Medical management of external biliary fistula following surgical treatment of hydatid cyst of the liver: Comparative study

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Summary

Background: External biliary fistula is a common complication following more conservative hydatid liver surgery .A high output biliary fistula (drainage of more than 300ml of bile /day), might be associated with increasing morbidity. In the absence of distal biliary obstruction, the time required for fistula closure would be dependent upon many factors, among which the Oddi sphincter pressure is the most important. Lowering sphincter pressure has been tried by many methods including endoscopic and pharmacological methods depending on documented manometric studies.

Objectives: To evaluate the effectiveness of combined oral administration of Nifidipin, Isosorbid dinitrate and hyocin butyl bromide in reducing the time required for closure of biliary fistula following hydatid liver surgery.

Patients and methods: Fifty patient with high output biliary fistula (drainage of bile of more than 300ml/day**)** who underwent surgery for hydatid cyst of the liver in Al – Diwaniya and Baghdad teaching hospitals, 30 patients were subjected to a trial of combined oral administration of Oddi sphincter relaxant drugs, to evaluate the efficacy of this approach, they were compared with 20 patients in whom placebo was administered with no other intervention adopted.

Results: The majority of patients **(** 93.33%), the fistula output converted to a low one within 5 days following the initiation of sphincter relaxants therapy, as compared to only 10% of patients in the placebo group with obvious statistical difference . 73.3% of patients in the study group exhibit complete cessation of bile drainage within 2-10 days as compared to 60% in the placebo group in whom complete cessation occur within 20-40 days the difference was statistically significant. 90.3% of patients in the study group were discharged within 7 days a period which significantly shorter as compared to 90% of patients in the placebo group whose discharged within 2-3 weeks in an average.

Conclusion: The administration of Oddi sphincter relaxant drugs may hasten the fistula closure with less morbidity and shorter hospital stay therefore it is a beneficial , safe and cost effective method in the management of external biliary fistula following hydatid liver surgery

الخلاصة

الناسور الصفراوي هو من المضاعفات الشائعة التي تعقب عمليات الأكياس المائية للكبد الأكثر تحفظية , مما قد ينجم عن زيادة في نسبة الوفيات.

في حالة عدم وجود انسداد في القنوات الصفراوية يعتمد الوقت اللازم لانسداد الناسور على عدة عوامل أهمها الضغط في صمام(اودي). عدة طرق تم دراستها لخفض هذا الضغط منها التداخل المنضاري أو استخدام العقاقير اعتمادا على دراسات قياسية لضغط الصمام.
الهدف من الدراسة هو لتقيم فعالية , nifidipin , isosorbid dinitrate و hyocin butyl bromide في تقليل الوقت اللازم لانسداد الناسور الصفراوي .
تمت دراسة خمسين مريضا يشكون من ناسور صفراوي ذو البزل العالي (اكثر من 300 مل في اليوم) , مجراة لهم عمليات الأكياس المائية في الكبد في مستشفى بغداد و مستشفى الديوانية التعليميين , ثلاثون منهم تمت دراستهم بإعطائهم العقاقير التي تساعد على انبساط صمام اودي. أما العشرون مريضا الباقين تم دراستهم كمجموعة مقارنة وذلك بإعطائهم عقار placebo .
أظهرت الدراسة ان 93.33% من مرضى الدراسة (30) قد تحول الناسور من البزل العالي الى البزل الواطئ في خمسة أيام بالمقارنة مع 10% فقط من مجموعة المقارنة. واظهرت الدراسة ان 73.3% من مجموعة الدراسة أن الناسور قد توقف بالكامل خلال فترة 2- 10 ايام بالمقارنة مع 60% من مجموعة المقارنة حيث توقف الناسور عن البزل في فترة 20-40 يوم في فرق إحصائي واضح. وقد اوجدت الدراسة ان 90.3% من مرضى الدراسة قد غادروا المستشفى بعد 7 أيام ,بالمقارنة مع المجموعة الأخرى حيث أن 90% منهم غادروا بعد 2-3 أسابيع.
الاستنتاج إعطاء المرضى لعقارات تساعد على انبساط صمام اودي قد تسرع من عملية انسداد الناسور الصفراوي بأقل مضاعفات واقل وقت رقود في المستشفى.

Introduction

External biliary or bilocutaneous fistula a tract connect between any part of the biliary system and the skin either develop spontaneously or post operatively [1,2] , the one that complicate surgery of hydatid cyst of the liver is rather commonly encountered problem especially following more conservative surgery of cyst evacuation and cavity drainage [3,4,5] It present classically in the immediate or early post-operative period as excessive bile drainage if peritoneal drain was provided or following percutaneous drainage of bilioma [6].

Any patient found to have leakage of bile exceeding 30 ml⁄ days lasting more than 3days through the drain in the postoperative period is considered to have biliary fistula [6]. External biliary fistula has been classified by some authors into low and high output fistula depending on whether the fistula output is less or greater than 300ml/day, respectively [6, 7] it may be distressing problem associated with increasing morbidity[4] due to bile loss and associated fluid and electrolytes exhaustion[1], in addition to septic complications and longer hospital stay[6,8].

The overall estimated incidence of post-operative biliary fistula was 16% and 22.5%in patients under went cyst evacuation and drainage [3,6]

Cessation of bile drainage is usually depend on the **presence** or **absence** of distal extra hepatic ductal obstruction , in the former case , the fistula will not close until the obstruction is relieved [9]. The time required for complete spontaneous cessation of fistula drainage in the absence of distal obstruction will depend on the nature of the pathology, size of the communication [10, 11] and pressure oddi sphincter. [9, 12]

Lowering the distal pressure of bile duct is the easiest and safest way to cope with biliary fistula; Geenen et al noted the common bile duct pressure to be 10±2 mmHg and the basal sphincter of oddi pressure to an average of 18±3mmHg. The common bile duct to duodenum pressure gradient is found to be 10±1mmHg. According to this pressure gradient, in an intact ductal system, bile flows along an open fistula tract following the path of least resistance. [13, 14].

Several attempts have been evaluated in order to reduce the intra biliary pressure by decreasing the oddi sphincter tone depending on the documented manometric studies among these are the use of nifidipin, isosorbid, hyosin butyl bromide, botilinum toxin injection, glucagon, somatostatin analogue, and endoscopic sphincterotomy [15, 16, 17] trials which primarily designed for treatment of post cholecystectomy syndromes and biliary dyskinesia, depending on these studies we designed our trial.

Aim of the study: To evaluate the effectiveness of the use of sphincter relaxant drugs *in the management of high output biliary fistula following surgery of hepatic hydatid cyst.*

Patients and method

50 patients with biliary fistula (excessive bile drainage) , following surgery for hydatid cyst of the liver were studied between February 2005 and September 2009 in al Diwaniya and Baghdad teaching hospitals , their age range between 21-63 with mean age 41 year , there was 28 male and 22 female . All patients suffered from excessive bile drainage of 300- 1500 ml of bile (high output fistula) through drain system which has been provided during surgery, most bile drainage manifested in the 1st post-operative day, and only 2 patients manifested in the 3rd post-operative day . Patients with fistula drainage of less than 300ml of bile (lowoutput fistula) were excluded from the study. All patients were subjected to an MRCP exam, and patients with distal biliary obstruction were excluded from the study. 30 patients (study group) were subjected to a trial of combined oral administration of Oddi sphincter relaxant drugs hyocin butyl bromid 10mg, nifidipin 10mg and isosorbid 10mg in 3 divided doses (15,16) another 20 patients (control group) were given a placebo (glucose powder capsules) and observed for fistula closure without any other intervention. In each individual patient, the amount of bile drainage is calculated daily and the time documented first when the amount of bile drainage reach the low output fistula level and second at the time of fistula closure. All patients were observed for the development of drugs side effects.

Statistical analysis: The data were analyzed by EPIver 6.2 software system the statistical significance of the calculated estimate of the risk (OR) was assessed by chi square test. P value less than the 0.05 level of significance considered statistically significant

Results

50 patients with biliary fistula were included in the study, in which 30 patients were subjected to a trial of administration of Oddi sphincter relaxant drugs, with other 20 patients as a control group in whom placebo was administered, the study revealed that the high output fistula converted to a low out put one, in 40%, 53.33%, and 6.66% of patients within 1-2, 2-5 and 5-10 days respectively, following the initiation of sphincter relaxant drugs therapy, while 10%, 15%, 20%,35%,and 20%of patients in the control group, low output fistula drainage was reached within 2-5, 5-10, 10-20, 20-30, and 30-40 days respectively. {Table 1}

Complete cessation of bile drainage within 2- 10 days was observed in the majority (73.3%) of patients received sphincter relaxant drugs, while the majority of patients (60%)in the placebo group, complete cessation of

bile drainage occur within 20-40 days. {Table 2}

Regarding the average hospital stay, the study revealed that the majority (93.3%) of patients received relaxant drugs were discharged within the 1st week as compared to 90% of non-intervention group who were discharged within 2-3 weeks on average

{Table 3}

No significant difference found in the rate of occurrence of drugs side effects between the study group and the placebo group (P value 0.1) { table 4}

Table 1. Initial response to pharmacological therapy

Time /day	1-2 days	2-5 days	5-10 days	10-20 days	20-30days	30-40 days	total
Placebo	0	2 10%	3 15%	4 20%	7 35%	4 20%	20
Relaxant drugs	12 40%	16 53.33%	2 6.66%	0	0	0	30
P value	0.0011	0.0017	0.33				

Table 2. Complete cessation of bile drainage

Time/days	1-2	2-5	5-10	10-20	20-30	30-40	40-50	total
Placebo	0	0	0	4 20%	5 25%	7 35%	4 20%	20
Relaxant drugs	5 16.7 %	9 30%	13 43.3%	3 10%	0	0	0	30
P value	0.054	0.007	0.004	0.3				

Table 3. Average hospital stay

Time in weeks	1	2	3	total
Placebo	4 20%	9 45%	7 35%	20
Relaxant drugs	28 93.3%	2 6.7%	0	30
P value	0.000012	1.2	1.4	

Table 4. development of drugs side effects.

Drugs side effects	Study group no=30	Placebo group no=20
Nifidipin	6	3
Isosorbiddinitrate	10	5
Hyoscin butyl bromid	7	3
total	23 p=0.1	11

Discussion

Biliaryfistula is one of the common complications following surgery of the hepatic hydatid disease accounting for 22.5%, 4-28% in other series [3, 18, 19] and if the amount of bile loss is large i.e. high output fistula [7], it may become a source of many problems including water and electrolytes disturbance, prolonged hospital admission together with septic complications, the occurrence and severity of which would be dependent upon the time interval during which bile is draining. [3,20] High output external biliary fistula following surgery for liver hydatid disease tend to close spontaneously over a period of 2- 4 months in one series [3,8] and low output fistula closed within mean time of 30 days in other series [6,21]. In our study we found that the use of combined oral administration of hyocin butyl bromid, isosorbid and nifidipin have a beneficial effect to reduce the fistula drainage, first for initial response to convert a high output in to a low output fistula we found that the majority 93.33% of patients in whom relaxant drugs was used the, bile drainage was halved within 5 days in comparison to only 10% in the placebo group (P value 0.001). Regarding complete cessation of bile drainage we

found that 90% of the study group patients have their fistula drainage ceased within 10 days (P value 0.054, 0.007 and 0.004). Regarding the hospital stay we found that the average hospital admission in the majority of patients in the study group 93.3% was one week as compared to only 20% of patients in the placebo group a result which is comparable with one series that stated an average length of hospitalization of patients with biliary fistula of 22.7±5.3days. [3] No significant diff-erence found in the rate ofoccurrence of drugs side effects between the study group and the placebo group (P value 0.1). In reviewing other series some preferred to use endoscopic intervene-tion with sphincterotomy, stenting or nasobiliary drainage [21, 22, and 23] methods is believed to minimize the intabiliary pressure and promote early fistula closure even in the absence of distal biliary obstruction [21]. According to our results, we thought that the trial of oral administration of sphincter relaxant drugs may hasten fistula closure before rushing into other interventions which should be saved for patients with distal biliary obstruction or those in whom con-servative treatment is failed to bring about cure within a time in which the patient may be compromised by excessive morbidity.

Recommendation

We recommend the use of sphincter relaxant drugs in cases of biliary fistula complicating surgery for hydatid cyst of the liver. In all cases mechanical obstruction of the distal biliary tree must be ruled out.

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