Narcotic drug abuse and other risk factors in 100 operated patients for acute cholecystitis in Birjand, Iran

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ABSTRACT

الأهداف: معرفة تأثير الإفراط في تناول العقاقير المخدرة وتحديداً مشتقات الأفيون، وعوامل الخطر الأخرى للمرضى المصابين بالتهاب حاد في المرارة.

الطريقة: في هذه الدراسة الوصفية على شريحة عرضية، تم الحصول على المتغيرات مثل العمر، الجنس، والوزن، ومدى الإفراط في تناول العقاقير المخدرة، وتعاطي الهرمونات، وعدد مرات الحمل، والأمراض المشتركة التي تم تسجيلها في النماذج قبل التعيين لمئة مريض خضع لجراحة التهاب المرارة الحاد، في الفترة ما بين أكتوبر 2001م إلى يونيو 2005م، بمستشفى الإمام رضا بمدينة برجاند – إيران. تم تطبيق الاختبارات الإحصائية المماثلة باستعمال (SPSS) النسخة (13.0.).

النتائج: المرضى الذين تمت دراستهم (62 أنثى، 38 ذكر)، بمعدل (60.8 ± 15.9 عاماً) 66 منهم كانت أوزانهم منخفضة، 23 كانت أوزانهم زائدة، و11 مريضاً كانت أوزانهم طبيعية. معظم المرضى (76) يعانون من التهاب في المرارة، من بينهم 50 أنثي (65.8%) و26 ذكر (34.2%) على التوالي. أصيب سبعة إناث (11%) و14 ذكراً (37%) باليرقان ($p<0.002$). لدى الغالبية منهم (72%) تاريخ مرضي بالإفراط في تناول العقاقير المخدرة، 69 منهم (95.8%) تعاطوا الأفيون، وثلاثة منهم (4.2%) تعاطوا المنشطات. تبين وجود علاقة ملحوظة ($p<0.01$) بين التهاب المرارة الحاد وإدمان الأفيون. كان إدمان الأفيون الأكثر شيوعاً لدى المرضى في المناطق الريفية من المناطق المدنية ($p<0.03$). كان لدى سبعة عشر من المرضى الإناث (27.4%) تاريخ بتناول موانع الحمل عبر الفم. معظم المرضى من السكان ذوي الدخل الاقتصادي والاجتماعي المنخفض ومن المناطق الريفية.

خاتمة: إن الإدمان على تعاطي الأفيون يعد عامل خطر رئيسي في ظهور التهاب المرارة الحاد في هذه المنطقة.

Objective: To study narcotic drug abuse, particularly opiate addiction, and other risk factors in patients with acute cholecystitis.

Methods: In this prospective cross sectional study, variables such as age, gender, weight, narcotics drug abuse, hormone taking, number of pregnancies, and coexistent disease(s) were recorded in pre-designed forms for 100 consecutive patients who underwent operation for acute cholecystitis between October 2001 and June 2005 in Imam Reza Hospital, Birjand, Iran. Relevant statistical tests were applied, using SPSS version 13.0.

Results: From the studied patients (62 females, 38 males) with a mean±SD of 60.8±15.9 years, 66 were underweight, 23 were overweight, and only 11 patients had normal weight. Most of the patients (76) had calculous cholecystitis, of which 50 (65.8%) were female, and 26 (34.2%), were male. Seven females (11%), and 14 males (37%) revealed jaundice ($p<0.002$). Most (72%) had a history of narcotics abuse, of which 69 (95.8%) abused opiates constantly, and 3 (4.2%) abused recreationally. A significant ($p<0.01$) relationship was found between acute cholecystitis and opiate addiction. Opiate addiction was more common in patients from rural areas than urban ($p<0.03$). Seventeen female patients (27.4%) had a history of taking oral contraceptives. The patients were mostly from low socio-economic populations, and rural areas.

Conclusion: The study revealed that narcotic opiate addiction is a major risk factor for occurrence of acute cholecystitis in this area.

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The global epidemic of opiate use continues to spread, and is an increasing burden especially in developing countries, particularly in the Islamic Republic of Iran due to its border with Afghanistan, the largest producer of opium in the world.[1] While prescription opioids can improve quality of life through pain relief, they are susceptible to misuse and abuse, even in developed countries like Canada.[2] Acute cholecystitis is a common disease particularly in female adults. Its pathophysiology is known, however, there is increasing controversy on the risk factors associated with this disease. Male gender has been reported as a risk factor for severe symptomatic cholelithiasis.[3,4] However, the severity of acute cholecystitis is based on clinical assessment, although biochemical analyses and imaging are required in this respect.[5] Several reports[3,4,6,7]concerning the risk factors, especially narcotics, in the pathogenesis of gallbladder and biliary calculus, did not reveal any association. We consider the lack of associations was probably due to retrospective studies or small number of studied patients. We thus aimed to carry out an extensive, and prospective study on 100 acute cholecystic operated patients considering regional risk factors, and socio-economic life conditions with special reference to narcotic drug abuse.

In order to carry out this study, the following queries were put forward: 1) at what age, and in which gender is acute cholecystitis most common? 2) is the disease more prevalent in obese or thin people? 3) is it more prevalent in narcotic drug abusers, lower socioeconomic condition, and higher multigravida, or in patients with coexistent diseases, or those who had taken medications, particularly hormones?

Methods. Following approval of the Medical Ethics Committee of the Birjand University, written informed consent was obtained from patients or their close relatives for this study. The patients with clinical symptoms and signs of acute cholecystitis who were hospitalized, and underwent emergency or semi-emergency operations in Imam-Reza Hospital (the main teaching hospital of Birjand University of Medical Sciences), Birjand, Iran between October 2001 and June 2005 were studied. Out of more than 200 patients, 100 consecutive patients who met the study criteria were investigated. Acute cholecystitis was confirmed by investigations such as ultrasonography, computed tomography scanning, magnetic resonance imaging, magnetic resonance cholangiopancreatography and laparoscopy. The diagnosis was also reconfirmed during the operation. A questionnaire consisting of 28 queries was designed, and filled out by trained medical assistants, gathering information from patients or their close relatives/attendants, and from their medical files including history, clinical, and para-clinical investigations, operation reports, and pathological results. Variables such as gender, age, weight, opiate drug abuse, taking medications particularly hormones, coexisting diseases, job, marital status, and gravities were also recorded. History of opiate drug abuse, particularly opium, heroin, and synthetic opiate such as codeine and diphenoxylate were also recorded, and considered for their medical treatment. The patients were divided into 3 groups, namely, overweight, normal, and thin according to the standard body mass index (BMI). On the basis of the above index, men and women with respective higher indexes of more than 24.1 and 24.2 was regarded as overweight, and those with lower than 18.5 and 18.6, were known as underweight.

The obtained data were analyzed by the Statistical Package for Social Sciences software (SPSS version 13.0), using statistical tests such as ANOVA, $X^{2,}$ and Fisher, at $p<0.05$ as the significant statistical level.

Results. Out of 100 patients, 62 were females and 38 were males. The patients aged varied from 20 to 99 years with a mean±SD of 60.8±15.9 years. Frequency of age distribution is summarized in **Table 1**. Out of 100 patients, 66 were underweight, 23 overweight, and only 11 patients had normal weight. It is of interest that 17 females were overweight compared with 6 of the males, however, the difference was not statistically significant

Table 1 - Frequency of age decade distribution of patients.

Age (years)	No. of patients
20-39	9
40-49	14
50-59	24
60-69	25
70-79	17
80-89	8
90-99	3
Total	**100**

Table 2 - Relative frequency of the type of surgical procedure in 100 patients with acute cholecystitis.

Type of surgical procedure	n	(%)
Cholecystectomy	63	(63)
Cholecystectomy & choledoch exploring & choledochoduodenostomy	25	(25)
Cholecystectomy + choledoch exploring	11	(11)
Cholecystectomy + sphincterotomy	1	(1)
Total	**100**	**(100)**

(p=0.39). Most of the patients (76) had calculous cholecystitis, of which 50 (65.8%) were females and 26 (34.2%), were males, however, the difference was not statistically significant (p=0.16). The remainder (24 patients) revealed noncalculous cholecystitis. Seven females (11%), and 14 males (37%) revealed jaundice (p=0.002). Calculous and acalculous acute cholecystitis in age decades of 100 patients is shown in **Figure 1**. Type of surgical procedures were summarized in **Table 2**. The study revealed that 72% of patients with acute cholecystitis had a history of narcotics abuse, 37% of them had abused narcotics (mainly opium, codeine and diphenoxylate) orally, 20% by inhalation (opium and heroin), and 15% both orally and through inhalation. Sixty-nine of the addicts (95.8%) abused narcotics constantly, and 3 of them (4.2%) abused narcotics to manage their pain of acute cholecystitis. It is of interest that narcotic drug abuse, mainly opiates, were significantly (p=0.03) more common in patients from rural areas (village) than urban (city), as shown in

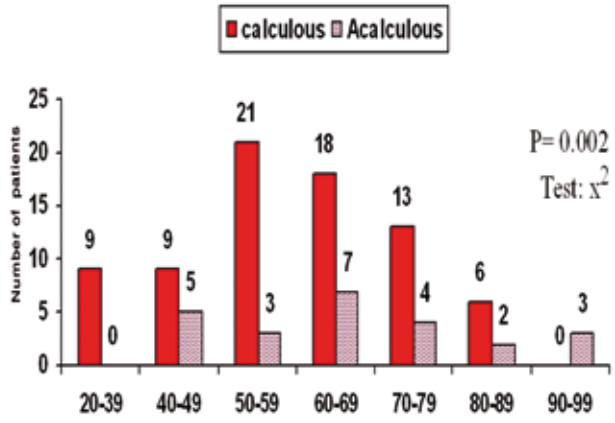

Figure 1 - Age decades and type of acute cholecystic disease in 100 patients.

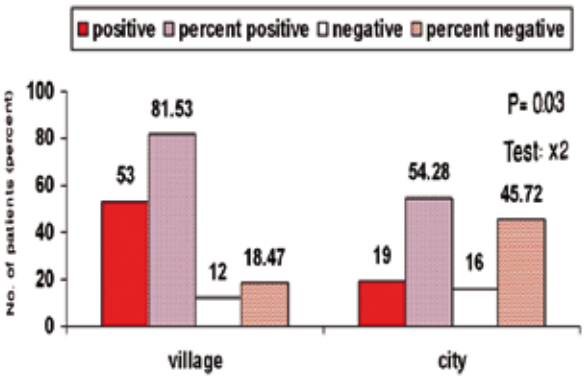

Figure 2 - Comparison of narcotic drug abuse (mainly opium and heroin) in 100 acute cholecystatic patients from rural area (village), with those of urban (city) areas.

Figure 2. Seventeen of the female patients (27.41%) had a history of taking contraceptives. The majority of the women under study (44 patients, 70.96%) had 5-10 deliveries, and even 9.67% (6 patients) of them had a history of more than 10 deliveries. Ninety-eight patients were married, 61 were housewives, 20 were farmers, 11 were laborers and clerks, and the rest were unemployed. They were mostly from low socio-economic populations and rural areas. Seventeen patients suffered from hypertension, and 2 were diabetics.

Discussion. Narcotic drug abuse particularly opiate addiction is very common in the Islamic Republic of Iran. It has induced a lot of cultural, health, and socio-economic problems over the past decade in this country. Based on the United Nation statistic in 2006, out of 220 million narcotic addicts in the world, 9 to 12 millions are opioid addicts, of which according to different statistics 3-4 million have been recognized in Iran.[8] It is even more common in the villages and cities nearest to the border of Afghanistan. Birjand, the capital of South Khorassan is located on the south east of Iran, which has a longer border with Afghanistan, and the University Hospital of Imam Reza is the referral medical center for this state.

The occurrence of biliary calculi is frequent in Asia. Prevalence of pure cholesterol stones, as the origin of biliary calculi, as a result of environmental and nutritional factors is growing. In Africa, the occurrence of biliary calculi, due to genetic and nutritional factors, is more prevalent. In USA and Western Europe, 10% of the population suffer from biliary calculi, 20-30% of whom are symptomatic.[9] It seems that it is even higher in Iran, unfortunately, we have no statistics on this matter.

The basic role of the gallbladder is concentration of bile through water and sodium absorption. Although the gallbladder is mainly an absorbing organ, mucus secretion also occurs, and this causes acute problems especially in pathologic cases such as lithogenesis, and cystic obstruction.[9] Factors causing filling and emptying of the gallbladder include hormonal, neural, pharmaceutical, and mechanical ones. Any change in the kinetic activity of the gallbladder and biliary ducts disturb the normal movement of bile, and impairs ileohepatic movement of biliary acids. This causes diseases of the gallbladder and formation of biliary calculi. Kinetic disturbances of the gall bladder and bile movement is known as dyskinesia.[9,10] The most common cause of cholecystitis (80-95%) is the obstruction of cystic ducts due to biliary calculi. In our study, 76% of the patients had calculous cholecystitis. The main known pathogenic agents for biliary calculi are high cholesterol level, deficiency of bile salts, and hyperbilirubinemia.[5]

Epidemiologic studies have clearly shown a linear relationship between age increase and biliary calculi incidence. Although biliary calculi are very rare in children, those suffering from hemolytic disorders, and small intestine are prone to pigmented calculi. With increasing age, some factors increase lithogenesis. In older men, as a natural phenomenon, changes in the ratio of androgen to estrogen occur, which leads to changes in the metabolism of bile fat, and contractile movements of gallbladder, and may be a cause for an increase of biliary calculi. Ultrasonography studies show that with age increase, gallbladder sensitivity to cholecystokinin, which is the main hormone for gallbladder contraction, decreases.[9] We could not find any age related cholecystitis. Although acute cholecystitis is more common in females than in males, the severity is higher in males than in females. In one study, male gender was identified as a risk factor, however, outcome for men after laparoscopic cholecystectomy was not significantly different from that for women.[4] In another study, besides the above findings, the distribution of age curve in male patients showed a significant shift to a younger age compared with the female patients.[3] In our study, the severity of acute cholecystitis, as judged by clinical pictures, particularly jaundice, was significantly higher (p<0.002) in male patients than in female patients, and calculous cholecystitis was higher in younger and middle aged than in elderly patients (**Figure 1**).

As far as female hormones are concerned, for centuries, a higher prevalence of biliary calculi in women and their relationship with number of deliveries, critical prevalence of biliary colic in pregnant women in the second and third trimester of pregnancy, and cholecystitis following delivery, have been confirmed. During pregnancy, the contractile movement of the gallbladder decreases, and it is not emptied sufficiently. For this reason, after contraction, the total volume of remaining bile is higher compared to other individuals. This is due to progesterone, which is followed by deficiency of gallbladder emptying, and biliary dyskinesia. Estrogen taking, especially before menopause, causes a decrease in the secretion of hepatic enzymes responsible for transforming cholesterol into biliary acids, thus, bile saturated more with cholesterol rather than other lipid components of bile. Biliary dyskinesia and increase in biliary saturation, provides a suitable condition for formation of cholesterol stones.[9,10] Almost one third of the female patients in our study had taken oral contraceptives. Obesity is a risk factor known to cause biliary cholesterol stones. Epidemiologic evidence revealed biliary calculi incidence 2 fold to 3 fold in obese individuals, compared to people with normal weight. More than 50% of the women who had BMI between 25 and 35 had gallbladder disease, and biliary calculi. Moreover, those who were excessively fat are more resistant to medicinal lithotripsy than individuals with normal weight. Metabolic studies show that cholesterol in the bile secreted by the liver in obese patients has a higher concentration. Patients who underwent surgery to lose weight or have already had cholecystectomy are prone to biliary calculi.[9,11]

The principal known risk factors adversely affect volume, concentration, ileohepatic cycle of bile, normal bile movement, and contractile activity of the gallbladder.[9,10] In the present study, an unprecedented finding was obtained. It was the role of opiate addiction in causing somatobiliary injuries, and biliary calculi. This is scientifically justifiable since opiates affect the biliary tract, especially the sphincter of the common biliary duct.[6] Several reports[3,4,6,7] did not reveal any association between opiate use/abuse, and acute cholecystitis. However, in these reports, the patients were rarely opiate drug abuser, whereas in our study, most of the patients (72%) who underwent cholecystectomy were opiate drug abuser. It should be added that some patients (4.2%) used opiates for their pain management due to acute cholecystitis. In a report, it was indicated that lithogenesis is 2 fold in patients that undergo vagotomy contrasted to ordinary people.[9] In another study, incidence of biliary calculi in babies and children who were operated for heart-transplant, and also adults whose bodies receive solid organs have a high frequency. In addition, increase in lithogenesis following changing of heart valves and replacing with artificial ones has been pointed out.[12] These were not the case in our study. In diabetics the risk of biliary calculi formation increases due to high-cholesterol bile, decrease in biliary acids, and contractile deficiency of gallbladder. In addition, present evidence approves that insulin treatment increases proneness to biliary calculi due to an increase in bile cholesterol saturation.[9] This was not a problem in our patients, as we only had 2 patients with diabetes mellitus.

Common clinical features of acute cholecystitis include moderate to severe abdominal pain, nausea, vomiting, fever, jaundice, and leukocytosis, which were observed in our patients. Acute cholecystitis may also be coincidental with complications to induce higher morbidity and mortality,[13] fortunately, that was not a problem in our study, and all patients survived. Patients with Crohn's disease are more prone to biliary calculi due to the involvement of the major part of the second half of the small intestine.[14] The incidence of acute cholecystitis, especially the calculus-free type, has been diagnosed in very ill patients who have undergone non-biliary operations.[15] These were not observed in our study. It should be noted that it was not possible for us to employ a control group.

In addition, some of the studied variables such as history of medication particularly hormones and narcotics were subjective, and there were no facilities to monitor these risk factors objectively. However, in addition to the recognized risk factors such as age, gender, obesity, and taking oral contraceptives, we found a significant relationship between history of narcotics abuse, particularly opium addiction and acute cholecystitis in 100 patients. This is scientifically justifiable since opiates affect the biliary tract, especially the sphincter of the common biliary duct. Thus, opiate drug abuse and addiction is apparently a possible risk factor in the occurrence of acute cholecystitis. However, further studies are required to reach a general conclusion.

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