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From the Editor

First let me start by expressing my sincere apologies for the undue delays that we faced at the Middle East Journal of Internal Medicine. We had to change our servers, our host and reorganize to better serve you. We promise our authors and readers that this will not happen again. Things are settled and we should be on track.

This issue is very rich in original quality work done by our contributing authors. Dr Rezeq paper on cataract surgery documented better results with local anesthesia and Drs Nawaiseh & Ajarma confirmed that laparoscopic cholecystectomy is safe and a valid alternative to open procedure in patients with acute cholecystitis. Drs Al-abashneh and Abu-Zeid reemphasized the importance of antibiotic resistance surveillance programs in promoting the optimal use of antibiotics in hospitals and especially in ICU. Dr Bin Selm provided us with a nice study documenting the high prevalence of nonalcoholic fatty liver in Yemen which is closely associated with obesity, diabetes, hypertension and hyperlipidemia.

We have included two papers that are related to dermatology and internal medicine. A study from Iraq where stress is understandably very high, a close association between dermatosis and stress is nicely documented. Another study suggests that increased reactive oxygen species along with insufficient total antioxidant capacity may be involved in the pathogenesis of psoriasis. A paper in the field of women’s health noted that lisuride significantly reduces prolactin levels to normal values, improves fertility and ameliorates symptoms of hyperprolactinemia.

On the educational front, a study from Iran documented the importance of medical students’ input in highlighting the strengths and weaknesses in teaching program. Another study documented the need to educate our health care physicians and personnel about anticoagulation aiming at therapeutic for better outcome.

Thank you for your continued support.

Ahmad Husari (Chief Editor)

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FROM THE EDITOR
Prevalence and risk factors for Atrial Fibrillation and quality of anti-coagulation treatment in the medical ward

ABSTRACT

Objective: To assess the risk pattern of atrial fibrillation (AF) in our patients and to determine whether the patients were properly investigated and adequately treated with anti-thrombotic therapy, or not.

Method: A retrospective chart review of all patients admitted to the medical ward of King Abdul Aziz University Hospital with AF. Patients’ demographics, thyroid function test (TFT), echocardiogram and treatment were recorded.

Results: 163 patients with AF were admitted. The age range was 61-95 years. Hypertension was found in 58.3% of patients, IHD in 50.9%, DM in 41.1%, cardiomyopathy in 17.8%, and RHD in 19.6%. Echocardiogram was done in 22%, TFT in 15.3%. Warfarin was prescribed to only 63.8% and only 35% were therapeutically anticoagulated. Digoxin was given to 52.1% of patients, beta blockers to 39.3%, and amiodarone to 26.4%.

Conclusion: AF is an important cause of cardiac morbidity that requires acute medical admission. TFT and echocardiogram as a work up for AF are underutilized. Anticoagulation aiming at therapeutic INR and cardioversion should be emphasized for better outcomes.

Atrial fibrillation is an increasingly common cardiac disorder particularly in the elderly, and affecting 5% of persons 65 years of age or older (1-9). It is associated with an annual incidence of thromboembolic stroke of 2-6 % (9,10).

Oral anticoagulation has been shown in clinical trials to prevent embolic stroke in patients with chronic atrial fibrillation (11,12,13,31) but prior studies suggest that warfarin is markedly underused in these patients,(14-20)

Key words: atrial fibrillation, AF, Anticoagulation

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Objectives
The objective of the study was to analyze the risk factors associated with AF in our group of patients, to determine whether warfarin was appropriately used in the treatment of AF and if the patients on warfarin were adequately anticoagulated or not and to compare our results with those done elsewhere. The other aim of the study was to determine the drugs used to control the heart rate and whether the patients were properly investigated or not.

Methods
A retrospective study where the charts of all patients admitted to the medical ward of King Abdul Aziz University Hospital between November 2006 to November 2007 were studied. Patients age, sex, and nationality were recorded. Risk factors like DM, IHD, hypertension, rheumatic valvular heart disease, cardiomyopathy, heart failure, thyroid status and smoking were recorded. Numbers of patients using warfarin, aspirin, clopidogrel, unfractionated heparin or low molecular weight heparin as an antithrombotic therapy were charted. The anti-arrhythmic drugs used to control the heart rate were also recorded.

Statistical analysis was done on SPSS 15.4 (Statistical Package for Social Sciences)

Results
King Abdul Aziz hospital is a tertiary teaching hospital in the western province of Saudi Arabia.

Out of 2,748 of acute admissions to the medical ward, 163 patients were admitted with AF with an incidence of 16.8%. The age range of patients was between the ages of 61-95; 30.1% were between 41-60 whereas 11% were in the age group of 15-40. (Table 1).
Among the risk factors hypertension was the main cause in 58.3% of patients followed by IHD and DM respectively at 50.95 and 41.1%. Cardiomyopathy and rheumatic valvular heart disease was found in 17.8% and 19.6%. Mitral regurgitation constituted 33.1% of rheumatic heart disease and mitral stenosis 16% (Table 2).

Echocardiogram showed poor cardiac function with ejection fraction below 35% in 27% of patients. Although echocardiogram is an essential tool in investigation of patients with AF it was not done in 22% of patients.

From the antithrombotic treatment warfarin was prescribed to 63.8% of patients followed by aspirin 61.3% whereas clopidogrel, unfractionated heparin and LMWH were given to a small number of patients. From those who were given warfarin only 35% were therapeutically anticoagulated with INR (international normalized ratio) between 2 to 3; more than half (56.4%) had below therapeutic INR. Stroke developed in 23.9% of patients. The most frequent antiarrhythmic drug used was digoxin 52.1%, beta blockers in 39.3%, amiodarone in 26.4%, and clopidogrel 16%. (Table 3) Cardioversion was minimally used only in 3.7%, to restore sinus rhythm.

Similarly thyroid function was tested in 15.3% of patients only.

**Discussion**

The prevalence of AF is on the rise due in part to an aging general population and to increased survival from improved medical care among patients with coronary artery disease, heart failure and all chronic conditions which predispose to AF (21, 22, 23). Warfarin has been proven to reduce stroke incidence by two thirds of high risk AF patients, yet surveys repeatedly indicate that many patients who should be anticoagulated are not (14 - 20, 24-30). Furthermore those who would benefit the most from treatment are the elderly people who are the group least likely to be treated (13, 14, 20). This is in consistency with our study where the majority of our patients were elderly, 58.3%. Although warfarin was used in 63.5% of our patients still a large proportion of patients (56.4%) were not therapeutically anticoagulated and hence not benefiting from the use of warfarin (18,19,20). Aspirin was the second most common antithrombotic drug used in our study (61.3%) but as shown in previous studies, aspirin decreases the risks of stroke in these patients but to a lesser extent than warfarin (32). Common risk factors of AF in our study, in decreasing frequency, were hypertension, IHD, DM, cardiomyopathy and rheumatic valvular heart disease. Similar results were reported by Shatoor AS et al, in a study from the southern province of Saudi Arabia (3) and studies in other parts of the world. Although thyroid disease is an important cause of AF in both the young and the elderly, it has been shown to be under investigated (8,23). Only 25 of our patients had TFT.
Conclusion
Atrial fibrillation remains a prevalent cardiac disorder in the elderly among acute medical admissions and is considered as one of the three growing cardiovascular epidemics of the new millennium, in association with heart failure DM and metabolic syndrome. The literature and our results indicate varying proportions of those patients are treated with anticoagulation with varying intensity of anticoagulation. There is still reluctance to start anticoagulation especially in elderly patients. Standard investigations are under utilized and cardioversion is considered infrequently. Although rheumatic heart disease still remains common in Saudi Arabia, hypertension IHD, DM, and heart failure are emerging as new risk factors for AF as shown in our study and studies in other parts of the world. Undoubtedly it is vital to educate doctors to fully implement the current recommendation for anticoagulation for patients aged 65 or more with AF, and hence decrease the financial cost of the already stretched resources.

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32. AF investigators risk factors for stroke and efficacy of anti thrombotic therapy in AF - analysis of pooled data from 5 randomized controlled trial Arch Intern Med 1994 -154 : 1449-57
Prevalence of bacteremia in critical care unit and drug resistance

ABSTRACT

Objective: To determine the pattern of antibiotic resistance among gram-negative bacteria in relation to antibiotic use in ICU admission in King Hussein Medical Center (KHMC)-Jordan

Materials and Methods: One hundred consecutive gram-negative bacterial isolates from different sites were collected from patients admitted to the ICU at KHMC. The susceptibilities of the strains to 12 antibiotics were performed and interpreted. The quantities and the numbers of the patients discharged on antibiotics and the quantities consumed were obtained from the hospital pharmacy records.

Results: The most common isolate was P. aeruginosa (n=21). The most common site of isolation was the respiratory tract (65%). The highest susceptibility was to piperacillin/tazobactam (78%), and the lowest was to cefuroxime (34%). The aminoglycosides gentamicin and amikacin were active against 71% and 73% of the isolates respectively. Ciprofloxacin was active against 75% of the isolates. The most frequently used antibiotics were the third-generation cephalosporins ceftriaxone and ceftazidime, followed by imipenem and amikacin.

Conclusion: Antibiotic resistance surveillance programs associated with registration of antibiotic consumption are necessary to promote optimal use of antibiotics. Rational prescribing of antibiotics should be encouraged through educational programs, surveillance and audit. Proper infection control measures should be practiced to prevent horizontal transfer of drug-resistant organisms.

Key words: Antibiotic, Resistance, Gram-Negative Bacilli.

Introduction
Gram-negative bacilli such as Enterobacteriaceae and Pseudomonas aeruginosa are the leading causes of nosocomial bloodstream infections. Antibiotic-resistant strains have emerged among the gram-negative bacilli and are being increasingly recognized (1, 2). This marked increase in the incidence of infections due to antibiotic-resistant gram-negative bacilli in recent years is of great concern. It is presumed that infections caused by antibiotic-resistant bacteria result in greater mortality, longer hospitalization, and higher costs, than infections caused by antibiotic-susceptible bacteria, although little data are available to support this intuitive concept (3, 4, and 5). The assumption that infections caused by antibiotic-resistant bacteria are associated with a higher mortality rate is based on the possibility that appropriate antimicrobial therapy for such infections might be initiated later than for infections caused by antibiotic-susceptible bacteria (6). Appropriate antimicrobial therapy has been shown to reduce mortality among patients with gram-negative bacteremia (7, 8) and, when initiated early, to have a favorable effect on outcome in critically ill patients with bacteremia or other serious infections (9, 10, 11, 12, 13, 14). However, this issue has not been studied in detail, and several reports have noted that appropriate antimicrobial therapy did not result in a notable difference in the outcomes of patients with severe infections (15, 16, and 14). In addition, although appropriate antimicrobial therapy has been shown to reduce mortality rates in gram-negative sepsis, little information exists about whether inappropriate initial empirical antimicrobial therapy given during the first 48 to 72 hours, before microbiological results are available, adversely affects outcome. Thus, we have evaluated the effect of inappropriate initial antimicrobial therapy on survival in patients with antibiotic-resistant gram-negative bacteremia. The aim of the study was to identify the risk factors for mortality and to explore the overall association between increased mortality and inappropriate empirical therapy in antibiotic-resistant gram-negative bacteremia. Since the discovery of antimicrobial agents, micro-organisms have developed virtually unlimited resistance to them. (17) Hospitals and particularly intensive care units are an important breeding ground for the development of antibiotic-resistant bacteria. This is the consequence of heavy antibiotic use. In addition, a high-density patient population in frequent contact with health care staff and the attendant risk of cross-infection contributes to the spread of antibiotic-resistant micro-organisms. This in turn increases the morbidity and mortality associated with infections and contributes to rising costs of health care. (18, 19)

Materials and Methods

Specimen Collection and Identification of Isolates:
One hundred consecutive gram-negative bacterial isolates from different sites were collected from patients admitted to the ICU at King Hussein Medical Center Jordan, during a 24-month period (from January 2008 to December 2009). The clinical significance of the isolates was confirmed by analysis of patient’s records and discussion with the treating...
clinician. All bacterial strains were identified by their colonial morphology, gram reaction, the oxidized and other biochemical reactions as performed by either API 20E, or API 20NE (bioMerieux, France).

**Susceptibility Testing:**
The susceptibilities of the strains to 12 antibiotics (co-amoxiclav, cefuroxime, cefotaxime, ceftiraxone, cefta-zidime, aztreonam, piperacillin, piperacillin/tazobactam, imipenem, gentamicin, amikacin, and ciprofloxacin) were performed by determining the minimum inhibitory concentration (MIC), using the E-test (AB BIODISK, Sweden), with E. coli NCTC 10418 and P. aeruginosa NCTC 10662 as controls. The interpretation standards for MICs of the NCCLS were used to determine antibiotic susceptibilities. To detect extended spectrum β-lactamases (ESBL), ceftazidime-resistant strains of E. coli and Klebsiella spp. were further tested against ceftazidime/clavulanic acid. Isolates with a reduction of ceftazidime MIC by >3 two-fold dilutions in the presence of clavulanic acid were considered ESBL producers, and thus resistant to other cephalosporins.

**Antibiotic Consumption:**
The quantities of antibiotics consumed in the ICU during the period of the study were obtained from the hospital pharmacy records and the numbers of the patients discharged were obtained from the hospital records. The estimated days of antibiotic treatment were calculated from the antibiotic daily dose, the total amount consumed and the number of patients who left ICU during the period of study. The antibiotic consumption is expressed as days of treatment per 100 patient discharges.

**Results**

**Bacterial Isolates:**
The frequency of the bacterial isolates and their sites of isolation are shown in Table 1. The most common isolates were P. aeruginosa (n=21), Klebsiella spp. (n=20), E. coli (n=13), Enterobacter spp. (n=12), and Stenotrophomonas maltophilia (n=9). The most common sites of isolation were the respiratory tract (65%), urine (14%), wounds (11%) and blood (7%). P. aeruginosa was the most frequent isolate from the respiratory specimens; E. coli was the most from urine and P. mirabilis from wounds.

**Susceptibility Patterns:**
Antibiotic susceptibilities of the bacterial strains are shown in Table 2. The highest in vitro susceptibility was to piperacillin/tazobactam and ciprofloxacin (78% and 75%), and the lowest was to cefuroxime and coamoxiclav (34%, 20%). The susceptibility of the isolates to cephalosporins ranged from 71% for ceftazidime to 34% for cefuroxime. Only 55% of strains were susceptible to ceftriaxone and 52% to ceftaxime. Ceftazidime showed good activity against P. aeruginosa, and P. mirabilis, inhibiting 81% and 100%, respectively. Resistance to cephalosporins was encountered with Enterobacter spp. and Acinetobacter spp. Aztreonam showed similar activity to ceftazidime against all strains. The aminoglycosides gentamicin and amikacin were active against 71% and 73% of the isolates, respectively. Four strains, two Klebsiella spp., one P. aeruginosa, and one S. maltophilia were resistant to amikacin but sensitive to gentamicin. Imipenem inhibited 69% of the isolates, but only 11% of S. maltophilia. Two of the six P. mirabilis isolates were resistant to imipenem but sensitive to cefuroxime and co-amoxiclav. Ciprofloxacin was active against 75% of the isolates but only 50% of Enterobacter spp.

**Rates of Antibiotic Consumption:**
The consumption of antibiotics in the ICU is shown in Table 3. The total amount of antibiotics consumed was equivalent to 916 estimated days of treatment/100 hospital discharges. The most frequently used antibiotics were the third-generation cephalosporins ceftriaxone and ceftazidime, followed by imipenem and amikacin. Among the least consumed were co-amoxiclav and piperacillin.

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### Table 1: Types of bacterial strains and sites of isolation

<table>
<thead>
<tr>
<th>Micro-organism</th>
<th>Total</th>
<th>Respiratory</th>
<th>Urine</th>
<th>Wound</th>
<th>Blood</th>
<th>Others*</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>21</td>
<td>19</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>Klebsiella spp.</em></td>
<td>20</td>
<td>14</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>13</td>
<td>1</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><em>Enterobacter spp.</em></td>
<td>12</td>
<td>7</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><em>S. Maltophilia</em></td>
<td>9</td>
<td>7</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><em>Acinetobacter spp.</em></td>
<td>6</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other gram negative bacilli</td>
<td>13</td>
<td>10</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>All gram negative bacilli</td>
<td>100</td>
<td>65</td>
<td>14</td>
<td>11</td>
<td>7</td>
<td>3</td>
</tr>
</tbody>
</table>

*Others = central line tip (2), abdominal drain site (1)
IMP = imipenem; CAZ = ceftazidime; ATM = aztreonam; CRO = ceftriaxone; CTX = cefotaxime; CXM = cefuroxime; PIP = piperacillin; PTZ = piperacillin/tazobactam; AUG = co-amoxiclav; GM = gentamicin; AMK = amikacin; CIP = ciprofloxacin.

*Pseudomonas spp (5), Morganella morganii (3), Citrobacter spp (1), Weesella zoohecum (1)

Table 2: Antibiotic susceptibilities of the bacterial strains

Table 3: Antibiotic consumption

Discussion

During the study period, every 100 patients treated in the ICU received an average of 916 days of antibiotic treatment, mostly third-generation cephalosporins, imipenem, ciprofloxacin and amikacin which was 50% higher than the consumption in Oman in 1996. (21)

As for the individual antibiotics, there was a four-fold rise in the consumption of ciprofloxacin and a three-fold rise in the consumption of imipenem and ceftazidime. Given this substantial use of antibiotics, it is not surprising to note the change in the microbial ecology, with predominance of multiresistant strains of P. aeruginosa, Klebsiella spp., Enterobacter spp. and S. maltophilia. It is well documented that the indiscriminate use of antibiotics has led to the
selection and dissemination of antibiotic-resistant organisms. Several authors have reported the association of resistance to β-lactam antibiotics with prior use of third-generation cephalosporins. A common mechanism of cephalosporin resistance among Klebsiella spp. and E. coli is the production of ESBL. In this study, three Klebsiella spp. (15%) and two E. coli (15%) were resistant to third-generation cephalosporins and aztreonam, suggesting production of Extended Spectrum β-Lactamases (ESBL) by these strains. This was confirmed by their susceptibility to cefazidem. However, with this test alone inhibitor-resistant TEM (IRT) mutants may not be detected. Nevertheless, we believe that IRT mutants are probably prevalent in our hospitals, since 62% of E. coli in this study was resistant to co-amoxiclav, suggesting the possibility of IRT production. IRT-producing mutants have been reported in both general practice and hospitals.

Nosocomial outbreaks of Klebsiella spp. resistant to the third-generation cephalosporins due to the production of ESBL have been reported worldwide. Although there was an increase in the consumption of cephalosporins in 1998 when this study was conducted, the incidence of probable ESBL producers was much lower than that in 1996, a fact which we are unable to explain. Carbapenems, being strong inducers of class C β-lactamases, could also have contributed to the resistance to β-lactams, including third-generation cephalosporins. Furthermore, it has been shown that treatment with imipenem, but not with other β-lactam drugs, is a major risk factor for the development of imipenem-resistant P. aeruginosa in hospitalized patients. Imipenem resistance in this study was high, particularly among P. aeruginosa and Enterobacter spp., compared to the study done in 1996, when fewer carbapenems were used. Furthermore, patients receiving carbapenems, particularly those on mechanical ventilation, are at an increased risk of colonization or infection with class B metallo-enzyme producers such as S. maltophilia. Indeed, with the increased use of carbapenems, more strains of S. maltophilia were isolated compared to the earlier study. About 70% of these strains were resistant to imipenem, and most were isolated from the respiratory tract of mechanically ventilated patients.

Overuse of carbapenems in our ICUs has also provoked a unique type of resistance among P. mirabilis. Two strains (33%) of P. mirabilis were resistant to imipenem but sensitive to cefuroxime and co-amoxiclav. Medeiros (1997) attributed this resistance to an altered penicillin-binding protein to which imipenem cannot bind, but other β-lactams can.

Resistance to gentamicin and amikacin in our study was relatively high. Four isolates were resistant to amikacin but sensitive to gentamicin. This is probably due to selective pressure associated with the high consumption of amikacin in our ICU. This phenomenon has been reported in similar situations, due to aminoglycoside-modifying enzyme N-acetyl transferase (ACC6-[1]) that hydrolyses amikacin, tobramycin, and netilmicin, but not gentamicin. There was an alarming increase in the level of resistance to ciprofloxacin in our hospital, as only 75% of the isolates were inhibited, compared to 94% in 1996. This is probably a result of the increased consumption of ciprofloxacin in 1998, leading to the selection of resistant mutants. The emergence of resistance to fluoroquinolones in virtually all species of bacteria was recognized after the introduction of these compounds for clinical use.

The gravity of the problem of antimicrobial resistance continues to receive global attention, as evidenced by the pan-European meeting in Copenhagen. Given this escalation in resistance and the overwhelming evidence of overuse of antibiotics, the pragmatic and essential approach to control antibiotic resistance is control of antibiotic use. Apparently, there are reasons for optimism, as studies in various centers showed rapid reversal of resistance. National guidelines on this topic and good diagnostic and therapeutic protocols are important.

Conclusion
Continued surveillance of prevalent strains and their resistance patterns is fundamental as a means of establishing the significance of resistance in clinical infection, and in the determination of hospital-prescribing policies. Antibiotic resistance surveillance programs associated with registration of antibiotic consumption are necessary to promote optimal use of antibiotics. Rational prescribing of antibiotics should be encouraged through educational programs, surveillance and audit. Proper infection control measures must also be practiced to prevent horizontal transfer of drug-resistant organisms.

References


Association between stress and skin disease

ABSTRACT

Background: It is widely believed that factors such as stress and anxiety may not only be a result of certain diseases but can themselves exacerbate disease, and sometimes may be the cause.

Objective: To clarify the association between stress and some dermatoses using an objective scale.

Patients and Methods: This is a case control study conducted at the Dermatology Clinic in Tikrit Teaching Hospital. A total of 735 subjects were included in the study. Among them there were 139 with psoriasis, 159 with vitiligo, 172 with alopecia areata, and 265 with acne vulgaris. The Perceived Stress Scale (PSS) was used to determine the stress level. In addition, two control groups were used in the study. The first was a diseases control group and the second was a healthy individuals group.

Results: This study indicated that stress made the state of disease studied, worse. According to patients view, there was a highly significant association between stress and diseases such as psoriasis (OR=8), acne (OR= 7.45), vitiligo (OR= 4.35), and alopecia areata (OR= 4.026). When the data of all the above four diseases was collected together, there was also a positive association between these diseases and stress (P < 0.05; OR= 5.76). There was a significant difference in the mean perceived stress scale (PSS) values between the group of patients who claimed presence of positive association and those who did not. In addition, there was a significant correlation between PSS values and disease grading scales in patients with psoriasis (r=0.77; P<0.0001) and acne (r=0.82; P<0.0001). However, the correlation was significantly higher in patients claiming a positive association (Psoriasis: r=0.76,P<0.0001; Acne: r=0.72,P<0.001) as compared to those who claimed absence of association (Psoriasis: r=33,P<0.05; Acne: r=0.43,P<0.001).

Conclusion: The dermatoses included in this study are being activated by stress as a significant association was demonstrated depending on patients view or by determination of PSS. Thus, it is recommended to use psychological therapies in the management of these skin disorders. Abrogation of mast-cell activation seems to be a promising approach.

Key Words: Stress, Vitiligo, Psoriasis, Alopecia, Acne, Dermatoses

Introduction

It is widely believed that factors such as stress and anxiety may not be only a result of certain diseases but can themselves exacerbate disease, and sometimes may be the cause. The concept of some skin diseases (psoriasis, vitiligo, acne, and alopecia areata) being the result of a nervous disorder was supported by the reported association of these diseases with emotional or physical stress and trauma.(1) An increasing number of studies (1-9) support the pathogenic link between chronic stress and exacerbation of disease. Evidence that psychological stress may influence the course of dermatological disease is also growing.(5,6,10-16) We present a case control study involving cases of psoriasis, acne, vitiligo, alopecia areata and a control group with dermatological diseases other than the above mentioned dermatoses in addition to atopic dermatitis and urticaria. The study protocol was approved by Tikrit University College of Medicine Ethical Committee and informed written consent was taken from each participant. The aim of the study was to clarify the association between these dermatoses and stress exposure.

Subjects and Methods

This is a case control study conducted at the Dermatology Clinic in Tikrit Teaching Hospital, during the period from January 2000 to October 2007. A total of 735 subjects were included in the study, and among them there were 139 with psoriasis, 159 with vitiligo, 172 with alopecia areata, and 265 with acne vulgaris. Their ages ranged from 18 - 62 years. A control group had other skin dermatoses excluding the above diseases, and also atopic dermatitis and urticaria. The control group included 1696 subjects and their data was used for analysis of association between stress and the above dermatoses from the patient’s point of view. Another control group was composed of 90 healthy subjects from the general population without dermatological or psychological conditions, who were also volunteers that agreed to participate in the psychological assessment. Their ages ranged from 18 -54 years.

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Each patient who agreed to participate in the study was interviewed. The Perceived Stress Scale (PSS); a 14 item questionnaire that measures the perception of life stress, including how often subjects perceived their life to be uncontrollable, unpredictable and overwhelming(17) was used in this study.

**Statistical analysis**

Odd ratio and X2 were used to determine the significance of association between stress exposure and exacerbation of studied dermatoses from the patient’s point of view. Student t test was used for determination of significance of mean PSS among groups, while regression analysis was used to determine the correlation between PSS and grading scale in psoriasis and acne cases.

**Results**

The present study indicated that stress can make the state of the studied diseases worse. According to the patients’ view, there was a highly significant association between stress and diseases such as psoriasis (OR=8), acne (OR= 7.45), vitiligo (OR= 4.35), and alopecia areata (OR= 4.026). When the data of the above cited four diseases was collected together, there was also a positive association with stress (P < 0.05; OR= 5.76).

<table>
<thead>
<tr>
<th>Index</th>
<th>Psoriasis</th>
<th>Vitiligo</th>
<th>Alopecia</th>
<th>Acne</th>
<th>Total cases</th>
<th>Control</th>
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<tbody>
<tr>
<td>Presence association</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Number)</td>
<td>96</td>
<td>87</td>
<td>91</td>
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<td>453</td>
<td>370</td>
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<td></td>
<td>43</td>
<td>72</td>
<td>81</td>
<td>86</td>
<td>282</td>
<td>1326</td>
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<td>159</td>
<td>172</td>
<td>265</td>
<td>735</td>
<td>1696</td>
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<tr>
<td>OR</td>
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<td>4.02</td>
<td>7.46</td>
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<td>5.5-11.7</td>
<td>3.1-6.0</td>
<td>2.9-5.5</td>
<td>5.6-9.9</td>
<td>4.8-6.9</td>
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<td>84.75</td>
<td>81.21</td>
<td>238.25</td>
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<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td></td>
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</tr>
</tbody>
</table>

Table 1: Stress effect on diseases exacerbation from patients’ view

<table>
<thead>
<tr>
<th>Disease</th>
<th>Perceived stress scale Mean [SD]</th>
<th>Disease grading</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes association association</td>
<td>No association</td>
</tr>
<tr>
<td></td>
<td>Yes No Total</td>
<td>Yes No Total</td>
</tr>
<tr>
<td>Alopecia</td>
<td>37.0 [10] 23.0 [8.1] 30.4 [11.5]</td>
<td></td>
</tr>
<tr>
<td>Vitiligo</td>
<td>41.2 [6.8] 26.4 [6.8] 34.5 [10.1]</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>37.5 [9.3] 23.0 [7.2] 31.9 [11.1]</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Perceived stress scale in studied diseases
Table 3: Correlation between PSS and disease grading for psoriasis and acne

When the association between stress and diseases was evaluated by determination of PSS, there was a significant difference in the mean PSS values between the group who claimed presence of a positive association with those who did not (Table 2). In psoriatic patients the PSS mean value was significantly higher (P<0.0001) in the patients group who claimed a positive association (40.2± 8.5) and those who claimed absence of an association (23.2± 4.6). In addition, the disease grading of psoriasis shows a significant difference (P<0.05) between the two psoriatic groups (positive claim group 23.1± 6.7; and negative claim group 14.3± 5.30).

In acne patients the PSS mean value was significantly higher (P<0.0001) in patients who claimed an association (34.5±9.5) as compared with those who claimed no association (20.23±4.2). In addition, the mean value of disease grading scale mean value was significantly higher (P=0.0001) in patients with a positive claim of association (7.48±2.1) as compared with patients who claimed absence of association (3.11±1.3).

In the group of vitiligo, the patients with a positive claim of association (41.2±6.8) had a significantly higher mean PSS value (P<0.0001) compared with patients who claimed absence of association (26.4±6.8). The patients with alopecia areata showed a higher PSS mean value in those who claimed a positive association (37±10) as compared with patients who claimed absence of association (23±8.1) and the difference was highly significant (P<0.0001).

When all the data from each of the four diseases (positive and negative claims) were compared with the normal population, it was found that the mean PSS values for psoriasis (34.9±11.6), acne (29.9±16.6), vitiligo ( 34.5±10.1) and alopecia (30.4±11.5) were significantly different (P<0.001) from that of the general population (control group; 16.6±4.4). In addition, the mean PSS value of patients with a positive claim of association (37.5±9.5) was significantly higher (P<0.001) than those with negative claims (23±7.2). Furthermore, the PSS for all patients of the 4 disease s together was 31.9±11.1 and it is significantly higher (P<0.001) than that in normal population (control group).

There was a significant correlation between the values of PSS and disease grading scale in patients with psoriasis (r=0.77, P<0.0001) and acne (r=0.82, P<0.0001). However, the correlation was significantly higher in patients claiming a positive association (Psoriasis: r=0.76, P<0.0001; Acne: r=0.72, P<0.001) as compared with those who claimed an absence of association (Psoriasis: r=33, P<0.05; Acne: r=0.43, P<0.001).

Discussion

The results of this study support the association of stress with exacerbation of certain skin diseases, whether the association was determined according to patients view or by determination of PSS. These findings were consistent with that reported before(5, 8, 18) Both the beginning and the progression of dermatoses may be significantly influenced by stress, emotional disturbances and psychiatric disorders(16, 19).

Central nervous system and skin are embryologically derived from the ectoderm. This may form the basis for the association between stress and etiology or exacerbation of dermatoses, i.e. skin and brain may reciprocally influence each other(16). The cause of primary disorders of psycho-dermatological conditions may be either dermatologic or psychiatric. It is very important for dermatologists or psychiatrists to recognize and to manage psycho-dermatologic disorders(5), thus patients are not under diagnosed and get the correct treatment. In the studied sample, the PSS was significantly higher in patients who claimed an association between their dermatoses and stress as compared to those who claimed no association. The mean degree of psychological distress, assessed on PSS, was 37.5 points in those who claimed presence of association. This PSS was significantly higher than that in patients who claimed no association. Furthermore, when the data was collected together for each disease, their mean PSS value was significantly higher than that of the normal population.

Skin as an external organ, plays an important role in interpersonal relationships(8). Skin appearance due to skin diseases may produce rejection by community members, especially chronic dermatoses in exposed areas(8). The consequence of this ‘impaired appearance’ will be a depression of self-esteem and self-image(15). This is the main reason why patients with dermatoses are so often psychologically disturbed(20). In two community based studies performed in Iraq the patients with skin diseases were unsatisfied in 61.4%(21) and 54.6% (19). Furthermore, 83.7% of patients had a feeling of stigma with an impact on their family relations, social relations, and work and school. Several studies had reported the importance of emotions(22,23), unconscious conflicts(24,25), personality traits(15,26,27), the presence of anxiety(8,28-30), the association with stressful life events(19,21,31-33) and etiology or exacerbation of dermatological diseases.

Acne vulgaris is a common inflammatory condition of the skin affecting more than 80% of teenagers and 25% of
adults(3). Adults who have acne admit to feeling embarrassed or self-conscious because of their skin(19,34). Despite the prevalence of this condition and considerable research, there is still much unsubstantiated myth surrounding the causes of acne. Specifically, stress is often cited as playing a role in acne flares, even though there is little research to support this claim. Although, it is well known that acne can be a source of significant stress and anxiety(35,36), scientific evidence outside of anecdotal reports that stress itself may worsen acne has been lacking.

In this study, from the patients’ perspective, there is an association between exacerbation of acne and stress. Furthermore, subjects who claimed association between acne exacerbation and stress demonstrated greater value of PSS as compared with those who claimed no association, and to the control group. In addition, the PSS correlated significantly with acne grading scale in groups of subjects who claim presence of association and for total acne patients. However, the correlation was lower in subjects who claimed a negative association between acne exacerbation and stress. This finding was consistent with that reported recently by Chiu et al(3), as changes in acne severity correlate highly with increasing stress, suggesting that emotional stress from external sources may have significant influence on acne.

Various mechanisms have been proposed for why stress may potentially aggravate acne vulgaris. Some investigators believe that increased glucocorticoids and adrenal androgens, both hormones known to worsen acne and possibly induce sebaceous hyperplasia, are released during periods of emotional stress. During stress response the body coordinator, the corticotrophin-releasing hormones, were found to increase sebaceous lipogenesis and upregulate sebocyte conversion of androgen precursors to testosterone(38). In addition, other studies(39,40) suggested that stress can induce release of neuroactive substances within the epidermis and can activate inflammatory processes in the skin. Recently, substance P, a neuropeptide elicited from peripheral nerves by stress, was shown to stimulate the proliferation of sebaceous glands and to up-regulate lipid synthesis in sebaceous cells(41).

Psychological stress can slow wound healing by up to 40% (42), which could be a factor in slowing the repair of acne lesions. The relationship between stress and acne is clinically relevant and worth exploration because possible behavioral interventions may become viable options for patients, as may therapeutic approaches that can be adjusted during times of known stressors(3).

It is widely accepted that genetic-environmental interaction, plays a role in the development of psoriasis. Although, the genetic influence on psoriasis is well established, the role of environmental factors is less precisely defined(7). Stressful life events are considered as potentially important causative factors(7). This study confirms that stress has correlated with psoriasis exacerbation in patients’ views. In addition, the mean PSS was significantly higher in patients who claimed the presence of an association between stress and psoriasis as compared with the patients group who claimed no association. Furthermore, PSS mean values were significantly higher in psoriatic patients (when data from all patients with psoriasis were added together) than that of the normal population. Also there is an association between disease severity grading scale and PSS. Regression line analysis indicates a significant association between PSS and disease grading scale of psoriasis for the patients group who claim a positive association. However, psoriatic patients group who claim no association between psoriasis and stress show a low level of correlation. Furthermore, when all are patients collected together in one group, regression line analysis demonstrated a significant level of correlation.

Previous studies have provided some evidence for the association of psoriasis with stressful life events(7). In spite of being frequently reported as a trigger, there is limited and conflicting evidence concerning the role of psychological stress in relation to the onset or exacerbation of psoriasis(7,9,10,44,45). Our study has confirmed these previously reported associations and provide evidence that stress is linked to psoriasis and its exacerbation and severity. Several tentative biological explanations can be suggested for this association. There is some evidence to suggest that psychological stress may modulate immune functions in humans and in experimental animals, depending on the nature of the stressor and the immune variable under consideration(46). It has been documented that stress-induced anxiety related to a T- helper 1- like response(47). Based on experiments where psychological stress was applied before immunization, it has been proposed that stress exerts an adjuvant effect on Dendritic Cells by promoting enhanced migration to lymph nodes and resulting in increased antigen-specific T cell response(7). Such an effect appears to be due to modulated release of norepinephrine by sympathetic nerve ends(48).

There is a complex neuro-immuno-cutaneous-endocrine network that may account for a mind-body connection in the skin(39). This network may mediate the interplay between psoriasis and stress. In vulnerable individuals, stress induced release of neuroimmune substances, including neuropeptides(33) might adversely affect cutaneous homeostasis through activation of inflammatory processes in deeper skin layers(39,49). Stress can also alter the epidermal permeability barriers(12), and a barrier abnormality might facilitate the development or persistence of inflammatory skin diseases through the activation of an epidermal initiated cytokine cascade(50). Furthermore, continuous stress can compromise the skin wound healing response(51).

The major pathogenic abnormalities in psoriasis are the abnormal differentiation and hyperproliferation of keratinocytes and the infiltration of inflammatory components into the skin(52). Research findings suggest an altered stress-induced increase in CD8+ T lymphocytes among psoriatic patients(53). Personality is also likely to play a role in the pathophysiological processes because personality traits can influence the immune response to stress, possibly by influencing the perception and appraisal of stress situations and thereby the physiological reaction(54). High levels of
hostility correlated with high cortisol and norepinephrine responses to stress, and with greater increases in the number and activity of NK cells(55,56).

Lymphocytes express adrenergic receptors and respond to catecholamine stimulation with the development of stress induced lymphocytosis and distinct changes in lymphocyte trafficking, circulation, proliferation and cytokine production(57,58).

Acute stress increases the skin content of CRH, which may derive from dorsal root ganglia(59). This may lead to local changes in immune response that may be responsible for exacerbation of psoriasis; a story may be similar to the recurrences of cold sore after exposure to stress or sunlight. Stress induced mast cell degranulation in the skin probably has immediate and prominent central CNS effects, which may sustain a vicious, stress- induced cycle of proinflammatory events. Thus mast cells induce a multitude of tissue effects necessary for the initiation of inflammation by production of large series of mediators and cytokines(60). In animal models, exposure to stress severely impairs mechanisms of immune tolerance in various organs(61). Using this model, it has been shown that stress exerts severe skin inflammation, affecting, for instance the aggregation of experimental atopic dermatitis(62).

NGF directly stimulates activation of mast cells via functional neurotrophin receptors (63), thus aggravating cutaneous neurogenic inflammation. Furthermore, in response to stress, mast cells may secrete proteases which may subsequently trigger additional cytokines release, cell migration, recruitment of leucocytes and endothelial cell activation(64). Tryptase releasing mast cells can be found in close proximity to proteinase-activated receptor -2 - expressing cells such as keratinocytes, dermal endothelial cells, and C fiber during inflammation. These mechanisms probably act synergistically with NGF and SP to upregulate the neurogenic inflammation cascade(65). These changes as a response to stress may explain subsequent exacerbation of psoriasis following stress exposure as this study indicated.

The etiology of vitiligo is uncertain, although genetic, immunological and neurogenic factors seem to play a role (65). Certain triggers (e.g. trauma to the skin, hormonal changes, and stress), may be necessary for the disease to become apparent(31,66,67). The present study indicated a positive association between exacerbation of vitiligo and stress exposure from the patient’s perspective. Furthermore, the mean value of PSS was significantly higher in the patient group claiming association of stress exposure with vitiligo exacerbation as compared to the patient group who claimed an absence of association. However, all groups of vitiligo were with significantly higher PSS mean values than those in the normal population. ACTH stimulates the production and secretion of cortisol or corticosterone by the adrenal cortex, which counteracts the effect of the stressors by suppression of the HPA axis through a negative feedback mechanism (68). Mammalian skin expresses proopiomelanocortin (POMC) and produces the POMC-derived peptides, ß endorphin, ACTH, a-melanocyte stimulating hormone and ß-lipoprotein(65,69). In light of the existence of a local neuroendocrine skin axis, it has been proposed that the cutaneous defense against stressors is organized similarly to the classical HPA axis(65). Effectors of this axis (CRH, urocortin, and POMC peptides) are capable of regulating skin pigmentation, immune, epidermal, dermal and adnexal systems (70). In this context environmental challenges such as UV light and biological or chemical stress trigger multiple pathways involving structurized or simultaneous local production of CRH- related and POMC derived messages(71), may possibly counteract the local effects of the environmental stress. This complex response would be susceptible to feedback inhibition by cortisol and / or corticosterone, which are produced locally in the skin(71,72). These sequences of events may explain in part the association between depigmentation in vitiligo and stress exposure. Furthermore, theoretically, stress may also affect melanocyte stem-cells, for example in the hair follicle during premature, stress induced graying or in the epidermis during vitiligo, which may be triggered or aggravated by stress, as this study indicated and is also reported by others(73).

From the patient’s point of view, this study indicated that exacerbation of alopecia areata (AA) was significantly associated with stress exposure. In addition, PSS mean value in patients who claimed an association, was significantly higher compared to those who claimed absence of association. Furthermore, PSS mean values in all groups were significantly lower than that in the normal population. The concept of AA being the result of a nervous disorder was supported by reported associations of AA with emotional or physical stress and trauma(1). More recently, it has been reported that there is a high prevalence of mood, adjustment and anxiety disorders in patients with AA(74). Affected scalp skin areas from patients with AA, which may be precipitated by psychological stress, show increased expression of CRH-R2 around hair follicles(75).

In animal models, it has been shown that stress exerts severe skin inflammation affecting hair growth(76). In a distinct, complementary rodent stress model, mice exposed to foot shock showed inhibition of hair growth in a similar way(77). In this marine model of chronic psychological stress, exposure to sound stress induced neurogenic skin inflammation characterized by increased NGF expression, upregulated perifollicular mast cell degranulation, and perifollicular accumulation of antigen-presenting cells, thus inhibiting hair growth by down regulating proliferation and upregulating apoptosis of hair follicle keratinocytes and by prematurely triggering hair follicle regression(78). Therefore, in this model, psychological stress activated a defined, hierarchically organized cascade of events in which NGF, SP, and mast cells play key roles(65). Future research in the analysis of cutaneous stress response patterns should focus on crucial-skin cell population that may be especially vulnerable to stress, and on care critical to skin homeostasis and regeneration(65). One such cell population could be hair follicle epithelial stem cells, which are vital for maintenance of any cyclic renewal of the pilosebaceous apparatus(80).
In mice stress upregulates the number of apoptotic cells in the bulge region of the hair follicle and attracts dense potentially autodestructive perifollicular cell infiltrates consisting mainly of activated macrophages to this crucial epithelial stem cell region of the hair follicle (75,76,81). These places of the hair follicles are at risk of irreversible damage by induction of programmed hair follicle organ deletion (65) and this could in part explain the exacerbation of AA as a consequence to stress exposure.

In conclusion, the dermatoses included in this study are being activated by stress as association had been demonstrated as significant depending on patients’ views or by determination of PSS. Thus, it is recommended to use psychological therapies in the management of these skin disorders. In addition, abrogation of mast-cell activation seems to be a promising approach. An effective therapeutic intervention to abrogate stress-triggered telogen effluvium would be an effective approach to treatment of AA. Neurokinin-1-receptor antagonists might be useful in alleviating stress-induced hair loss and skin inflammation. Lastly, dermatologists should become far more attentive to the effect of psychological stress on skin disorders. In addition, skin is a very clinically relevant model system for exploring neuroimmunology.

References


70. Bohm J Invest Dermatol 2006;126:


ABSTRACT

The study has been conducted on 50 hyperprolactinemic infertile women aged between 19 and 40 years and 30 controls aged between 21 and 35 years. All patients complained of infertility with or without galactorrhea, oligomenorrhea and amenorrhea. The effects of lisuride on serum prolactin concentration, luteinizing hormone (LH) and follicle stimulating hormone (FSH) at day 2 of menstrual cycle, thyroid stimulating hormone (TSH), and progesterone at day 21 of menstrual cycle and kidney function parameters before and after four months, were studied. All the patients were clinically examined by a gynecologist and patient complaints including galactorrhea, amenorrhea or oligomenorrhea have been recorded before and after drug administration. This study was conducted from 15 November 2008 to 30 July 2009 in the Azadi General Hospital in Kirkuk city. Data obtained from the study revealed a significant drop of serum prolactin concentration after lisuride therapy. Normoprolactinemia has been achieved in 98% of women treated with lisuride and 46% of them become pregnant, while galactorrhea disappeared in 93.71% and restoration of normal menstrual cycle was noted in 81.81%. No significant changes in kidney function parameters were noted. No correlation between serum prolactin concentration and LH, FSH, TSH have been reported before and after drug therapy, but a significant inverse correlation was noted between serum prolactin concentration and serum progesterone concentration.

The study concludes that lisuride significantly reduces prolactin levels to normal values and improves fertility and ameliorates symptoms of hyperprolactinemia and significantly increases serum progesterone level but within normal values. In addition it had no undesirable effects on kidney function parameter.

Key words: Lisuride, Hyperprolactinemia, Infertile Women.

Therapeutic effects of Lisuride in hyperprolactinemic infertile women

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There are many other causes of a mildly elevated serum prolactin (PRL) concentration such as stress and physical and breast examination. Hyperprolactinemia may result from a PRL secreting adenoma (5, 6) or from a non-functioning disconnection, tumour in the region of the hypothalamus or pituitary, which disrupts inhibitor influence of dopamine on PRL secretion. Hyperprolactinemia could also be because of hypothyroidism, polycystic ovarian syndrome and several drugs, i.e. the dopaminergic antagonists like phenothiazines, domperidone and metoclopramide.

The management of hyperprolactinemia centers on the use of dopamine agonists (7, 8). Most patients show a fall in PRL levels within a few days to a few weeks of commencing the therapy (9, 10). Bromocriptine is considered the gold standard for dopamine agonist therapy; however it is associated with a range of side effects, leaving some patients intolerant to treatment (11). Furthermore, its half-life is short so that it must be given two or 3 times daily (12). Bromocriptine administrated via the vaginal route may reduce incidence of side effects and offer an alternative to the oral form (13).

Lisuride, in contrast to all other marketed ergot-derived drugs, is an 8-?-ergoline (iso-ergoline), which is a structure, not found in natural ergot. It is a very potent peripheral serotonin (5-HT) antagonist used for migraine prophylaxis. Lisuride was also discovered to be a potent dopamine agonist for the treatment of hyperprolactinemia and pituitary tumours and Parkinson’s disease (14).

Data concerning comparison before and after Lisuride therapy on serum PRL level and symptoms due to hyperprolactinemia and other related hormones and data concerning the effects of Lisuride on kidney function are scanty.

Introduction

Hyperprolactinemia is the most common endocrine disorder of the hypothalamic-pituitary axis. It occurs more frequently in women than in men. Clinical symptoms are amenorrhea, infertility, and galactorrhea in women and decreased libido and impotence in men (1,2) and in some cases, gynecomastia. (3) Often but not invariably it is associated with microadenoma (4) of the anterior pituitary gland. Hyperprolactinemia is the commonest pituitary cause of amenorrhea.
The aim of the present study was designed to compare the effects before and after Lisuride therapy on serum PRL level and other related hormones, symptoms of hyperprolactinemia and kidney function parameters in infertile patients.

Materials and Methods
This study was conducted from 15 November 2008 to 30 July 2009 to compare the effects of 4 months treatment with Lisuride (Dopergin®, 0.2 mg tablets, manufactured by Schering AG, Germany) before and after, on serum prolactin level and other related hormones, symptoms of hyperprolactinemia and kidney function parameters in infertile patients. The patients were recruited from Azadi General Hospital, Department of Obstetrics and Gynecology in Kirkuk city.

Patients
The study involved 50 patients, with ages ranging between 19 and 40 years (mean= 28.76). All were infertile with or without amenorrhea, oligomenorrhoea and galactorrhea. Their serum prolactin concentration was over the normal range which was considered 5-35 ng/ml by minividus.

Exclusion criteria
Patients with presence of pituitary macroadenoma, disorders that could prevent normal menstruation, hyperprolactinemia related to polycystic ovary disease, thyroid or adrenal disorder, renal or hepatic disease, history of allergy to ergot derivatives, women using drugs that affect secretion of prolactin from the pituitary such as neuroleptics, and any other diseases, were excluded from the study.

Controls
Thirty healthy volunteer women were also included in the study as a control group. Their age ranged between 21-35 years with mean=28.26.

Doses of Lisuride
Patients received 0.1 mg of Lisuride on the first day at night and 0.1mg in the morning and evening on the second day, and 0.1 mg three times daily from day three and onwards.

Sampling
Five ml of blood was taken from each patient and control every visit, using disposable syringes. The blood was allowed to clot in a plain tube at room temperature and then serum was separated by centrifugation at 3000 rpm for three minutes. The serum was then used for estimating renal function tests (blood urea and serum creatinine by ELIZA), serum prolactin and TSH at any time of the menstrual cycle, and serum LH and FSH on the second or third day of the menstrual cycle and serum progesterone levels at day 21 of the menstrual cycle by minividus (ELFA).

Statistical analysis
All data are expressed as means± standard error means (M±SEM) and statistical analysis was carried out using statistically available software (SPSS Version 11.5). Statistical analyses were carried out using one-way analysis of variable (ANOVA) and Chi-square test. The comparison between groups was done using Duncan test.

Results
Effect of Lisuride on serum prolactin level in hyperprolactinemic infertile patients
Serum prolactin level was reduced from 52.42 2.56 to 17.05 1.79 after 2 weeks of Lisuride administration, which is statistically significant and to 8.93 1.12 after 4 months which is also significant, as shown in Table 1.

![Table 1: Serum prolactin level in healthy subjects (n=30) and in patients before and after treatment with Lisuride (n= 50 patients)](image)

The different letters indicate there is significant difference at P < 0.05

Table 1: Serum prolactin level in healthy subjects (n=30) and in patients before and after treatment with Lisuride (n= 50 patients)

Table 2: Serum LH, FSH and TSH of the healthy subjects (n=30) and patients before and after treatment with Lisuride (n=50)

![Table 2: Serum LH, FSH and TSH of the healthy subjects (n=30) and patients before and after treatment with Lisuride (n=50)](image)

The different letters mean there is significant difference at P < 0.05
Effect of Lisuride on serum progesterone in hyperprolactinemic women

Lisuride was increasing serum progesterone level from 3.48 ± 0.64 ng/ml to 10.98 ± 1.03 ng/ml after four months of therapy, which is statistically significant as shown in Table 3.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Healthy</th>
<th>Mean ± SE</th>
<th>after 4 months of Lisuride</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>progesterone</td>
<td>7.86 ± 0.76</td>
<td>3.48 ± 0.64</td>
<td>10.98 ± 1.03</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table 3: Serum progesterone concentration in healthy subjects (n=30) and patients before and after treatment with Lisuride (n=50)

Effect of Lisuride on fertility

Lisuride significantly improves fertility in hyperprolactinemic infertile women. Table 4 shows that 44% of the patients become pregnant after four months of Lisuride administration, which is statistically significant.

<table>
<thead>
<tr>
<th>Pregnancy</th>
<th>No.</th>
<th>Before Lisuride %</th>
<th>After 4 months of Lisuride %</th>
<th>Improved %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0%</td>
<td>23</td>
<td>46%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 4: Outcome of Lisuride on hyperprolactinemic infertile women (n=50)

Effects of Lisuride on female menstrual cycle and hyperprolactinemia-galactorrhea syndrome

Lisuride returned menstrual cycle to a normal state as shown in Table 5. It significantly eliminated galactorrhea in hyperprolactinemic patients.

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>No.</th>
<th>Before %</th>
<th>After %</th>
<th>Improved %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amenorrhea</td>
<td>3</td>
<td>6%</td>
<td>1</td>
<td>66.66%</td>
<td>NS</td>
</tr>
<tr>
<td>Oligomenorrhea</td>
<td>8</td>
<td>16%</td>
<td>1</td>
<td>87.5%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Galactorrhea</td>
<td>16</td>
<td>32%</td>
<td>1</td>
<td>93.75%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NS= Not Significant

Table 5: Effect of Lisuride on syndromes of hyperprolactinemia (n=50)

Side effects of Lisuride on the patients

Lisuride has side effects; nausea and dizziness were the most prominent side effects in this study as shown in Table 6.

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Lisuride (n=50)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>13</td>
<td>26%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
<td>16%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13</td>
<td>26%</td>
</tr>
</tbody>
</table>

Table 6: Adverse effects of Lisuride, (noted in 15 women) during the period of study (n=50)
Effects of Lisuride on kidney function parameters

Lisuride had no significant effect on kidney function parameters after four months of administration in hyperprolactinemic infertile patients as shown in Table 7.

Table 7: Kidney function parameters in healthy subjects (n=30), cases before and after four months treatment with Lisuride (n=50)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Healthy subject</th>
<th>Mean ± SD</th>
<th>after 4 months of Lisuride</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea (mmol/L)</td>
<td>3.38 ± 0.20</td>
<td>4.19 ± 0.11</td>
<td>4.23 ± 0.12</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>73.6 ± 0.24</td>
<td>70.55 ± 1.82</td>
<td>70.66 ± 1.78</td>
<td>NS</td>
</tr>
<tr>
<td>CCl (ml/min)</td>
<td>96.81 ± 0.95</td>
<td>112.52 ± 2.94</td>
<td>112.20 ± 2.92</td>
<td>NS</td>
</tr>
</tbody>
</table>

The relationship between serum prolactin and serum progesterone

There is an inverse relationship between serum prolactin and progesterone level in hyperprolactinemic infertile patients. Figure 1 shows that the serum progesterone level significantly increased and serum prolactin level significantly decreased after four months of Lisuride therapy.

![Figure 1: Relationship between serum prolactin and progesterone concentration](image)

Discussion

Prolactin (PRL) is under dual regulation by hypothalamic hormones delivered through the hypothalamic-pituitary portal circulation. Under most conditions the predominant signal is inhibitory, preventing PRL release, and is mediated by the neurotransmitter dopamine. The stimulatory signal is mediated by the hypothalamic hormone thyrotropin-releasing hormone. The balance between the 2 signals determines the amount of PRL released from the anterior pituitary gland (6). Dopamine agonist is a compound that activates dopamine receptors, mimicking the effect of the neurotransmitter dopamine able to lower PRL levels, and restore ovarian function (15). Dopamine agonists have become the treatment of choice for the majority of patients with hyperprolactinemic disorders. Lisuride is an ergot derivative with high dopamine agonist potency. On the basis of pharmacological tests it was suggested that the unchanged drug and not a metabolite was responsible for this activity. Low doses of Lisuride were shown to stimulate dopaminergic receptors. One of the most important effects of Lisuride in humans appears to be to lower the endogenous PRL level in plasma, which is presumably mediated by its dopaminergic activity in the central nervous system (16).

This study showed that Lisuride significantly reduced serum PRL level to normal value after two weeks and four months of administration as shown in Table . This agrees with other studies that showed similar effects in hyperprolactinemic patients (17, 18).

Hyperprolactinemia and anovulation may be associated with primary hypothyroidism. Enlargement of the pituitary gland is frequently seen in long-standing primary hypothyroidism. A number of mechanisms may be involved. Firstly, the clearance of PRL tends to be decreased in hypothyroidism.
Secondly, patients with severe hypothyroidism may have elevated total and free estradiol levels, giving rise to increased PRL production stimulated by excess free estrogen. Thirdly, and possibly most significantly, the mechanism involves the inhibitory effects of T3 on TRH production and on thyroid releasing hormone (TRH) receptor expression. A decrease in T3 feedback in hypothyroidism may induce an increase in hypothalamic TRH production and in the number of TRH receptors in the lactotroph. Increased TRH action on the lactotroph, in turn, may stimulate PRL secretion (19).

On the contrary Lisuride had no significant effects on serum LH, FSH and TSH before and after four months of its administration in hyperprolactinemic infertile patients as shown in Table 2 which agrees with a study carried by Koizumi (20) who showed that there were no significant changes on the secretion of anterior pituitary hormones (LH, FSH and TSH) after administration of Lisuride.

Dopamine agonist treatment has been reported to correct luteal phase defect associated with hyperprolactinemia (21). If galactorrhea is present, even if the PRL is normal, ovulatory dysfunction responds well to dopamine agonist therapy. In the absence of galactorrhea, a PRL elevation may be subtle (such as an increase in nocturnal peaks), and this could explain occasional good responses to dopamine agonist treatment (22).

This study again demonstrated that Lisuride significantly increased luteal progesterone secretion and decreased serum PRL level in hyperprolactinemic patients after four months of treatment as shown in Table 3 and this result agrees with other studies (23,24) that showed that Lisuride significantly increased luteal progesterone secretion and decreased serum PRL level after four months of treatment. Figure 1 showed a significant inverse correlation between serum PRL and serum progesterone levels. At the same time, no significant correlations were found between serum PRL and serum LH, FSH and TSH.

Hyperprolactinemia is usually associated with anovulation, as exemplified by postpartum lactational amenorrhea and the galactorrhea-amenorrhea syndrome. Increased levels of PRL inhibit the hypothalamic-pituitary-ovarian axis. Both opioid peptides and hypothalamic dopamine regulate the pulsatile secretion of luteinizing hormone releasing hormone (LHRH). Hyperprolactinemia inhibits LHRH activity by interacting with the hypothalamic dopaminergic and opioidergic systems through a short-loop feedback mechanism or by a direct effect on LHRH neurons, in which PRL receptors are expressed. Both possibilities are consistent with the observation that suppression of PRL by the dopamine receptor agonist restores ovulatory function (25).

This study showed that Lisuride improved fertility in most infertile women due to hyperprolactinemia via restoring ovarian function. Table 4 indicated that 46% of the cases became pregnant after four months of Lisuride treatment which agrees with other studies which showed that more than one third of hyperprolactinemic infertile patients became pregnant after 4 months of using Lisuride (26).

Amenorrhea is sometimes associated with elevated PRL levels and this is due to PRL inhibition of the pulsatile secretion of gonadotropine releasing hormone (GnRH). The pituitary glands in these patients respond normally to GnRH (27). Nevertheless, treatment that lowers the circulating levels of PRL restores ovarian responsiveness and menstrual function. This is true whether the treatment consists of removal of a prolactin-secreting tumor or suppression of PRL secretion. Interestingly, postmenopausal women with elevated levels of PRL do not experience vasomotor symptoms (hot flushes) until PRL levels are restored to normal (28).

Moreover this study showed that Lisuride effectively restored normal menstrual cycles in 66.66% of amenorrheic patients and 87.5% of oligomenorrheic patients due to hyperprolactinemia as shown in Table 5. This agreed with the results of other research which showed restoration of menstrual cycle in more than 80% after three months of Lisuride therapy (29, 24, and 26).

The most common cause of galactorrhea is hyperprolactinemia (30). It is likely that most patients with so-called idiopathic galactorrhea with amenorrhea harbor microprolactinomas. Fifty-percent of patients with acromegaly also have hyperprolactinemia. Even in the absence of hyperprolactinemia, human GH is a potent lactogen and can cause galactorrhea when elevated (31). Treating the underlying cause of galactorrhea is usually effective. Treating prolactinomas with dopamine agonists reduces tumor size and PRL, and alleviates galactorrhea. If a pituitary tumor is not PRL-secreting, high PRL levels are normalized and galactorrhea is reduced by dopamine agonists but the underlying disorder is not addressed. For medication-induced galactorrhea, an alternative medication might be tried. Galactorrhea related to hypothyroidism should be treated with thyroid hormone replacement. If the galactorrhea is entirely due to inadequate thyroid hormone, thyroxin (T4) therapy should normalize both TSH and PRL secretion and suppress nonpuerperal galactorrhea (32).

Furthermore Lisuride effectively and significantly improved patients who presented with galactorrhea. In this study 32% of the cases presented with hyperprolactinemia-galactorrhea syndrome and more than 93% of these cases improved, as shown in Table 5. This result is similar to other studies which revealed that Lisuride effectively treated galactorrhea in most patients (33, 26, 17, and 34).

Side effects of dopamine agonists are common. The most serious side effect, postural hypotension, which can cause loss of consciousness, occurs infrequently and can often be avoided by careful dosing (35). Dopamine agonists may cause nausea, headache, lightheadedness, orthostatic hypotension, and fatigue. Psychiatric manifestations occasionally occur even at lower doses and may take months to resolve. Erythromelalgia occurs rarely. High dosages of ergot-derived preparations may cause cold induced peripheral digital vasospasm. Pulmonary
infiltrates may occur with chronic high-dosage therapy. Dopamine agonist therapy during the early weeks of pregnancy has not been associated with an increased risk of spontaneous abortion or congenital malformations (10).

Patients using Lisuride in this study developed side effects such as nausea and dizziness in 26% of the cases due to stimulation of dopamine receptors which is shown in Table 6. These side effects were mild and disappeared after a few days. Such findings are in accord with the findings of other studies that show that Lisuride has few, and mild, side effects and is more tolerable than bromocriptine (18, 23, 27).

Toxic effects on the kidneys related to medications are both common and expected. Any drugs have nephrotoxic potential and some of them can cause more than one pattern of injury (36). Glomerular, tubular and renal interstitial cells frequently encounter concentrations of medications and their metabolites, which can induce changes in kidney function and structure. Renal toxicity can be a result of hemodynamic changes, direct injury to cells and tissue, inflammatory tissue injury, and/or obstruction of renal excretion. Detection is often delayed until an overt change in renal functional capacity is measured as an increase in serum blood urea, nitrogen or creatinine (37).

Lisuride had no significant effects on kidney function parameters (blood urea, serum creatinine, creatinine clearance) as shown in Table 7 because only 0.05% of the dose excreted unchanged in urine in 24 hours (38). Review of the literature showed no study to agree or disagree with this finding.

Conclusions
1. Hyperprolactinemia is one of the important causes of female infertility.
2. Lisuride is one of the dopamine agonists that significantly decreases serum prolactin level to normal values.
3. Lisuride restores ovarian function and induces ovulation so that improves infertility due to hyperprolactinemia.
4. Lisuride regulates menstrual cycle abnormalities due to hyperprolactinemia.
5. Lisuride has no significant effect on serum LH, FSH and TSH levels.
6. Lisuride significantly increases luteal progesterone secretion especially in women with corpus luteum insufficiency.
7. Lisuride has no undesirable effects on kidneys, so it can be used safely.
8. Lisuride has mild and tolerable side effects.

References


ABSTRACT

Background: Psoriasis is a chronic inflammatory skin disease characterized by an accelerated turnover of epidermal cells and an incomplete differentiation in epidermis with lesion. However, the exact etiology of psoriasis is unknown. Abnormalities in essential fatty acid metabolism, free radical generation, lipid peroxidation, and release of lymphokines have been proposed.

Objective: To evaluate the serum lipids and oxidant / antioxidant levels in psoriatic patients.

Methods: The study group included 94 patients with psoriasis, and 100 sex- and age-matched healthy volunteers. Blood lipid profile, Malondialdehyde and total antioxidant capacity were determined using commercial kits.

Results: The mean levels of serum lipids (triglyceride, very low density lipoprotein, low density lipoprotein, and total cholesterol) and malondialdehyde in patients with psoriasis were found to be significantly higher than those of healthy subjects. High density lipoprotein and total antioxidant capacity mean serum levels were significantly lower in psoriatic patients compared to control.

Conclusion: This study finding suggests that increased reactive oxygen species along with insufficient total antioxidant capacity may be involved in the pathogenesis of psoriasis. Furthermore, this work strengthens the association between psoriasis and dyslipidemia.

Key Words: Psoriasis, Triglyceride, VLDL, HDL, LDL, Cholesterol, MDA, TAC, Dyslipidemia.

Introduction

Psoriasis is an immune-inflammatory mediated disease with an estimated prevalence of 2.3% in the Iraqi population [1]. The prevalence varies in different geographical regions of the world [2]. Psoriasis primarily affects the skin and sometimes the joints, presenting as inflammation, and pruritic and sometimes painful, skin lesions. Patients with psoriasis are not only burdened with its symptoms, but also have an increased likelihood of several debilitating and life threatening comorbidities [3].

Biochemical Changes in Psoriasis: 1. Lipid Profile, Oxidant and Antioxidant Markers

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The chronic inflammatory course of psoriasis is also thought to predispose patients to metabolic changes and inflammatory processes that may lead to other metabolic and inflammatory diseases [4]. Several reported studies demonstrate an association with metabolic changes such as dyslipidemia [5-10]. However, others failed to demonstrate such an association between psoriasis and dyslipidemia [11-14]. Furthermore, Baz et al reported a change in oxidant and antioxidants in psoriatic patients [15]. In this study, our purpose was to investigate the lipid profile, and oxidant/antioxidant status in patients with psoriasis.

Materials and Methods

Study population

Subjects for this case-control study were selected from Community-Based Health Promotion Research [CBHPR], that was conducted by Tikrit University College of Medicine [TUCOM], Iraq. CBHPR was performed in Salahuldean Governorate as part of research programmes conducted by faculty members of TUCOM. One of these is the Regional Study of Dermatologic Diseases [RSDD]. This study was conducted between May 2007 and May 2009 in the Dermatology Clinic, Tikrit, Iraq. Ninety-four patients with psoriasis (53 men and 41 women, aged 11 to 64 years) with a mean age of 29 ± 13.6, were included in the study. One hundred age and sex matched healthy individuals (50 women and 50 men, between 1 and 63 years of age) with a mean age of 30 ± 14.7, were selected as controls. Both patients and controls had no history of any topical or systemic drug therapy for at least one month prior to blood collection and none of them had any other co-existing disease. All patients and control subjects were examined for serum Triglycerides, High Density Lipoprotein [HDL], Total Cholesterol [TC], Malondialdehyde [MDA] and Total Antioxidant Capacity [TAC]. The study was approved by the Ethical Committee of Tikrit University College of Medicine and written informed consent was taken from each participant.
Determination of Total Antioxidant Capacity (TAC):
The materials used in the determination of TAC in serum were a gift from Dr. V. Tsaoousis, Medicon Hellas SA, Gerakas, Greece. They include, 2,2'-Azobis-(2-aminodipropene)dihydrochloride (ABAP), 6-hydroxyl-2,5,7,8-tetramethylchromane-2-carboxylic acid (Trolox C) from Sigma-Aldrich. ABAP was dissolved just before use with a 10 mM phosphate buffer (pH 7.4) at a concentration of 5 mg/ml. Trolox came from the association of Saffron producers, Krokos, Kozani, Greece. Trolox stock solution was prepared in phosphate buffer (10 mM, pH 7.4) at a concentration of 20 µM with buffer.

The method for serum TAC determination was as previously described by Kampa M et al [16]. In brief, in each tube 400 µl of crocin and 200 µl of serum sample were pipetted. The reaction was initiated with the addition of 400 µl of pre-warmed (370°C) ABAP (5 mg/ml) and crocin bleaching was made by incubating the plate in an oven for 60 - 75 minutes. Blanks consisting of crocin, serum samples and phosphate buffer (400, 200, 400 µl respectively) were run in parallel. The absorbance was measured at 450 nm. A standard curve of the water soluble synthetic antioxidant Trolox, prepared prior to use, ranging from 0 - 10 µg/ml, was equally assayed under the same conditions.

Determination of Triglycerides:
Serum triglycerides were determined by using enzymatic colorimetric test kit, a product of Linear Chemicals, Spain. The test was performed according to manufacturer instructions. The method is based on the enzymatic hydrolysis of serum triglyceride to glycerol and free fatty acids (FFA) by lipoprotein lipase (LPL). The glycerol is phosphorylated by adenosine triphosphate (ATP) in the presence of glycerokinase (GK) to form glycerol - 3 - phosphate (G - 3 '-P) and adenosine diphosphate (ADP). G-3-P is oxidized by glycerophosphate oxidase (GPO) to form dihydroxyacetone phosphate (DHAP) and hydrogen peroxide. A red chromigen is produced by the peroxidase (POD) catalyzed coupling of 4- aminoantipyrine (4-AA) and phenol with hydrogen peroxide, proportional to the concentration of triglyceride in the sample. Absorbance was measured at 500 nm.

Determination of Malondialdehyde:
As index of lipid peroxidation, serum MDA concentration was determined by measuring the thiobarbituric acid reactive substances (TBARS) according to the Spectrophotometric method of Janero [17]. The TBARS was determined using OXITEK TBARS Assay kit from Zeptometrix Company. A 100 ul of sodium doedecyl sulfate was added to the tubes that contain either serum sample or standard and mixed thoroughly. Then 2.5 ml of thiobarbituric acid/ buffer reagent was added down the side of each tube. The tube was covered and incubated at 95 o C for 60 minutes. The tube was then removed and cooled to room temperature in an ice bath for 10 minutes. After cooling the samples centrifuged at 3000 rpm for 15 minutes. The supernatant was removed from samples for analysis. The absorbance of supernatant was measured at 532 nm. Determination of MDA equivalent in µmol/ l in samples was by interpretation from standard curve.

Determination of Total Cholesterol:
Serum total cholesterol was determined using an enzymatic colorimetric test kit, a product of Biomaghreb, France. The indicator quinonemine is formed from hydrogen peroxide and 4- aminoantipyrine in the presence of phenol and peroxidase. This method is linear up to 600 mg/dl and if the cholesterol concentration is greater than 600 mg/dl, we dilute the serum sample 1:2 with saline solution and repeat the test. Then the concentration is calculated by multiplying the results by 2. The test was performed according to manufacturer instructions. The quantity of red dye formed is proportional to serum concentration of cholesterol. Absorbance measured at wave length of 505 nm.

Determination of Very Low Density Lipoprotein:
VLDL was determined by division of triglycerides by 5.

Determination of Low Density Lipoprotein:
LDL was determined by the following formula:

\[
LDL = \text{Total cholesterol} - (\text{VLDL} + \text{HDL})
\]

Determination of Oxidation Index:
The oxidation index was determined by using the following equation:

\[
\text{Oxidation Index} = \frac{\text{Malondialdehyde in µmol }/ \text{l}}{1000 \times \text{Total Antioxidant Capacity in µmol/l}}
\]

Statistical Analysis:
The values are reported as mean ± SD and 95% confidence interval. For statistical analysis between groups paired t test was used. Pearson test was used for correlation analysis. The levels of each marker were compared between the study groups and control group, using SPSS computer package. P values of < 0.05 were considered significant.
Results

This study indicated that there were no significant differences in mean age of patients and controls groups, even when the analysis was performed according to gender (Tables 1-4).

Serum HDL mean value was significantly (P=0.0001) lower in male (37.6 ± 2.5 mg/dl) as compared to female (45.2 ± 5.5 mg/dl) psoriatic patients. In addition, the mean serum values of triglyceride and VLDL were significantly higher in male (Triglyceride 184 ± 42.8 mg/dl, P = 0.015; VLDL = 36.8 ± 8.6, P =0.013) as compared to female psoriatic patients (Triglyceride = 164.9 ± 41.6 mg/dl; VLDL = 32.8 ± 8.4 mg/dl). In contrast, there were no significant differences in serum mean values of LDL, TC, MDA, and TAC between male and female psoriasis patients (Table 1).

The mean serum values of triglycerides, VLDL, LDL and MDA were significantly (P=0.001 to 0.000) higher in male psoriasis patients compared with male controls (Table 2). Furthermore, HDL and TAC serum mean values were significantly lower (P=0.000) in male patients compared with male controls. However, TC mean serum value was lower in male patients than in male controls, but the difference was statistically not significant (Table 2).

In female psoriatic patients, the mean serum values of triglycerides, VLDL, LDL and MDA were significantly higher in female psoriasis patients (P=0.001 - 0.000) compared to female controls (Table 3). Total cholesterol mean serum value was higher in female psoriatic patients (198 ± 27.9 mg/dl) compared with female controls (188.8 ± 27.1 mg/dl), but the difference was not significant. However, HDL and TAC mean serum values were significantly lower (P=0.000) in female psoriatic patients compared with female controls (Table 3).

The mean serum values of triglycerides, VLDL, LDL, TC, and MDA were significantly higher in psoriatic patients compared with control subjects. In addition, HDL and TAC mean serum values were significantly (P=0.000) lower in psoriatic patients compared with controls (Table 4).

There were significant correlations between MDA serum levels in psoriatic patients and serum levels of triglycerides (r=0.58; P=0.000), VLDL (r= 0.56; P= 0.000), LDL (r=0.68; P=0.000), TC (r = 0.63; P =0.000). However, there was an inverse correlation between serum MDA levels and serum HDL levels(r= - 0.36; P=0.000). Furthermore, there was a significant correlation between psoriatic patients’ age and serum MDA levels (r= 0.57; P=0.000) (Table 5).

Total antioxidant capacity serum levels were with inverse correlations with age (r= -0.51; P=0.000), triglyceride (r= - 0.58; P=0.000), VLDL (r = - 0.54; P= 0.000), LDL (r = -0.65; P=0.000) and TC (r= - 0.97; P=0.000). In contrast, there was significant correlation between TAC serum levels and HDL serum levels (r=0.65; P=0.000) (Table 5). The oxidation index was higher in patients with psoriasis as compared to controls, whether the analysis performed depends on gender or collected together (Table 6).

Table 1: Lipid profile, Malondialdehyde, and total antioxidant capacity in patients with psoriasis according to gender
### Table 2: Lipid profile, Malondialdehyde, and total antioxidant capacity comparison between psoriatic and control male groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients Male Mean (SD) 95% Confidence interval</th>
<th>Control Male Mean (SD) 95% Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in year</td>
<td>29.4 (12.5) 25.9 - 32.9</td>
<td>31.2 (13.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride mg/dl</td>
<td>184 (42.8) 174.3 - 193.7</td>
<td>121.7 (25.8) 110.7 - 130.7</td>
<td>0.000</td>
</tr>
<tr>
<td>Very Low Density Lipoprotein mg/dl</td>
<td>36.8 (8.6) 34.9 - 38.7</td>
<td>24.2 (5.1) 22.2 - 26.2</td>
<td>0.000</td>
</tr>
<tr>
<td>High Density Lipoprotein mg/dl</td>
<td>37.6 (2.5) 36.8 - 38.4</td>
<td>55.7 (3.2) 54.9 - 56.5</td>
<td>0.000</td>
</tr>
<tr>
<td>Low Density Lipoprotein mg/dl</td>
<td>126.3 (20.2) 121.1 - 131.3</td>
<td>114.5 (17) 109.2 - 119.7</td>
<td>0.019</td>
</tr>
<tr>
<td>Total cholesterol mg/dl</td>
<td>200.1 (26.3) 193.3 - 207</td>
<td>192.3 (23.9) 185.3 - 199.4</td>
<td>NS</td>
</tr>
<tr>
<td>Malondialdehyde µmol/l</td>
<td>4.5 (1.4) 4.0 - 4.8</td>
<td>2.2 (0.27) 2.1 - 2.3</td>
<td>0.000</td>
</tr>
<tr>
<td>Total antioxidant capacity µmol/l</td>
<td>757 (101) 729 - 789</td>
<td>1047 (207) 999 - 1095</td>
<td>0.000</td>
</tr>
</tbody>
</table>

### Table 3: Lipid profile, Malondialdehyde, and total antioxidant capacity comparison between psoriatic and control female groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients Female Mean (SD) 95% Confidence interval</th>
<th>Control Female Mean (SD) 95% Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in year</td>
<td>29.0 (13.6) 24.6 - 33.4</td>
<td>30 (14.7) 25.6 - 34.0</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride mg/dl</td>
<td>164.9 (41.6) 153.8 - 176.0</td>
<td>108.7 (30.3) 98.6 - 118.8</td>
<td>0.000</td>
</tr>
<tr>
<td>Very Low Density Lipoprotein mg/dl</td>
<td>32.8 (8.4) 30.6 - 35.1</td>
<td>21.7 (5.6) 19.7 - 23.7</td>
<td>0.000</td>
</tr>
<tr>
<td>High Density Lipoprotein mg/dl</td>
<td>45.2 (5.5) 43.8 - 46.7</td>
<td>54.2 (4.2) 52.9 - 55.6</td>
<td>0.000</td>
</tr>
<tr>
<td>Low Density Lipoprotein mg/dl</td>
<td>120.3 (22) 114.1 - 126.5</td>
<td>112.5 (18.1) 106.9 - 118.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Total cholesterol mg/dl</td>
<td>198 (27.9) 189.4 - 206.5</td>
<td>188.8 (27.1) 181.0 - 196.5</td>
<td>NS</td>
</tr>
<tr>
<td>Malondialdehyde µmol/l</td>
<td>4.6 (1.9) 4.0 - 5.2</td>
<td>2.35 (0.31) 2.2 - 2.4</td>
<td>0.000</td>
</tr>
<tr>
<td>Total antioxidant capacity µmol/l</td>
<td>752 (144) 707 - 796</td>
<td>1044 (198) 989 - 1099</td>
<td>0.000</td>
</tr>
</tbody>
</table>
### Table 4: Comparison between lipid profile, Malondialdehyde and total antioxidant capacity in psoriasis patients and control groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Psoriasis Patients Mean (SD) 95% Confidence interval</th>
<th>Control Subjects Mean (SD) 95% Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in year</td>
<td>29.2 (12.9) 26.5 - 32.0</td>
<td>30.9 (13.9) 27.8 - 33.2</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride mg/dl</td>
<td>175.7 (43.1) 168.3 - 183.1</td>
<td>114.7 (28.7) 107.5 - 121.9</td>
<td>0.000</td>
</tr>
<tr>
<td>Very Low Density Lipoprotein mg/dl</td>
<td>35.1 (8.7) 33.6 - 36.6</td>
<td>22.9 (5.7) 21.5 - 24.4</td>
<td>0.000</td>
</tr>
<tr>
<td>High Density Lipoprotein mg/dl</td>
<td>40.9 (5.6) 40 - 42</td>
<td>54.8 (3.8) 54.0 - 55.9</td>
<td>0.000</td>
</tr>
<tr>
<td>Low Density Lipoprotein mg/dl</td>
<td>123.6 (21.1) 119.7 - 127.6</td>
<td>112.2 (17.5) 109.7 - 117.3</td>
<td>0.0003</td>
</tr>
<tr>
<td>Total cholesterol mg/dl</td>
<td>199.2 (26.9) 193.8 - 204.5</td>
<td>191 (25.4) 185.4 - 195.7</td>
<td>0.023</td>
</tr>
<tr>
<td>Malondialdehyde µmol/l</td>
<td>4.5 (1.6) 4.2 - 4.8</td>
<td>2.31 (0.27) 2.2 - 2.5</td>
<td>0.000</td>
</tr>
<tr>
<td>Total antioxidant capacity µmol/l</td>
<td>755 (121) 730 - 779</td>
<td>1045 (194) 1007 - 1083</td>
<td>0.000</td>
</tr>
</tbody>
</table>

P Values for all correlations = 0.000

### Table 5: Correlation among Malondialdehyde, Total antioxidant capacity, age and lipid profile in patients with psoriasis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Malondialdehyde R² [95% Confidence interval]</th>
<th>Total antioxidant capacity R² [95% Confidence interval]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.57 [0.42 - 0.69]</td>
<td>-0.51 [0.34 - 0.65]</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>0.58 [0.43 - 0.70]</td>
<td>-0.58 [0.43 - 0.70]</td>
</tr>
<tr>
<td>Very Low Density Lipoprotein</td>
<td>0.56 [0.40 - 0.68]</td>
<td>-0.54 [0.38 - 0.67]</td>
</tr>
<tr>
<td>High Density Lipoprotein</td>
<td>-0.36 [0.17 - 0.52]</td>
<td>0.43 [0.25 - 0.58]</td>
</tr>
<tr>
<td>Low Density Lipoprotein</td>
<td>0.68 [0.55 - 0.78]</td>
<td>-0.65 [0.52 - 0.75]</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>0.63 [0.49 - 0.74]</td>
<td>-0.97 [0.96 - 0.98]</td>
</tr>
<tr>
<td>Malondialdehyde</td>
<td>-0.97 [0.96 - 0.98]</td>
<td>-</td>
</tr>
</tbody>
</table>
Discussion

Psoriasis is a common, chronic inflammatory skin disease characterized by a marked increase in keratinocyte proliferation, abnormal differentiation of keratinocytes, prominent alterations in dermal capillary vasculature and the presence of dermal and epidermal mononuclear leukocytes and neutrophils [18]. Increased capacity of chemotaxis and adhesion [19], and increased ROS production in neutrophils [20] have been reported in patients with psoriasis. It has been suggested that generation of ROS from neutrophils, keratinocytes and fibroblasts [20-22] can contribute to neutrophil activation, which plays an important role in the psoriatic process. This evidence supports the view that ROS may play a role in the pathogenesis of psoriasis [23-26].

The present study indicated that serum MDA was significantly higher in subjects with psoriasis compared with controls. In addition, TAC was significantly lower in psoriatic patients as compared to controls. These differences demonstrated whether the analysis was performed for males and females separately and when collected together. Insufficient antioxidant mechanisms may result in increased ROS production during the inflammatory process in psoriasis, which consequently leads to increased lipid peroxidation [14]. This fact may explain why the serum MDA mean value was higher in patients with psoriasis compared to controls and lower TAC mean serum level. ROS induced oxidation of polyunsaturated fatty acids in biological systems results in the formation of lipid peroxidation products such as MDA [27, 28]. The present study findings were consistent with reports of other research groups [29-31] and do not agree with others [32].

In this study we detected a lower serum TAC in patients with psoriasis, than in controls. TAC provides an overall indication of total enzymatic and non-enzymatic antioxidant status. This finding was in accordance with that reported previously [33-35]. However, Severin et al reported that plasma total antioxidant capacity did not differ between psoriasis patients and controls [26]. In our study we detected a decrease in TAC in patients with psoriasis compared with controls, and the serum levels of TAC were inversely correlated to triglyceride, VLDL, LDL, TC, and MDA serum levels of patients with psoriasis. In addition, TAC serum levels significantly correlated to HDL serum levels in patients with psoriasis.

Several reported studies demonstrate an association of psoriasis with dyslipidemia [6-13]. The present study demonstrated increased total cholesterol, LDL, triglyceride, and VLDL serum levels and a reduction in serum HDL in patients with psoriasis compared to controls. A cross sectional study indicated increased TC and triglyceride, decreased HDL and no alteration in LDL in psoriasis patients compared to controls [6]. In a hospital based cross sectional study in Iran, psoriasis patients were shown to have significantly higher mean levels of triglyceride, TC, VLDL, LDL and no alteration in HDL [7]. A cross sectional study of 84 psoriatic patients attending an outpatient hospital based study in Turkey compared with 40 age and sex matched healthy controls from the community, demonstrated higher mean triglyceride, TC, LDL and lower mean HDL for psoriatic patients versus controls [8]. The differences demonstrated in our study were influenced by age for all studied biomarkers in psoriatic patients. In addition, the above differences were influenced by gender, with male patients having significant differences from controls in serum triglyceride, VLDL, and HDL and non-significant differences for LDL, TC, MDA and TAC. Furthermore, comparison of male patients with male controls and female patients with female controls indicated significant differences for all examined biomarkers with the exception of TC. Thus both age and gender influence the lipid profile, and oxidant and antioxidant serum levels in psoriatic patients. According to this finding age and gender were important risk factors in psoriasis, which may lead to subsequent worsening of the disease state and may contribute to systemic complications such as metabolic and cardiovascular diseases. Monitoring of lipid profile, oxidants and antioxidant status in psoriatic patients is of vital importance as markers to prevent subsequent complications of psoriasis.

Several studies using varying population and analytical approaches have found an association between psoriasis and an increased prevalence of diagnosis of hyperlipidemia [5, 6, 9, and 10]. However, several studies demonstrated an association between psoriasis and dyslipidemia, and other reported studies have failed to find a consistent association [11-13].
Psoriasis is an immune-inflammatory skin disease and the disease is characterized by T-cell mediated hyperproliferation of keratinocytes and inflammatory processes [14]. In psoriasis there is expansion and activation of Th-1 cells, antigen presenting cells and Th-1 cytokines. Chronic Th-1 inflammation is an important pathophysiology of psoriasis and the inflammatory mediators produced subsequently have pleiotropic effects on lipid metabolism, immune cell trafficking and epidermal proliferation. Therefore, the metabolic aspect of the inflammation, angiogenesis and epidermal hyper-proliferation in psoriasis have the potential to impact on other conditions such as diabetes, atherosclerosis and thrombosis. Conversely, inflammatory molecules and hormones produced in conditions such as obesity, diabetes, and atherosclerosis may influence the pathogenesis of psoriasis by promoting susceptibility to the development of psoriasis or through increasing the severity of established psoriasis. It seems to be that chronic inflammation in psoriasis and continuous production of different cytokines, subsequently may lead to abnormalities in metabolism, inflammation and immune response. Thus it may be suggested that psoriasis starts as a local inflammatory disease in which genetics play a crucial role. Consequently due to multiple cascade sequences and abnormalities in immune response, inflammation and metabolism, may be converted into a systemic disease characterized by disequilibrium in oxidants and antioxidants, abnormal metabolic pathways and immune responses.

In conclusion, this study finding suggests that increased reactive oxygen species along with insufficient total antioxidant capacity may be involved in the pathogenesis of psoriasis. Furthermore, this work strengthens the association between psoriasis and dyslipidemia.

Recommendations
On the basis of the existing knowledge and these study findings, we suggest:

1. There is a need to develop new guidelines for psoriatic monitoring related to metabolic and inflammatory biomarkers, specifically as a risk factor for development of diabetes and cardiovascular diseases.

2. Additional well designed epidemiological studies in a large scale and broadly representative psoriasis population are necessary to determine the role of:

2.1 Metabolic disorders as a risk factor in developing psoriasis.

2.2 Comorbid metabolic disorder in modifying the severity of existing psoriasis.

2.3 Psoriasis activity and severity as independent risk factors for metabolic disorders, atherosclerosis, and myocardial infarction

2.4 Psoriasis treatment in ameliorating the risk for development of diabetes and cardiovascular diseases.

3. Performance of a large scale population study that clarifies the abnormalities in lipid profile, oxidants and antioxidants markers.

4. Performance of clinical trials to evaluate the therapeutic activity of drug combination for altering the dyslipidemia associated with psoriasis.

References


Abstract

Objectives: To compare between local and general anesthesia in patients undergoing cataract surgery. Results, complication, patient satisfaction and duration of surgery were compared in both groups.

Patients and methods: This was a prospective study that was conducted at King Hussein Medical Center during the period between January 2009 and July 2009. Two hundred patients undergoing cataract extraction with intraocular lens implantation were enrolled in the study. Half of them had the procedure under local anesthesia and the other half under general anesthesia. Duration of surgery and patient stay in recovery room, were compared in the two groups. Patient satisfaction using an analogue score, and complications, were also assessed.

Results: The mean age of patients was 67.3 years with a male to female ratio of 1.2:1. The two groups were comparable regarding patient’s age and presence of medical illnesses such as diabetes and hypertension. The mean duration of surgery for local anesthesia group (group 1) was 34.6 minutes compared to 42.3 minutes in the general anesthesia group (Group 2). Mean duration of patient’s stay in operating room and recovery room was 66.1 minute and 113.7 minutes in Group 1 and Group 2 respectively. Number of admissions was more in Group 2 and patient satisfaction score was higher in Group 1.

Conclusion: Cataract extraction under local anesthesia is less time consuming than general anesthesia with less number of admissions, complications and better patient satisfaction.

Keywords: Cataract extraction, local, general, anesthesia, satisfaction.

Introduction

Cataract surgery is performed under either local or general anesthesia, mostly based on the surgeon’s preference and the patient’s cooperation (1). Local anesthesia is becoming more popular than it used to be ten years ago as surgeons are becoming more experienced with it (2-4).

Patients having cataract surgery are usually elderly and have risk factors for ischemic heart disease, diabetes and hypertension that increase the risk of morbidity and mortality of general anesthesia (5-9). The aim of this study was to compare between local and general anesthesia in patients undergoing cataract surgery. Results, complication, patient satisfaction and duration of surgery were compared in both groups.

Methods

A prospective study that was conducted at King Hussein Medical Center during the period between January 2009 and July 2009. Two hundred patients undergoing cataract extraction with intraocular lens implantation were enrolled in the study. Half of them had the procedure under local anesthesia and the other half under general anesthesia. Duration of surgery, patient stay in recovery room, and number of admissions were compared in the two groups. Patient satisfaction using an analogue score and complications were also assessed.

All surgeries were done by the same surgeon in order to decrease bias regarding duration of surgery. In addition, the anesthesia team and settings were the same. All patients were fasted overnight and did not receive any pre medication. On arrival at the operating room intravenous access was established. Monitoring consisted of electrocardiography, pulse oximetry and blood pressure measurement. The general anesthesia group received fentanyl (1-2 microgram/kg) and propofol (2mg/kg) for induction. Laryngeal mask was used and vecuronium (0.1mg/kg) was used as muscle relaxant. Anesthesia was maintained using sevoflurane at an end expiratory concentration of 1%. The lungs were ventilated with O2/N2O in a fraction of 0.3: 0.7 using fresh gas flow at 1 litre/minute. Ventilation was adjusted to keep end tidal carbon dioxide within the normal range (36-40mmHg). In the local anesthesia group, local anesthesia was given by the surgeon. A 4 mL injection of a 1:1 mixture of lignocaine 2% and bupivacaine 0.5% was given via retrobulbar cannula.

A retrospective file analysis was also done for all cataract surgeries done during the years 2005 and 2008 at King Hussein Medical Center. Data collected included number of surgeries during the whole year, anesthesia choice, complications and number of admissions.
Results
The mean age of patients was 67.3 years with a male to female ratio of 1.2:1. The two groups were comparable regarding patient’s age and presence of medical illnesses such as diabetes and hypertension (Table 1). The mean duration of surgery for the local anesthesia group (Group 1) was 34.6 minutes compared to 42.3 minutes in the general anesthesia group (Group 2). Mean duration of patient’s stay in operating room and recovery room was 66.1 minute and 113.7 minutes in Group 1 and Group 2 respectively. Number of admissions was more in Group 2 and patient satisfaction score was higher in Group 1 (Table 2). Anesthesia related complications (bradycardia of < 15% of basal heart rate, decrease in oxygen saturation ratio of < 15%, increase of systolic or diastolic pressure of > 15% were more common in Group 2.

Retrospective file analysis for two different years (2005 and 2008) showed a higher number of cataract surgeries done with shift towards local anesthesia, less complications and admissions (Table 3).

<table>
<thead>
<tr>
<th>Feature</th>
<th>Local anesthesia group</th>
<th>General anesthesia group</th>
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</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Mean age and range</td>
<td>67.1 (31.6-82.7) years</td>
<td>67.5 (30.4-79.3) years</td>
</tr>
<tr>
<td>Male: female ratio</td>
<td>1:2:1</td>
<td>1:2:1</td>
</tr>
<tr>
<td>Number of patients with medical illness</td>
<td>45</td>
<td>43</td>
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</tbody>
</table>

Table 1: Demographic data

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<th>Feature</th>
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<th>General anesthesia group</th>
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<tbody>
<tr>
<td>Mean duration of surgery</td>
<td>34.6 min</td>
<td>42.3 min</td>
</tr>
<tr>
<td>Mean duration of stay in operating room and recovery room</td>
<td>66.1 min</td>
<td>113.7 min</td>
</tr>
<tr>
<td>Number of admissions</td>
<td>12</td>
<td>77</td>
</tr>
<tr>
<td>Mean satisfaction score</td>
<td>8.4</td>
<td>2.2</td>
</tr>
<tr>
<td>Anesthesia related complications</td>
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<td>4</td>
</tr>
</tbody>
</table>

Table 2: Data analysis in two groups

<table>
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<tr>
<th>Feature</th>
<th>2005</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of surgeries</td>
<td>617</td>
<td>823</td>
</tr>
<tr>
<td>Local:general anesthesia</td>
<td>209:408</td>
<td>619:204</td>
</tr>
<tr>
<td>Number of admissions</td>
<td>495</td>
<td>69</td>
</tr>
<tr>
<td>Anesthesia related complications</td>
<td>5</td>
<td>39</td>
</tr>
</tbody>
</table>

Table 3: Retrospective analysis during cataract surgeries in years 2005 and 2008

Discussion
Local anesthesia is becoming the anesthetic technique of choice for surgery on the eye in many instances (10). The expansion of day-case facilities has encouraged its use, and the development of less invasive surgical techniques has rendered general anesthesia largely unnecessary (11-12).

The results of our study showed that both groups were comparable regarding the patient’s age, gender and presence of medical illnesses. The latter included diabetes mellitus, hypertension and ischemic heart disease. To minimize bias, all surgeries were done by the same surgeon with the same approach. Local anesthesia was administered by surgeon and general anesthesia was given using the same anesthetic for all patients.

Table 2 shows the results of our study. Cataract surgery was less time consuming under local anesthesia compared to general anesthesia (34.6 minutes versus 42.3 minutes).
Duration of patient stay in recovery room was also less in the local anesthesia group. 12% of patients were admitted in Group 1 compared to 77% in Group 2. These points clearly show that local anesthesia decreases the consumption of hospital resources and human resources.

To assess patient satisfaction, we used an analogue scale. It is a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. For example, the amount of pain that a patient feels ranges across a continuum from none to an extreme amount of pain. One drawback is that such an assessment is highly subjective. These scales are of most value when looking at change within individuals, and are of less value for comparing across a group of individuals at one time point. The mean satisfaction score was 8.8 out of 10 for Group 1 and 2.2 for Group 2.

Anesthesia related complications (bradycardia of < 15% of basal heart rate, decrease in oxygen saturation ratio of < 15%, increase of systolic or diastolic pressure of > 15% were more common in Group 2 (4% compared to zero). Only 1 patient of Group 1 had retrobulbar hemorrhage that occurred after injection of the local anesthetic agent.

A retrospective file analysis during the years 2005 and 2008 showed an increase in number of surgeries done (823 versus 623) though there was no increase in number of surgical sessions. The explanation for this is that we are doing more local surgeries that are less time consuming thus increasing the number of surgeries done in the same session. In addition, number of admissions and anesthesia related complications decreased dramatically.

In conclusion, cataract extraction under local anesthesia is less time consuming than general anesthesia with less number of admissions, complications and better patient satisfaction.

References
Laparoscopic versus open cholecystectomy in the treatment of acute cholecystitis

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However, the patients are selected in some of these studies, and some are multicentric; additionally, certain studies have recently found that LC is a safe, efficient technique for cases of AC.(5-7)

Some of these studies do not compare the results of LC with those of OC, which is the safest technique for managing AC. This study describes a series of patients with AC who were treated with LC or OC and assesses the results of both techniques.

Patients and Methods
Between July 2008 and July 2009 we enrolled in the trial consecutive patients with acute cholecystitis, who gave informed consent to take part.

Preoperative data collected were characteristics of the patients, history, and the findings of physical examination, laboratory tests, and ultrasonography. In the LC group, patients with suspected bile-duct stones underwent preoperative endoscopic retrograde cholangiography followed by endoscopic papillotomy and stone extraction if necessary. In the OC group, when bile-duct stones were suspected intraoperative cholangiography was done. In both groups, antibiotics (intravenous cefuroxime and metronidazole) were given.

The final diagnosis of acute cholecystitis was made on the basis of clinical and operative findings and histology. All patients had constant right upper abdominal pain, lasting at least 24 hours. In addition, we required that at least three
of the following five criteria were met: temperature above 37.0°C; leukocyte count more than 10X109/L; thickening of gallbladder wall on ultrasonography; and fluid or edema in the pericholecystic space on ultrasonography.

Procedures
LC - all operations were done by the investigators. Two 10 mm trocars and two 5 mm trocars were used generally. The gallbladder was dissected by blunt technique and electrocauterisation, beginning from the neck of the organ. If inflammation, diffuse bleeding, or obesity caused excessive difficulties, one additional trocar was used for continuous suction or retraction of the fatty, inflamed tissues around the gallbladder. Aspiration of liquid contents of the gallbladder facilitated its grasping and dissection in several cases.

If there was extreme inflammation of the pericystic space distorting the anatomy and preventing exact dissection of the Calot’s triangle, dissection was started from the fundus and proceeded towards the neck of the gallbladder. This approach facilitated the identification of the cystic duct and artery and the common bile duct. The cystic duct and artery were closed with clips or by ligation with endoloop.

To avoid wound infection, the gallbladder was inserted into a disposable plastic bag (endopouch) before it was removed from the abdominal cavity. The abdominal cavity was extensively irrigated and all fluid was aspirated before closure. When indicated, the abdominal cavity was drained externally.

OC - right subcostal incision was used. Dissection was started from the fundus of the gallbladder and proceeded towards the junction of the cystic duct and the common bile duct. If indicated, cholangiography was done.

Postoperative follow-up
All patients were called for examination 1-2 months after the operation. The primary endpoints were hospital mortality and morbidity, length of hospital stay, and length of sick leave from work. The secondary endpoints were operating time and the rate of conversion to open surgery.

Statistical methods
In previous reports, the overall complication rate of OC in acute cholecystitis is 10 - 15%. Based on our preliminary studies and reasonable previous estimates, we expected the complication rate in LC to be somewhat smaller, and convalescence some days shorter. We did no formal sample-size calculation, because the reported complication rates of OC are based on studies from some time ago and vary significantly, and because no reliable estimate of the complication rate of LC in acute cholecystitis was available at the time of study design.

The results were analyzed by intention to treat; all patients for whom conversion to standard cholecystectomy was needed were included. Student’s t test was used for statistical analysis. Duration of hospital stay showed a skewed distribution, so the Mann-Whitney U test was used for statistical analysis. A p value less than 0.05 was taken as significant.

Results
All the patients met the clinical and operative criteria for acute or gangrenous cholecystitis. In the LC group, 11 patients had gangrene and two had empyema. In the OC group, the corresponding numbers were ten and three. One patient in each group had perforation of the gangrenous gallbladder with diffuse peritonitis. Of the 21 patients with gangrenous gallbladders, six had normal thickness of the gallbladder wall on ultrasonography. In these cases, at operation the gallbladder was found to be fragile with thin walls and complete exfoliation of the mucosa.

In the OC group, one patient had an anaerobic infection (Clostridium perfringens) causing gangrene and perforation of the gallbladder. In the LC group, two patients had Klebsiella pneumoniae with mixed aerobic infection in the gallbladder. In 16 patients in the LC group, there was extreme hyperaemia of the gallbladder with profuse oozing due to long duration of the disease, and an additional trocar had to be inserted for continuous suction of the diffuse bleeding.

Preoperative endoscopic retrograde cholangiography was done in four patients in the LC group, but endoscopic papillotomy and stone extraction were needed in only one patient. In the OC group, intraoperative cholangiography was done in 3 patients, and stones were found and removed in one patient.

Operative findings
In four patients in the LC group, the anatomy of Calot’s triangle was obscured by inflammation and local perforation of the gallbladder. In these patients the dissection started from the fundus, so that the bile duct and arterial anatomy could be clearly visualised and dissected safely. In seven patients (15%) in the LC group, conversion to OC was needed: in six cases the reason was gallbladder necrosis and local perforation with pericystic fluid collection causing distortion of the anatomy of the Calot’s triangle; one patient had perforation of the gallbladder and diffuse peritonitis.

The mean operating time was 88 minutes in the LC group and 77 minutes in the OC group.

There were no deaths and no bile-duct lesions in either group. The postoperative hospital stay was significantly shorter in the LC group than in the OC group (2 days for LC; 5 days for OC).
Postoperative outcome

Most of the patients were retired or unemployed and needed no sick leave. Among those who did need sick leave, the mean time was shorter in the LC group than in the OC group.

The complication rate was significantly higher in the OC group (20%) than in the LC group (14%). In the OC group, four patients (aged 35 - 75) had major and four patients (aged 47 - 88) had minor complications. The major complications were pneumonia and sepsis (aged 72), serious wound infection (two patients; aged 35 and 53), and retained stone in the common bile duct (aged 69). The minor complications were diarrhoea (two patients), and urinary infection (two patients).

In the LC group, five patients (aged 39 - 74) had major and one patient had minor complications. The major complications were pneumonia (three patients aged 40 - 70), post operative intestinal obstruction (two patients aged 52 and 76). The minor complication was urine retention in one patient.

Discussion

Even though the laparoscopic approach has become the method of choice for elective cholecystectomy, (8) conventional OC has remained the treatment of choice for acute cholecystitis. However, the mortality rate of OC in acute cholecystitis is high, ranging from 3% to 5% in patients older than 60 years, and increasing to 6 - 30% in high-risk - and critically ill patients.(9,10) The morbidity rate is also high - 10 - 25%, depending on the age of the patient.(11) Several retrospective studies have suggested that LC can be used safely for acute, non-gangrenous cholecystitis,(1, 6 - 8) However, we are not aware of any previous prospective comparison between LC and OC in acute or gangrenous cholecystitis.

In our series, there were no deaths in either group, but there were significantly more complications in the OC group than in the LC group. The morbidity rate of OC in our series is similar to the rates in previous retrospective studies (major complications 20% vs. 13 - 22% (12, 13)). Previous studies showed that the complication rate in OC increases in elderly patients (older than 60 years) and in those with severe systemic disease, as well as in patients with gangrenous cholecystitis. In our series, the two groups had similarly high proportions of patients older than 60 years, high-risk patients (American Society of Anesthesiologists classification III-IV), and patients with gangrenous cholecystitis.

Bile leakage (without overt bile-duct injury) is the most common biliary-tract complication of elective LC, with a frequency of 0.2 - 2.2% (14-16) The frequency of bile-duct injury is 0.1 - 0.25% in OC and 0.3 - 0.6% in LC.(17) The most common cause of major bile-duct injury during LC is mistaking of the common bile duct for the cystic duct. In many patients with acute cholecystitis, the cystic duct is indurated, thin, and shortened, lying in intimate contact with the common bile duct, which makes its identification difficult for the surgeon.

No bile-duct injuries or bile leakages occurred in our series. We believe the key to safe biliary surgery is careful scrutiny of the anatomy of Calot’s triangle and complete blunt dissection before division of any vital structures. This principle cannot be overcome by intraoperative cholangiography or by any other means. In acute cholecystitis intraoperative cholangiography may even be hazardous because the tissues are commonly severely inflamed and friable or even necrotic. Furthermore, cholangiography provides no guarantee against biliary injury and does not reduce the incidence of injury(18-19). Our overall complication rate of 14% in LC (one minor complication) is low compared with previously reported rates of 8 - 23%.(20-21)

The rate of conversion to open surgery (15%) is high compared with that in our series of elective LC (3-5% at our clinic and 6.3% in a collective Finnish series) (22,23) and other reports (1 - 5.0%), (17, 24) but far lower than that in an early series of patients with acute cholecystitis (41 - 57%) (25, 26) On the other hand, it is similar to the rates in later retrospective series (30%), (1, 27) despite the high proportion (41%) of gangrenous and empyematosus gallbladders in this series. The main reason for conversion was technical difficulties related to unclear anatomy.

Our policy in LC has been to undertake preoperative endoscopic retrograde cholangiography (and papillotomy with stone extraction when needed) whenever bile-duct stones are suspected. In this study, preoperative endoscopic retrograde cholangiography was done in four of the 48 patients in the LC group, revealing bile-duct stones in one patient. The same indications were applied for intraoperative cholangiography during open cholecystectomy. However, before the laparoscopic era we used to undertake intraoperative cholangiography routinely, and some surgeons still adhered to the old policy. However, the yield of bile-duct stones was the same - one patient (and one patient had retained bile-duct stones discovered postoperatively). No complications related to bile-duct stone diagnosis or treatment occurred in either group.

We conclude that Laparoscopic cholecystectomy is a safe, valid alternative to OC in patients with acute cholecystitis. The technique has a low rate of complications, implies a shorter hospital stay, and offers the patients a more comfortable postoperative period than OC.

References

Local Infiltration Anesthesia versus Spinal Anesthesia in Anal Fissure Surgery

**ABSTRACT**

**Objective:** To compare local infiltration anesthesia with spinal anesthesia for anal fissure surgery with respect to recovery time, postoperative complications and patient satisfaction.

**Methods:** A randomized clinical trial of 64 patients requiring lateral sphincterotomy was carried out at Prince Ali hospital in Jordan. The 64 patients were randomized into two groups; the local infiltration anesthesia group (n=32) received local anesthesia of 20 ml 0.5% bupivacaine infiltrated around the anal verge and the spinal anesthesia group (32) received 1.5 ml of 0.5% bupivacaine into the subarachnoid space as spinal anesthesia. Perioperative side effects, visual analogue pain scale score for three days, patient satisfaction and hospital stay were recorded and assessed.

**Results:** Patients in the spinal anesthesia group spent more time in the operating theater and recovery room. Two third of the patients in the local infiltration anesthesia group (65.6%) left the hospital on the day of surgery, compared to only (34.4%) in the spinal anesthesia group. About 91% were satisfied in the group with local infiltration anesthesia in comparison to 75% in the spinal anesthesia group. Postoperative complications occurred in 5 patients of the spinal anesthesia group (3 urinary retention, 2 spinal headache).

**Conclusion:** Local infiltration anesthesia for lateral internal sphincterotomy resulted in lower complications, shorter hospital stay and more postoperative patient satisfaction.

**Key words:** Anal fissure, local infiltration anesthesia, spinal anesthesia

**Introduction**

Anal fissure is the most common cause of severe anal pain. It is equally one of the most common reasons of bleeding per anus in infants and young children. The pain of anal ulcer is intolerable and always disproportionate to the severity of the physical lesion. It may be so severe that patients may avoid defecation for days together until it becomes inevitable. This leads to hardening of the stools, which further tear the anoderm during defecation, setting a vicious cycle. The fissures can be classified into 1] Acute or superficial and 2] Chronic fissure in ano.

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**Predisposing Factors** - It has been proved that constipation is the primary and sole cause of initiation of a fissure. Passage of hard stool, irregularity of diet, consumption of spicy and pungent food, faulty bowel habits, and lack of local hygiene can contribute to initiation of the pathology. In females, the ailment is usually triggered during pregnancy and following childbirth. It occurs as a superficial split in the anoderm that may heal by itself or may progress to a chronic fissure.

**Pathophysiology** - The anoderm is more adherent to the underlying tissue in the posterior midline. The sphincter fibers form Y-shaped decussation in the posterior midline that is anchored to the mucosa. Blood supply to the anoderm at the posterior midline is significantly lower. The reduced blood supply to the lesion is indicated by the absence of granulation tissue at the base of the fissure and a very slow growth of the anoderm even when the traditional conservative treatment eases the trauma due to hard faeces.

**Methods**
Sixty four patients with symptomatic anal fissure undergoing lateral internal sphincterotomy were randomized to the local infiltration anesthesia (LA) group, and the spinal anesthesia (SA) group. Only those patients classified as American Society of Anesthesiologists Grade 1 or 11 were included in the study.

In the (LA) group the patients were placed in the lithotomy position, and 20 ml of 0.5 % bupivacaine with 1:200, 000 epinephrine was infiltrated into the intersphincteric planes in the perianal region.
If sedation was requested, intravenous midazolam using 1.5 - 3 mg titrated within five minutes was used to give the desired effect. In the (SA) group patients received spinal anesthesia using a standard midline approach in the setting position, with the injection of 1.5ml of 0.5% bupivacaine in the subarachnoid space at L3-L4 interspaces. After that, patients were repositioned in the lithotomy position. The surgical procedure performed on the patients was by partial lateral internal sphinctretomy. Both groups of patients had perioperative monitoring with electrocardiograph, pulseoximetry and non-invasive blood pressure monitoring. The age, gender and weight of all patients were recorded. The total time in the operating room and the time for surgery were recorded. Any problems encountered by the surgeon or anesthetist were noted. After operation, all patients were sent to the recovery room. Breathing room air, continuous oxygen saturation monitoring using pulseoximeter and non invasive automatic blood pressure monitoring every 2.5 minutes were recorded. Patients were asked if they experienced any pain, nausea and vomiting. They were again questioned regarding symptoms of pain, nausea, vomiting, headache or urinary retention 30 minutes later. After returning to the ward, patients were asked to inform the nurses as soon as they felt pain at the operation site. The time elapsed from surgery to the first feeling of pain, was recorded. The type of analgesia required was also documented. Patients were discharged on the evening of surgery or the next morning, according to their preference. Just before hospital discharge, patients were asked if they were satisfied with the anesthetic, and if they would choose the same method of anesthesia again for perianal surgery. Each patient was given a chart to record visual analogue pain score at the third postoperative hour and daily thereafter until three days postoperatively. Patients were instructed that this pain score is from 1 - 10, where one is no pain and ten is the worst pain imaginable. Patients were subsequently seen after one week.

Results
Thirty-two patients (28 men and 4 women) were randomly assigned to the LA group, the mean age was 28 (ranged 23 - 54) year, and the mean weight was 85 (range 45 - 75) kg. Thirty two patients (29 men and 3 women) were randomized to the SA group. The mean age in this group was 26 (range 20 - 49 years) and the mean weight was 56 (range 41 - 84 kg). No significant differences regarding gender, age and weight were noted. There was a statistically significant difference in satisfaction between the two groups as 90.6% were satisfied in group LA in comparison to 75% in group SA (Table 1).

The mean time in the operating room was 25 minutes in the LA group, and 40 minutes in the SA group and surgery time was 10 minutes in both groups. In the SA group, the mean duration of anesthesia was 75 minutes while it was 55 minutes in LA group (Table 2). There was no difference in the oxygen saturation or pulse rates measured immediately after operation. There was no significant difference in symptoms of pain, nausea and vomiting between the two groups, but 3 patients developed urinary retention and 2 patients developed headache in the SA group. The mean time to initial experience of pain was 6.5 hours in the LA and 4.5 hours in the SA group. Postoperative analgesic requirements were similar in both groups as shown in the visual analogue pain scale score (Table 3). In the LA group 21 (65.6%) of patients left the hospital on the same day, while only 11 (34.4%) of patients in the SA group did so. At 6 weeks follow-up, no postoperative complications were reported in either group.

Discussion
The ideal operation for anal fissure should be simple, and require short or no hospitalization. There should be minimal pain, rapid return to normal activity and treatment should be cost effective. With this in mind, many surgical and anesthetic procedures have been advocated to reach this goal. Local anesthetic infiltration, spinal anesthesia and general anesthesia are commonly used anesthetic techniques for anal fissure surgery. However, the best anesthetic technique to reach our goals remains unknown. In our study, the use of local infiltration anesthesia provides significant advantages over spinal anesthesia. That is to say, patients with local infiltration anesthesia had shorter anesthesia time, shorter recovery room time and less postoperative admission. This agrees with other studies which studied regional and spinal anesthesia in anal fissure surgery and found that patients with local infiltration anesthesia had shorter time to home readiness, and lower overall costs with no side effects. But our study differs from theirs in that surgery time is shorter. For postoperative pain we found that there was no statistically significant differences in the visual analogue pain scale score between local infiltration anesthesia and spinal anesthesia, which was similar to findings of other study. The use of spinal anesthesia may lead to development of transient neurological symptoms, especially when short acting anesthesia such as lidocaine is used. Bupivacaine has been the best alternative to lidocaine, because transient neurological symptoms are absent. But spinal bupivacaine that we use in our study may delay recovery of motor function. Imarengiaye et al suggested that the ability to walk without assistance after spinal anesthesia requires a longer recovery period than predicted solely by gross motor recovery, making its return inadequate as sole marker of ambulatory ability and readiness for discharge. To overcome the delay in recovery of motor function, they used a low dose (5 mg), diluted solution of bupivacaine combined with 10 mg fentanyl. The mean time of anesthesia in their method was 60 minutes compared to 75 minutes in our study. This dose will avoid prolonged detrusal block and inability to void, which occurred in 3 patients in our study. Another complication we encountered in the SA group, was postdural puncture headache which occurred in 2 patients (6.2%), which is higher than was recorded by William et al (less than 1%). The reason for this low number probably reflects the well-known fact that the development of headache after dural puncture varies inversely with age. In the previous study, hernia tends to occur among older patients. However, in our study it is more among younger patients. In conclusion, the use of local infiltration anesthesia with sedation in anal fissure surgery resulted in shorter hospital stay, less complications and more patient satisfaction, when compared to spinal anesthesia.
Table 1: Demographic data and patient satisfaction

<table>
<thead>
<tr>
<th></th>
<th>LA group</th>
<th>SA Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>28/4</td>
<td>29/3</td>
</tr>
<tr>
<td>Mean age (year)</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>Mean weight (kg )</td>
<td>58</td>
<td>56</td>
</tr>
<tr>
<td>Patient satisfaction</td>
<td>90.6%</td>
<td>75%</td>
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</table>

Table 2: Duration of anesthesia, actual operation and operating room time

<table>
<thead>
<tr>
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<th>SA Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean time in operating room (min.)</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>Actual operation time (min.)</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 3: Mean visual analogue pain score of patient

<table>
<thead>
<tr>
<th></th>
<th>LA group</th>
<th>SA Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre operative</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>4th hour</td>
<td>3.5</td>
<td>4.8</td>
</tr>
<tr>
<td>1st day</td>
<td>3.9</td>
<td>4.5</td>
</tr>
<tr>
<td>2nd day</td>
<td>3.8</td>
<td>4.2</td>
</tr>
<tr>
<td>3rd day</td>
<td>3.6</td>
<td>3.7</td>
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References
The medical students’ perceptions about their clinical training in the pediatric ward of a teaching hospital

**ABSTRACT**

**Background:** Medical students’ views are important for evaluation of teaching programs in university hospitals.

**Purpose:** The goal of this prospective observational study was to determine the students’ perceptions about teaching programs in a pediatric ward.

**Methods:** We examined the students’ perception during a two year period (September 2005 - August 2007) by using a 5 - point scale questionnaire. Positive responses were considered to be scales 4 or 5.

**Results:** A total of 120 fifth-year (stager) and sixth-year (intern) medical students participated in the survey. The common positive views about the teaching programs of wards included: usefulness of introductory session at the beginning of ward (76.7%), adequate presence of attending physicians in ward (87.5%), and the ability of residents for teaching and problem solving (71.7%). The common negative views were as follows: lack of correlation between teaching program and ‘must learns’ (44.1%), inadequate improvement in physical examination (57.4%), and inadequate presence of attending physicians in the outpatient clinic (60.8%). There was a significant difference between the presence of specialists in ward and the OPD (P <0.006).

**Conclusion:** The findings highlight the perceived strengths and weaknesses in the teaching program of a pediatric ward. The data shows we require further effort to resolve the weaknesses of the program in order to achieve better students’ satisfaction.

**Key words:** perception, program, student, teaching

**Introduction**

Initial learning experiences in hospital environments aim to transfer basic clinical skills, while giving students the foundations for clinical practice. It might be postulated that such periods are highly important in influencing students’ development. Indeed positive experiences at this time may impact on subsequent career choices and attitudes to certain specialties (1).

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Hospitalists are physicians whose primary professional focuses are the general medical care of hospitalized patients. In teaching hospitals, hospitalists or attending physicians are playing an increasingly important role in medical education. Their activities include patient care, teaching, research, and leadership related to a variety of teaching program such as morning reports, journal clubs, and conferences (2). Good teachers involve the learners, asking questions, framing cases to solve, forming small groups for discussion, asking for the views of learners, pausing to allow students to think, and the efficient use of words (3). Students undergo a substantial period of adjustment during their training in the hospital learning environment (1). Exposure to teamwork early in training has been considered to improve basic communicative and collaborative skills of students after graduation. A series of planned programs such as forums and seminars, field trips, and clinical and community opportunities in underserved areas are important for exposure of the trainee to community health problems. An evaluation found that the majority of students believed that such programs influenced their interest for practice in underserved rural or urban areas (4). A newly qualified doctor must be able to fulfill the needs of the population, and primary health care must be included within the training program of general medicine and pediatrics wards (5). The opinions of 600 randomly selected doctors, on what should be taught to undergraduates in clinical years, were analyzed. The respondents gave a high priority to general medicine, pediatrics, general surgery, casualty, and gynecology (6). Students are a reliable and valid source of information about tutor performance in teaching hospitals and have often been used to evaluate tutors (7).
The purpose of this study was to describe perceptions of students undertaking their clinical pediatric course in the pediatric ward of a university hospital. The students were asked about major elements of hospital teaching and the educational climate in the pediatric ward. Data was generated by a questionnaire survey conducted over a 2-year period.

Materials and Methods
The pediatric ward of Taleghani medical center has 34 beds, including 10 beds as a neonatal intensive care unit (NICU) and 4 attending physicians. The ward has structured teaching programs or ‘must learn’ objectives for different levels of trainees. These learning syllabuses are introduced to students at the beginning of each course. In order to direct learning, all students are provided with a pamphlet containing a set of learning objectives or ‘must learns’ in each three domains of knowledge, clinical skills and attitudes. Out-patient department (OPD) is handled by an attending physician and a resident according to a weekly schedule. In order to evaluate the medical students’ perceptions about the teaching program a questionnaire-based survey was carried out in this ward. During the study period (September 2005 to August 2007) a total of 130 fifth and sixth year medical students attended the ward and 120 students (92%) participated in the survey.

A 10-item questionnaire was completed by each participant at the end of his/her course in the ward. The students were asked to mark their views with the following scales: very poor (1) - poor (2) - average (3) - good (4) - very good (5). Positive response to each statement was considered to be responses 4 or 5. The items were split into 2 main categories:
A) Students perceptions of the teaching program and the teaching environment.
B) Items related to perceptions about specific elements or characteristics of education.

The questionnaire also allowed for additional students’ comments. The questions in section A asked students’ view about the following items:
1) Definition of goals and tasks at the introductory session.
2) The correlation between examination and teaching materials.
3) The correlation between teaching material and must learns.
4) Adequacy of attending physicians’ presence in ward or the OPD.
5) Adequacy of residents’ presence in ward or the OPD.
6) Ability of residents for teaching medical students.
7) Availability of residents for problem solving.

The questions in section B included:
1) The amount of students’ achievement in the following fields: taking history, performing physical examination, extraction problem list, making plan.
2) The amount of usefulness of individual teaching programs including: morning report, grand round, attending round, residents’ round, conferences. Completed forms collected over 2 academic years were collected and analyzed statistically. Basic statistical analysis of the items was conducted by SPSS. The perceptions of two levels of students were compared by t-test. Statistical difference of <0.05 was considered significant.

Results
During the two years of the study period (September 2005 - August 2007) 130 students received their pediatric training in the pediatric ward of Taleghani medical center. Sixty-three were from 70 (90%) fifth-year students (stagers), and 57 from 60 (95%) sixth-year students (interns), completed the questionnaire. A total of 120 students (92%) participated in the survey. As usual, it happened that not every student responded to every question. These missing responses comprised less than 2 percent of total responses. Table 1 shows the students’ perception about the teaching program. As is shown in this table 92 (76.7%) respondents believed that the introductory session was a useful meeting for making clear their tasks and must learns. Seventy-two (60%) thought that the examination questions were correlated with the teaching material, but 42 (35%) thought that such correlation was poor or very poor. Half of the students (59; 49.2%) said that there was a positive correlation between the teaching program and the items of must learn, whereas the attitude of 53 (44.1%) about this correlation was negative. While the presence of teachers in the ward was considered good or very good by 105 (87.5%) participants, their attendance in the OPD was considered very poor to average by 73 (60%-8%) participants. There was a significant difference between the presence of attending in ward and the OPD (P < 0.006). The evaluation of residents’ presence in ward revealed 76.7% satisfaction, and the same evaluation in the OPD showed 59.2% satisfaction or approval. Eighty six (71.7%) respondents believed that the residents had enough capability to teach medical students and 81 (67.5%) said that the residents had enough supervision over the medical student’s performance.

Table 2 (page 48) summarizes the results of specific items of teaching materials. As it is shown in this table 76 (63.3%) students felt improvement in taking history, while only 50 (41.7%) were satisfied with improvement in physical examination, and 69 (57.4%) said that their improvement in physical examination was very poor to average. Eighty-nine (74.2%) reported positive improvement in extraction from a problem list, whereas only half of them reported the same level of improvement in making a plan. Seventy-six (63.4%) considered that the contents of the morning reports was good or very good. Approximately half of the students thought that the grand round was a good teaching program. Sixty - eight (56.6%) students thought that conferences were good or very good teaching programs and 40% reported it as a very poor to average teaching material. A total of 105 students did not express additional comment. Only 15 (12.5%) students gave their comments about the questions. Most comments were related to heavy clinical workload. The only comment that was entirely negative referred to the coverage of material that was not subsequently tested in examination. A majority of
comments (11/15) reported that they learned something new each day. We did not find any significant differences (P = 0.35) between the perceptions of stagers and interns.

Discussion
In this study we explored perceptions about pediatric training among a sample of medical students. A total of 120 out of 130 students (92%) participated in our survey. The high rate of responses to the questionnaire, by both years of students, suggests that they considered the process to be worthwhile, which represents a positive outcome of this study. Our data indicated that most students (96.7%) believed that the introductory session was useful for their acquaintance with the ward. In another study by Mathers et al, the introductory period at each hospital was viewed as very important by the students. A good introductory period was seen as facilitating effective learning. A lecture to start off the course in the introductory period or before, would help students to understand what they need to know (1). In the above survey however some students reported the learning objectives to be vague leaving them unsure of what they need to learn, to what depth and by when. The results of our study showed that only half of the students reported a positive correlation between the teaching program and the items of must learn. And 60% found a positive relationship between material of teaching and question of examination. The above findings impose additional effort by the medical staff of the ward to obtain more positive responses. Examination and other evaluations must match learning objectives and be reliable and valid. Grading must be fair.

Enthusiasm of individual teachers to teach, was perceived to be an important determinant of the quality of teaching. Within each hospital there exists a range of students’ experience and this can be attributed in part to the attitude and character of individual teachers. The teaching time has become compressed due to the competing demands of clinical work and research activities. Faculty members need to work as hard at teaching as they do at research or clinical practice (3). Inpatient teaching no longer reflects the full spectrum of pediatric practice and community- based programs with clearly defined aims and evaluation of learning are becoming increasingly important(8). The results of our survey showed that although the presence of our teachers in the ward was adequate, their attendance in the OPD was considered unsatisfactory by 60.8% of students. The inadequate presence of the attending physician in the OPD had a negative effect on students’ experiences in a wide spectrum of health care problems.

Table 1: Students’ perceptions about teaching program

<table>
<thead>
<tr>
<th>Items of teaching program</th>
<th>Very Poor N (%)</th>
<th>Poor N (%)</th>
<th>Average N (%)</th>
<th>Good N (%)</th>
<th>Very good N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introductory explanation about the tasks and must learn</td>
<td>-</td>
<td>7 (5.8)</td>
<td>21 (17.5)</td>
<td>53 (44.2)</td>
<td>39 (32.5)</td>
</tr>
<tr>
<td>Correlation between learning objective and examination</td>
<td>2 (1.7)</td>
<td>13 (10.8)</td>
<td>29 (24.2)</td>
<td>46 (38.3)</td>
<td>26 (21.7)</td>
</tr>
<tr>
<td>Correlation between teaching program and must learns</td>
<td>3 (2.5)</td>
<td>13 (10.8)</td>
<td>40 (33.3)</td>
<td>42 (35)</td>
<td>17 (14.2)</td>
</tr>
<tr>
<td>Availability of attending for problem solving</td>
<td>Ward 1 (0.8)</td>
<td>4 (3.3)</td>
<td>10 (8.3)</td>
<td>55 (45.8)</td>
<td>50 (41.7)</td>
</tr>
<tr>
<td></td>
<td>OPD 22 (18.3)</td>
<td>28 (29.3)</td>
<td>23 (19.2)</td>
<td>18 (15)</td>
<td>14 (11.7)</td>
</tr>
<tr>
<td>Availability of residents for problem solving</td>
<td>Ward 5 (4.2)</td>
<td>7 (5.8)</td>
<td>15 (12.5)</td>
<td>56 (46.7)</td>
<td>36 (30.0)</td>
</tr>
<tr>
<td></td>
<td>OPD 8 (6.7)</td>
<td>6 (5.0)</td>
<td>20 (16.7)</td>
<td>39 (32.5)</td>
<td>32 (26.7)</td>
</tr>
<tr>
<td>Ability of residents to teach medical students</td>
<td>Ward 6 (5.0)</td>
<td>7 (5.8)</td>
<td>20 (16.7)</td>
<td>54 (45)</td>
<td>32 (26.7)</td>
</tr>
<tr>
<td></td>
<td>OPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residents’ supervision on students performance in ward</td>
<td>Ward 5 (4.2)</td>
<td>14 (11.7)</td>
<td>18 (15)</td>
<td>54 (45)</td>
<td>27 (22.5)</td>
</tr>
</tbody>
</table>
ABSTRACT

The symptomatology of gallstone disease is varied. Often nonspecific, the symptom may be acute, chronic or totally absent when diagnosed incidentally. Although palpability of gallstone is rare, presentation as hard lump is even rarer. Large gallstones could be palpable in thin built patients on careful examination. But presentation as lump abdomen in average built patient has not been reported in medical literature as far as we know. We are reporting a case of cholelithiasis presenting as lump abdomen with chronic cholecystitis.

Introduction

Gallstones are completely asymptomatic in the majority of patients (60%-80%). Patients with mild symptoms have a higher risk of developing both common and less frequent complications. Usually this type of gallstone attains a bigger size. But palpable gallstones are too rare to report in world literature. We are reporting this unusual case of gallstone presenting as a hard lump in right hypochondrium. Diagnosis was made only by ultrasonography and no further investigation was required. Due to the larger size of the stone, dissection of Calot’s was difficult, so laparoscopic procedure was converted into open surgery, and cholecystectomy was accomplished.

Case Report

A 45 year old average built female patient presented in surgical OPD with complaints of off and on pain in the right upper abdomen since 5 years and a hard lump since 1 month. Palpation of the lump causes the patient to seek medical consultation. There was no history of jaundice, malena or significant weight loss. On examination a hard lump was palpable just below the right costal margin. The lump was smooth, non-tender and moving with respiration. Clinical diagnosis of carcinoma of the gall bladder was made.

On ultrasound cholelithiasis was diagnosed with a large stone of size 10×4×4cm almost filling whole of the gall bladder cavity. Wall thickness of the gall bladder was 4mm. The patient was planned for elective cholecystectomy.

Laparoscopic cholecystectomy was initially tried, but due to the large stone, the gall bladder was difficult to manipulate and Calot’s could not be dissected. The decision of conversion to open cholecystectomy by fundus as the first method, was taken and the gallstone was delivered by an incision given at the fundus.

During removal of the stone, it broke into two parts, a large globular gallbladder part and a small tubular Hartmann’s part. The weight of the stone was 110grams. After removal of the stone Hartman’s pouch was reached, and the operation was completed.

Histopathological examination of the gallbladder showed hypertrophic and atrophic mucosal folds. Rokitansky-Aschoff sinuses and infiltration of chronic inflammatory cells. The patient recovered well and was discharged on the third post operative day.

Discussion

Gallstone disease is one of the commonest clinical entities that needs surgical intervention. Although diagnosis of cholelithiasis is now very simple with the invention of ultrasonography, having high sensitivity and specificity, still its presentation is often non-specific until complications occur. Uncomplicated gallstones usually cause non-specific
upper abdominal discomfort, and indigestion mimicking gastritis. Very few people seek medical advice for these symptoms. Sometimes patients present years after the commencement of these symptoms. Often they underestimate the symptoms, until they cause right upper abdominal pain and fever due to cholecystitis.

In a developing country like India where health facilities are not easily available to the rural population, palpation of a hard lump in the abdomen is one of the symptoms that need medical attention. Most of the times these cases were clinically diagnosed as carcinoma, even in the above case, but it was surprising when ultrasonography showed it as a benign gallstone.

Pre-operatively the gall bladder looks clearly benign with minimal adhesion. We had initially tried laparoscopic removal but failed because the stone was firmly attached to the gall bladder wall leading to difficult handling and we converted to open cholecystectomy. For such types of stones fundus first method is valuable and the stone should be retrieved before dissection of the gall bladder bed. It helps in easy handling of the gall bladder and careful dissection of Calot’s structures.

Conclusion
Palpable gallbladder always alerts to possible complications but sometimes long standing gallstones can be palpable on deep and careful palpation.

References
Figure 2: Stone of gall bladder shape