overall mechanical function of their lungs in ranging between 40-50% of predicted normal values[11].

Our observations was similar to Bowler and Mitchell study[13], who found the improvement of PEFR and scoring of illness over the 12 days of treatment were not influenced by the steroid dose.

Robert *et al*, had shown no apparent advantage in using the higher dosage of corticosteroids by comparing two groups of patients with severe asthma after a trial of 20 mg, 125 mg of methylprednisolone sodium succinate given intravenously every 6 hours for seven days[19], which is in an agreement with our results.

Conclusion:

1. Significant improvement in PEFR readings was independent of steroid dose, and the rate of improvement may be related to the severity of asthma.
2. The advantage of using low dose corticosteroids will reduce the cost of treatment of asthmatic patients in the hospital, and probably with fewer side effects.
3. There is no advantage in using high dose corticosteroids both I.V. initially and orally in reducing the time of response to treatment in patients with acute asthma.

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CAUSES OF SUPPURATIVE KERATITIS IN IRAQ

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Abstract

Aim: To define the commonest micro-organism responsible for suppurative keratitis in Iraq and to define the most appropriate antibiotics that can be used in the initial therapy.

Patients & Methods: Consecutive new patients presented to Ibn Al-Haytham Eye Hospital from 1st June 2000 till 1st June 2002 were entered this study if they had clinical signs of suppurative keratitis. Scrapping of the ulcers done under slit lamp visualization. The materials were inoculated in to blood, chocolate, sabauraud's agars, thioglycolate and brain-heart borth. Bacterial sensitivity to antibiotics was tested by disc diffusion assay.

Results: 86 patients were enrolled in this study. Positive cultures were obtained in 54 cases. Bacterial growth was obtained in 40 cases, fungal growth was obtained in 13 cases and only one case showed mixed growth (bacteria and fungus). Most common bacteria isolated was pseudomonas spp. (19 cases), staphylococcus spp. (17 cases). 92.5% of isolated bacteria were sensitive to ciprofloxacin.

Conclusions: Micro-biological investigations are an essential step in the management of suppurative keratitis. Psudomonas spp., staphylococcus spp. And fungi are the most common micro-organisms responsible in suppurative keratitis in Iraq. Fluoroquinolones are the drugs of choice in the initial therapy of suppurative keratitis.

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Introduction

Suppurative keratitis is a vision threatening condition that requires urgent identification and eradication of the causative agent. The spectrum of micro-organisms responsible for suppurative keratitis varies according to the geographical location and to the risk factors.

In Iraq no previous study was done about the identification of the causative agents of suppurative keratitis. Corneal scraping for diagnostic culturing is seldom done, and treatment is not based on microbiological investigations.

The objectives of this study are: to ascertain the importance of microbiological investigations in suppurative keratitis. To identify the commonest micro-organisms responsible for suppurative keratitis in Iraq. To identify the most appropriate antibiotics that can be use in the initial therapy of suppurative keratitis before the result of micro-biological investigations appear.

Methods

Consecutive new patients presenting to Ibn Al-Haetham eye hospital, Baghdad, from 1st June 2000 till 1st June 2001 were entered into this study if they had clinical signs of microbial corneal infection with loss of epithelium over more than 2 mm in diameter and underlying stromal infiltration. Patients were excluded if they had clinical pictures of viral ulcers (dendritic or amoeboid ulcers) which are not secondary infected.

Clinical Examinations, patient's age, sex, occupation and place of residence were recorded. Full history was taken including medical history, past ophthalmic history, the circumstances in which the eye became infected and any prior treatment received. Every patient was examined with Slit Lamp recording the size, the shape and the appearance of the margins of the ulcers. The size of stromal infiltration and the height of hypopyon if present were also recorded.

Microbiological Examination: If corneal sensation is present local anesthesia without preservative was instilled and a sterile bend tipped 21 gauge needles was used to scrap the margins of the ulcer. The material was inoculated into:-

1. Blood agar incubated in aerobic condition at 37°C for 24-72 hours.
2. Chocolate agar incubated under 10% CO_2 at 37°C for 24-72 hours.

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3. Sabauraud agar incubated aerobically at 25°C for 10 days.
4. Thioglycolate broth incubated aerobically at 37°C for 24-72 hours.
5. Brain heart infusion broth incubated aerobically at 37°C for 24-72 hours.

Further corneal scrapings were taken for smears on two glass slides. These were labeled and stained with routine Gram's Method. Slides were examined under x10, x40 and finally under x 100 (oil immersion) lens to identify bacteria, hyphae and other fungal elements.

In Culture positive cases final identification of bacteria were performed by API system. The isolated bacterial sensitivities to antibiotics were performed by Kirby-Bauer disc diffusion assay. We choose five antibiotics which are commonly used in the treatment of corneal ulceration; these are ciprofloxacin, garamycin, cephalothin, rifampicin and chloramphenicol.

Results

A total number of 86 consecutive cases with suppurative keratitis were entered this study .The demographic and social characteristics of these patients are shown in table 1.

Table 1: Demographic and social characteristics of 86 patients with microbial keratitis

Characteristics	No. of Cases	% out of 86 Cases
Age (years)		
<16		8
6-30		21
31-45		18.5
46-60		36
>60		16.5
Sex		
Male		53.5
female		46.5
Place of residence		
Baghdad		34.8
Alanbar		14
Salah Al- Deen		9.5
Hella		7
Diala		7
Waset		5.8
Kerbala		3.5
Najaf		3.5
Thekar		3.5
Basra		2.3
Sulemanea		2.3
Kerkuk		2.3
Kadessea		2.3
Duhok		1.1
Messan		1.1
Occupation		
Farmers		51
Traders and free jobs		21
Retired / Unemployed		17.5
Students		6
Factory workers		2.25
Babies		2.25

Patient's ages ranged from 3 months to 78 years. 53.5% of patients were males. Patients were from different places of the country, the majority are from rural areas. Different occupations were presented, the largest groups were farmers.

Positive corneal culture was obtained from 54 cases (62.7%). Bacterial growth alone was obtained from 40 cases (46.5%) while fungal growth alone was obtained from 13 cases (15%). Only one case showed mixed growth of bacteria and fungus (Table 2).

Table 2: Results of culture from 86 cases with suppurative keratitis

Results of Culture	Number of cases	Percentage out of 86 cases
Bacterial growth only	40	46.5%
Fungal growth only	13	15%
Mixed bacterial +fungal	1	1.16%
Total positive culture	54	62.7%
No growth	32	37.3%
Total	86	100%

The commonest bacteria isolated were Pseudomonas aerogenosa which was isolated from 19 cases out of 41 cases of bacterial isolate, (46%). Isolates of Staphylococcus coagulase negative were obtained from 11 cases followed by Staphylococcus coagulase positive (6 cases) Streptcoccus viridans was isolated from two cases while streptococcus pneumonia was isolated from one case. Eschirichia coli and Serratia ordoifera were isolated each one from one patient (Table 3).

Table 3: Type, number and percentage of bacteria isolated from corneal ulcers

Bacterial isolates	No. of cases	% out of 41 bacterial isolates	% out of 86 cases with SK
Pseudomonas aeurogenosa	19	46%	22%
Staphylococcus coagulase negative	11	27%	13%
Staphylococcus coagulase positive	6	14.5%	7%
Streptococcus viridens	2	5%	2.25%
Streptococcus pneumonia	1	2.5%	1.15%
Eschirichia coli	1	2.5%	1.15%
Serratia ordorifera	1	2.5%	1.5%
Total	41	100%	47.5%

SK = suppurative keratitis

Gram's stain of ulcer's samples examined directly under microscope was positive for organisms only in six cases out of 54 culture positive cases (10.5%).

Blood agar and chocolate agar were superior for growth of most isolates, 91% of culture positive

cases were cultivated in blood and chocolate agar .There was no significant difference in the quantitative growth of isolates between blood and chocolate agar .However five isolates (9%) were cultivated initially from liquid media (Brain heat infusion broth and thioglycolate broth).

All bacteria isolate were tested for antibiotics sensitivities with Kirby Bauer disc diffusion assay (Table 4).

Table 4: Antibiotics sensitivities to bacterial isolates cultivated from corneal ulcers

Bacterial isolates	Number of cases sensitive to				
	Ci	Ga	Ri	Ce	Ch
Pseudomonas aeurogenosa	19	7	0	0	0
Staph.coagulase negative	11	5	8	6	0
Staph. Coagulase positive	6	4	6	4	0
Strep. Viridans	0	0	2	2	0
Strep.pneumonia	0	0	1	1	0
Eschirichia coli	1	0	0	0	0
Serratria ordorifera	1	1	0	0	0
Total no. of bacterial isolates sensitive to specific antibiotic	38	17	17	13	0
% of cases sensitive to specific antibiotic out-of 41 positive bacterial isolates	92.5%	41.5%	41.5%	31.5%	0%

Ci = ciprofloxacin, Ga = Garamyci, Ri = Rifampcin, Ce = Cephalothin, Ch = Chloramphenicole.

Sensitivity of Pseudomonas aeurogenosa to ciprofloxacin and garamycin was 100%, 40% respectively, while it was completely resistant to rifampicin, chloramphenicol and cephalothin.

Staphylococci coagulase negative Sensitivity to ciprofloxacin rifampicin, cephalothin and garamycin was 100%, 80%, 60% and 50% respectively, it was completely resistant to chloramphenicol.

Staphylococci coagulase positive isolates were found completely sensitive to ciprofloxacin and rifampcin 100% and predominantly sensitive to garamycin and cephalothin 75%, while it was completely resistant to chlaomphenicol.

Strepococci viridans and pneumonia isolates were found sensitive to rifampicin, cephalothin 100% while it was resistant to garamycin, ciprofloxacin and chloramphenicol.

Serratia ordorfera was sensitive only to ciprofloxacin; E.coli isolate was sensitive to ciprofloxacin and garamycin while it was resistant to the other antibiotics.

Discussion

Causative Agents: The prevalence of different organisms responsible for microbial keratitis varies with geographical regions and with the risk factors

The vast majority of isolates from microbial keratitis, in temperate climates are aerobic bacteria[1]. Staphylococcal species are the most frequent organisms isolated from corneal ulcers in northern United States[2] and in Canada[3]. Pseudomonas infections are more common in warmer climates[4] and it is the most common agent in southern United States[3], and is becoming more frequently seen in other areas associated with soft contact lenses use.

Fungal infections of the cornea are rare causative agent of microbial keratitis in cold climates its incidence in New York is 1%[2] but it becomes an important factor in the equatorial regions, in reports from Bangladesh the proportion of suppurative keratitis, due to filamentous fungi reach up to 33%[5]. In southern Florida fungi accounted for 35% of isolates[6]. In Accra, Ghana, it was found that fungi alone were responsible for 44% of positive cultures and if mixed fungal and bacterial infections were included fungi occurred in 56% of cultures[7].

In this study we find that Pseudomonas aeurogenosa was the commonest agent for suppurative keratitis (22%) followed by Staphylococcal species (20%) then fungal infections (16.25%) while streptococcal infections accounted for 3.35% of the total cases of suppurative keratitis

Media: In this study culture positive cases were 62.7% of the total cases of suppurative keratitis. Most isolates were cultivated in blood on chocolate agar (91%). So we are in agreement with other studies, that consider plating in blood or chocolate agar is a reasonable alternative to sending multiple cultures[8].

Gram's stain: Several studies had been attempted to evaluate correlation between Gram's stain and culture finding in microbial keratitis[2,9,10]. The usefulness of Gram's stain in determining the appropriate initial therapy in microbial keratitis is still unsettled. In this study Gram's stain, of ulcer's samples were positive for organisms in only 10.5% of culture positive cases and accordingly were not considered useful in determining the initial therapy of corneal ulcers.

Therapeutic approach: Suppurative keratitis is a vision threatening disease that requires urgent use of broad spectrum antibiotics based on local epidemiological information regarding likely infecting agents till the result of culture and antibiotics sensitivities appear[1].

In this study 92.5% of bacteria responsible for microbial keratitis are sensitive to ciprofloxacin. While 41.5% of bacteria are sensitive to each of gentamycin and rifampicin, only 31.5% of bacteria are sensitive to cephalothin, while none of the bacteria are sensitive to chloramphenicol (Table 4).

Conclusions

1. Microbiological investigations are an essential step in the management of suppurative keratitis. Corneal scraping for diagnostic culturing has to be done in every case of suppurative keratitis to identify the causative agent and to treat it accordingly.
2. Ciprofloxacin (fluoroquinolones) is the most effective antibiotics against bacteria causing suppurative keratitis. We recommend using ciprofloxacin eye drops as an initial therapy for suppurative keratitis before the results of microbiological investigations appear.
3. Fungal infections are one of the important causative agents of suppurative keratitis in Iraq. Specific topical antifungal eye drops (Natamycin 5%, Econazole 1%, Amphotercin B) have to be available to treat this blinding disease if not properly treated.

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BREAST FEEDING AND DIAPER DERMATITIS

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Abstract

Objectives: To test whether breast feeding has a protective property against diaper dermatitis.

Design: A case-control study.

Setting: The study was conducted in a private clinic and in Al Khansa Maternity and Children Teaching Hospital in Mosul during the period from the 1st January 2002 to the 30th June 2002.

Participants: One hundred and seventy eight children less than one year of age visiting the private clinic and the consulting rooms of Al-Khansa Hospital with diaper rash during the study period. Other 178 babies with no diaper rash were used as a control group.

Main outcome Measures: Information was taken from their mothers including feeding pattern, type of nappy, frequency of changing the nappy, habit of exposure, any associated illness, family history. Stool PH was done to 38 breast fed babies and skin culture was not done because of lack of facilities.

Results: The majority of the babies were under 6 month of age (70.2%). Fifty two babies (29.2%) were breast fed while 88 (49.4%) of the control group were breast fed (P 0.000). Ninety two (51.6%) were bottle fed while 61(34.2%) of the control group were bottle fed (P<0.001). Which means breast feeding is protective against diaper rash. No difference was found between the patients and the control group regarding the type of diaper, frequency of changing the diaper but some difference was found regarding the habit of exposure (P<0.05).

Conclusion: Breast feeding has a protective property against diaper dermatitis.

Keywords: Breast feeding, diaper dermatitis.

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Introduction

Diaper Dermatitis also known as diaper rash (nappy rash) indicates inflammation of the skin in the area covered by diapers, the highest prevalence in infants 9 to 12 months of age[1,2].

The rash appears as confluent shiny erythema that spares the folds of the skin. Papules, vesicles and secondary erosions may occur. Candidal dermatitis is bright red erythema that involves the folds with satellite pustules. Bacterial superinfection may occur with yellow crust and occasional bullae. Seborrheic dermatitis presents as confluent erythematous macular eruption that involves the folds with scattered greasy yellow scale with signs of seborrhea on other area of the body[3]. The most common factors associated with diaper dermatitis are: elevated skin wetness, elevated PH, fecal enzymes and microbial agents. These agents augment the activity of each other[3]. ***Physical:*** such as increase in skin wetness which compromises the physical integrity of the skin and is more susceptible to mechanical, chemical, microbial and enzyme damage[4], increased wetness increases friction coefficient of skin which augments the damage from chafing and abrasion[5]. This physical damage is compounded by the increased permeability of wet skin, which allows penetration of irritating substances[6]. ***Chemical:*** higher PH in the diaper environment also increases the risk for diaper dermatitis. Bacterial ureases (found in the stool) split urea and release ammonia (ammoniacal scald)[7] and this result in increased PH[6], which is further increased under occlusion of the diaper[8].

Fecal enzymes (proteases and lipases) have direct irritant effect on the skin[9] and bile salts increase the activity of these enzymes[10,11]. Both of these actions are increased by an increased PH. ***Microbial:*** the perineal area is susceptible to candidal colonization and there is a definite relationship between candidal colonization of the stool and diaper dermatitis[12] Other infections are less common as Bacteriodes[13] and Staphylococcus aureus[14] and herpes simplex virus[15] and cytomegalovirus in an immune compromised host[16].

It is important to emphasize the prevention of this common and sometimes remitting condition. The most effective prevention is to keep the skin clean and dry. Increased frequency of diaper changes (> eight per day) significantly lowered the prevalence of diaper dermatitis[1] Also, the

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more time that infants spend without diapers, the less dermatitis they experience, but a practical balance must be struck. Gentle cleansing and barrier creams are beneficial, together with infection control.

Finally any recalcitrant diaper dermatitis must be further investigated to uncover underlying disease[3].

The aim of the study: To test whether Breast feeding is protective against diaper dermatitis.

Patients & Methods

One hundred and seventy eight babies less than one year of age with diaper rash were collected from the private clinic and from the consulting rooms of Al-Khansa Maternity and Children Teaching Hospital in Mosul during the period from the 1st January 2002 to the 30th June 2002. Ninety six (53.9%) were boys and 82 (46.1%) were girls.

Information taken from their mothers regarding the type of feeding (Breast, Mixed, Bottle), the type of nappy used (disposable, cloth material with nylon), frequency of changing the nappy, habit of exposing the baby after changing the nappy, history of diarrhoea or any other illness. Family history of same problem. Examination done concentrating mainly on the perineal area for the presence of erythmatous macular eruption, papules, vesicles, secondary erosions, satellite pustules, bullae, greasy yellow scale and looking for involvement of skin folds or not. Then all the body was examined as the head (for cradle cap), face (for any rash on the cheeks), axillae for any involvement, nails, flexures of the Joints and systemic examination.

Stool PH was done to 38 breast fed babies. Skin culture was not done because of lack of facilities. Other 178 babies with no diaper rash were taken as a control group for comparing the feeding pattern, type of diaper, frequency of changing the diaper, and the habit of exposure.

The results were analysed using X^2 and OR with C.l. Every patient was given the proper treatment.

Results

All the babies were infants less than one year of age and the majority of them 125 (70.2%) were under 6 months of age. Ninety six (53.9%) were males and 82 (46%) were females, whereas the control group consists of 109 (61.2%) males and 69 (38.8%) females. Type of feeding is shown in Table 1.

Table 1: Feeding Pattern

Type of feeding	Case	Control	Total	X^2	P value	OR	95% CI
Breast	52 29.2%	88 49.4%	140	15.257	0.000	0.42	0.27-0.65
Mixed	34 19.1%	29 16.2%	63	0.482	0.487	1.21	0.71-2.07
Bottle	92 51.6%	61 34.2%	153	11.015	0.001	2.05	1.34-3.13
Total	178 100%	178 100%	356	15.935	0.000		

From the table, it is clear that 51.6% of the patients were bottle fed and 29.2% were breast fed, which is highly statistically significant (P<0.000). Type of diaper used by the patients and the control is shown in Table 2.

Table 2: Type of diaper used

Type	Case	Control	Total
Cloth Material+Nylon	152 85.4%	152 85.4%	292
Disposable	26 14.6%	38 21.3%	64
Total	178	178	356

X^2=2.743, P-value=0.098, OR= 1.59, C.I.=(0.92-2.75)

From the table, the majority of the patients and the control group were using cloth material and nylon and the minority of them was using disposable diaper which is not statistically significant. Frequency of diaper change is shown in Table 3.

Table 3: Frequency of diaper change

Frequency	Case	Control	Total
< 8 times	37 20.8%	43 24.1%	80
≥ 8 times	141 (79.2%)	135 (75.8%)	276
Total	178	178	356

X^2=0.580, P-value=0.446, OR= 0.82, C.I.=0.49-1.37

From the table, the majority of the mothers in both groups claimed that they change the nappy of their babies frequently > 8, and minority of the mothers showed the feeling of being guilty and were shye because they didn't change the nappy frequently and this is also not statistically significant. The habit of exposing the perineal area by the mothers is shown in Table 4. From the table, the minority of mothers expose their babies for a while after changing the nappy which is marginally significant P =0.059.

Table 4: Habit of exposure of the perineal area

Exposure	Case	Control	Total
No	136 76.4%	136 76.4%	256
Yes	42 23.6%	58 32.6%	100
Total	178	178	356

X^2=3.560, P-value=0.059, OR= 1.57, C.I.=0.98-2.51

One hundred and five babies (58.9%) showed the presence of satellite pustules with involvement of skin folds (Candidal infection), and 51 (48.5%) of them had history of diarrhoea and had oral thrush on their tongue. Six babies (3.3%) had features of atopic dermatitis with infantile eczema on the cheeks and flexure of the joints and all of them had positive family history of atopy. Three babies (1.6%) showed the features of seborrhoeic dermatitis with yellow greasy scales and involvement of skin folds but only 2 of them had cradle cap. The remaining 64 patients (36%) had purely ammoniacal dermatitis. The other rare causes of diaper rash as psoriasis, Histiocytosis X (letterer - Siwe disease), Acrodermatitis enteropathica, Biotin deficiency... etc was not encountered. The stool PH was acidic (<6) in all the patients in whom it was done.

Discussion

The majority of the patients (70.2%) were under 6 month of age, but Longhi[2] mentioned that the highest prevalence of diaper dermatitis is in infants 9 to 12 months of age.

Fifty two (29.2%) babies were on breast feeding while 92 (51.6%) and 34 (19.1%) babies were on bottle and mixed feeding respectively, this proves that breast feeding is protective against diaper rash where OR is 0.42, this is because breast fed infants have lower stool PH, which may explain the lower incidence of diaper rash in these infants[1].

The majority of the mothers of the patient and the control groups (85.4%) and 78.6% respectively were using cloth material and nylon as a nappy and only 14.6% and 21.3% of them respectively were using a disposable nappy, this is because the latter nappy is so expensive because they are not made in our country and are imported from other countries by foreign money and most of the people can not offer to buy them in the present situation of the unfair embargo on our dear country. And by using cloth diapers skin wetness is increased and this leads to increased coefficient of friction, increased ease of abrasion, and overall microflora load. Also skin wetness is proportional to diaper wetness and because cloth diapers stay wet they keep the skin more wet than do disposable diapers[17]. This is clinically relevant because, compared with cloth diapers; disposable diapers provide a lower prevalence and severity of diaper dermatitis[1].

The majority of the mothers in both the patient and the control groups (79.2%, 75.8% respectively) claimed that they change the nappy of their babies frequently (≥8 times a day), this is doubtful because if they had done that, their babies would not get diaper rash because the most effective prophylactic measure against diaper rash is frequent change of diaper[1].

Regarding the habit of exposing the perineal area of the baby after changing his / her nappy there was some difference which was not statistically significant between the mothers of the control group and the patient group (32.6%, 23.6% respectively) (P = 0.059) and most of them don't expose their babies and this is not a good habit as occluded skin elevates the PH of the gluteal region with all its harmful consequences compared with nonoccluded skin[8].

Nearly 59% of the patients were complicated by candidal infection and controversy exists as to whether some infections are a primary cause of the diaper dermatitis or a secondary event. Whatever the sequence of events, candidal infection of the perineat area is an important contributing factor in diaper dermatitis. In one series[12] skin culture from 92% of infants with diaper dermatitis revealed Candida albicans.

Six babies (3.3%) were found to have atopic dermatitis because there is an increased incidence of diaper dermatitis in atopic patients who have lower threshold for irritation of the skin and increased colonization by S. aureus[2].

The superabsorbent diapers available now have the smallest increase of skin wetness[18] and decrease urine contact with the skin so patients who wear them have less prevalence of rash[19] and have less environ- mental fecal contamination[20] Also cloth diapers without overpants are usually impractical.

Conclusion

Breast feeding has a protective property against diaper dermatitis which should be highly encouraged and advised for its enormous advantages.

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TREATMENT OF SPLENIC HYDATID CYST DISEASE BY SPLENIC PRESERVATION WITHOUT USING SCOLICIADAL AGENTS

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Abstract

Background aim: Study was undertaken to determine the outcome of conservative surgical procedure for treating splenic hydatid cyst without scolicidal agent.

Patients & Methods: In twenty three patients who had surgery for splenic hydatid disease, they underwent splenic preservation without injection of scolicidal agent.

Results: Follow up of all patients after two years showed that obliteration of the cavity was complete and the spleen was retained successfully with smooth post operative course.

Discussion: Splenic preservation procedures were done in splenic hydatid diseases without injection of scolicidal agent; it is less invasive, and safe with encouraging short term results.

Key words: Hydatid disease, Splenic cyst, Splenic preservation.

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Introduction

The treatment of choice for hydatid cyst of spleen is spleectomy. However such operation carries certain complications like post splenoctomy sepsis[1,2], with higher incidence in the early years of life[3,4]. After splenectomy the primary antibody response is decreased and the secondary response is abnormal in that there is an impairment of the normal switching from IgM to IgG antibody production, the spleen also influences opsonization of pneumococci in non-immune individuals and is involved in the function of the alternative pathway of complement activation[5]. The spleen is the third most common organ affected by hydatid disease after the liver and lung[6].

Since 1980 there has been an increasing tendency to use conservative surgical methods of treatment as splenic preservation has become desirable. In this study splenic preservation operation is used without injection of scolicidal agents.

Material & Methods

Twenty three cases of hydatid cyst of spleen operated on over a period of six years (1989-1994), their ages ranged between 12-66 years.

Ten of them are males and thirteen are females. Size of the cyst varies from 5-30 cm. Three cases were infected cysts. In ten cases there were associated hepatic cysts. All of the cases were diagnosed by ultrasound only. Chest x-ray was taken preoperatively to exclude pulmonary hydatid.

Approach was through left paramedian incision for pure hydatid disease of the spleen and through transverse incision for hydatid of both liver and spleen. Good packing around the cyst done, no injection of scolicidal agent was performed then aspiration of fluid by syringe, after near complete decompression of the cyst and incision done on the surface of the cyst ,evacuated from its contents with good inspection of interior of the cyst in order not to miss any part of the membrane or daughter cysts. Finally the cyst either placated by stitches as in small cyst and projecting from splenic surface or commonly drained by tube drain as in large cyst, deeply imbedded in the spleen and in cases of infected cysts.

Results

Follow up of all patients over a period of two years by ultrasound showed that obliteration of the cavity was complete and the spleen was retained successfully, without complications and short hospital stay. Post operatively three patients developed recollection, treated by drainage operation only, with uneventful convalescence.

Discussion

Treatment of hydatid cyst of the spleen is still primarily surgical. Radical treatment is splenectomy, but the conservative operation advocated in this study was removal of the cyst only without injection of scolicidal agent. All

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cases operated on had smooth post operative course without complications locally or systemically with short hospital stay 2-5 days. This alternative procedure seems to be safe, simple, and particularly useful in difficult cases either due to sever adhesions of the cyst to adjacent structures like pancreas, stomach, colon, or diaphragm, or because of multiple cysts in the spleen which can not be mobilized at all.

Certainly such conservative operation has been used for the management of liver hydatid cyst, so there is no reason why the same principle can not be applied to the same pathology in the spleen, in addition there is no bile in the spleen as in some cases of liver hydatid cyst.

Radical surgery has the advantage of complete cure because the organ itself is removed, but the risk is higher. All patients post operatively received albendazole tablet 10mg/kg/day three times daily for one month.

Follow up of all cases were done by ultrasound for two years with complete collapse of the cavity, but in three cases there were recollection and were treated by drainage operation only.

No scolicidal agent is safe and effective. The killing action observed in vitro may be hampered in vivo by the instability of the substance, an unpredictable dilution by hydatid fluid, and difficulties in penetrating daughter cysts[7].

Splenic preservation operation for splenic hydatid disease was performed previously but with scolicidal agent as absolute alcohol[8] or povidine iodine[9], but in this study no scolicidal agent applied with the same post operative result.

Conclusion

Splenic preservation operation for splenic hydatid disease without scolicidal injection is safe, simple, effective and less invasive procedure as compared to radical operation with possible injury to other structure as well as the risk of systemic complication like post splenectomy sepsis and thromboembolic complication[10].

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