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A PROSPECTIVE STUDY OF PREDICTORS AND CAUSES OF POST-CHOLECYSTECTOMY PAIN.

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Aim. *A proportion of patients complain of pain after cholecystectomy. The aim of this study was to prospectively identify clinical predictors and causes of post-cholecystectomy pain.*
Methods. *Forty patients with symptomatic gallstones were interviewed to assess their pain and associated symptoms before and 6 months after cholecystectomy. Patients who suffered from pain (Visual analogue scale - VAS ≥4) after cholecystectomy had an ERCP performed with sphincter of Oddi (SO) manometry study.*
Results. *Nine patients (22.5%) suffered from pain after cholecystectomy. Univariate and multivariate logistic regression identified vomiting as the only independent predictor of post-cholecystectomy pain. Two patients refused further treatment. During ERCP and SO motility study a bile duct stone was detected and extracted in one patient. SO manometry was performed to the other six patients. Abnormal SO motility was found in five patients and a classical sphincterotomy was performed to all patients. After a median of 10 (6-18) months follow-up patients were satisfied with the results of sphincterotomy as their VAS decreased from a mean ± SD of 7.0 ± 2.2 to 1.8 ± 0.43.*
Conclusion. *Cholecystectomy rids patients of their gallstones but not necessarily their pain. SO dysfunction is the cause in the majority of patients with post-cholecystectomy pain.*

Keywords: *sphincter of Oddi, manometry, sphincterotomy*

INTRODUCTION

It is well established that the preferred line of treatment for patients with symptomatic gallbladder stones is surgical excision. However, a substantial number of patients will still suffer from symptoms after surgery.[1] Although, the mean number of abdominal symptoms significantly decreases after surgery from 3 symptoms to 1 symptom per patient,[2] an alarming number of patients, which sometimes reaches 40%, will not be symptom free after surgery.[3]

The term 'post-cholecystectomy syndrome' is often used to describe these symptoms. Of these, post-cholecystectomy pain is the most distressing, to both patients and surgeons, as it represents a failure in achieving the main expected outcome from gallbladder removal, which is pain relief. Post-cholecystectomy pain has been reported with all forms of cholecystectomy. Reports on post-cholecystectomy pain after open cholecystectomy range from 7% to 41%[1] Furthermore, recent reports have shown that post-cholecystecomy pain follows laparoscopic and mini-laparotomy cholecystectomy as 16%-31%[4] of patients will suffer from pain after these surgeries.

Post-cholecystemy pain is caused by a wide spectrum of psychological, organic and functional biliary and non-biliary conditions. Nevertheless, most patients investigated will be found to harbour a biliary cause for their pain and a subset of them will have sphincter of Oddi dysfunction (SOD). The frequency of SOD in reported series varies considerably as a result of the variability in patient selection criteria, definition of SOD, type of SOD, and diagnostic tools used.

The aim of this study is to assess prospectively in a cohort of patients elected for open cholecystectomy the prevalence of post-cholecystectomy pain, its features, its preoperative clinical predictors, and its association with the clinical and manometric criteria of SOD.

PATIENTS AND METHODS

Patient population and inclusion criteria. The study population was composed of patients with gall bladder stones, diagnosed through an in-house abdominal ultrasound, and elected for cholecystectomy at the Medical Research Institute, University of Alexandria.

Exclusion criteria. Patients were excluded from the study if they had suffered from pancreatitis or cholangitis, had previous abdominal surgery, or endoscopic retrograde cholangiopancreatography (ERCP) whether diagnostic or therapeutic.

Clinical work-up. Patients were interviewed and clinically examined using a standardised questionnaire before and 6 months after cholecystectomy. During both interviews, each patient was asked by an independent examiner to quantify his/her pain on a visual analogue scale (VAS). Patients who were found to still suffer from pain (VAS $\geq$ 4) after cholecystectomy had their pain reassessed using Rome II criteria[5] for biliary pain as shown in table 1. They also had their liver function tests and abdominal ultrasound repeated. In addition an upper gastrointestinal endoscopy, ERCP and sphincter of Oddi manometry were performed. Patients who were considered to have sphincter of Oddi dysfunction were classified according to a modified Milwaukee classification[6] as shown in Table 1.

Sphincter of Oddi motility study. Sphincter of Oddi manometry was performed after an overnight fast under light sedation with diazepam 10 mg. Manometry was performed using a triple lumen polyethylene water-perfused manometry catheter (Wilson Cook Medical Incorporated, Winston-Salem, North Carolina). The catheter was perfused with sterile bubble-free water from a pneumohydraulic perfusion pump (MUI Scientific Pump Perfusion System, Mississauga, Ontario, Canada) at a rate of 0.25 ml/min and a constant reservoir pressure of 750 mm Hg. Pressure changes within the perfusion system were recorded via transducers of a multi-channel recorder plotted on a computerized polygraph (Sandhill Scientific Incorporated, Denver, Colorado, USA). The perfusion catheter was passed through the instrumental channel of a side-viewing duodenoscope into the duodenum. Baseline duodenal pressures were measured and were considered as the zero reference. The perfusion catheter was then introduced into the bile duct and baseline ductal pressures were recorded. Sphincter basal and phasic measurements were obtained using the "station pull-through technique". The catheter was withdrawn at 2 mm intervals while pressure measurements were continuously observed and entry into the sphincter zone was recognized by an increase in the basal bile duct pressure. The catheter was then positioned such that sphincter pressures recordings were obtained by all three lumens. Pressure changes within the sphincter of Oddi including baseline pressure, phasic amplitude, phasic frequency, and phasic duration were obtained for a period of 2 minutes. The effects of subject and catheter movement, spontaneous duodenal activity, respiration, coughing, and retching were assessed during manometry and tracing artifacts were excluded from the analysis.

ERCP and endoscopic therapy. On completion of all necessary measurements an ERCP was obtained. A sphincterotomy was performed and if stones were seen on ERCP they were extracted with a balloon catheter.

Statistical analysis. Fisher's exact test was used for comparison of nominal data. Preoperative symptoms (independent variables) were tested for association with post-cholecystectomy pain (dependent variable) is a series of univariate logistic regression models. Variables with $p < 0.25$ were then entered into multivariate logistic analysis to identify independent predictors of post-cholecystectomy pain. The unpaired t-test was used for comparison of two continuous unmatched data sets. All comparisons were two tailed and a 5% level of significance was chosen.

Ethical considerations and informed consent. The study protocol was approved by the local ethical committee. The study was explained to each patient and his/her informed consent obtained prior to entry into the study.

RESULTS

Patient characteristics

The study was carried out on 40 patients with chronic calcular cholecystitis presenting to the Department of Experimental and Clinical Surgery, Medical Research Institute, University of Alexandria. Patients characteristics, VAS, and associated symptoms are shown in Table 2. All patients had an open cholecystectomy with an uneventful postoperative period. During the follow-up period of 6 months none of the patients suffered from incisional hernias, jaundice, or sepsis.

Pain assessment

Patient interview and pain assessment at the 6-month follow-up visit revealed that 31 (77.5%) patients were satisfied with the result of cholecystectomy and considered themselves to be free of pain (Fig. 1). Their VAS had decreased from a mean ± SD of 8.2 ± 1.2 to a mean ± SD of 1.3 ± 0.9 as shown in Fig. 2. Nine (22.5%) patients were not

satisfied with the result of cholecystectomy and considered themselves to still suffer from pain that interfered with their daily activities. Their VAS had decreased from a mean ± SD of 8.8 ± 0.8 to a mean ± SD of 6.5 ± 2.2 as shown in Fig. 2.

Clinical predictors of post-cholecystectomy pain

All items listed in Table 2 were assessed as predictors for the development of post-cholecystectomy pain. Vomiting was found to be significantly associated with post-cholecystectomy pain as 7 out of 9 (77.78%) patients with preoperative vomiting developed post-cholecystectomy pain (Fisher's excat test: p = 0.023). Univariate and multivariate logistic regression identified vomiting to be the only independent predictor of post-cholecystectomy pain (p = 0.02 – OR [95% CI] = 8.17 [1.41 - 47.22] and p = 0.03 – OR [95% CI] = 7.14 [1.2 – 42.59], respectively). Pre-operative VAS was not found to be a predictor for post-cholecystectomy pain as the preoperative VAS of patients who developed post-cholecystectomy pain was not statistically different from the preoperative VAS of the rest of the patient population (8.8 ± 0.8 versus 8.2 ± 1.2, respectively; t test: p = 0.359).

Management of patients with post-cholecystectomy pain

Patients who were found to suffer from post-cholecystectomy pain had their pain re-assessed and were found to partially fulfill the Rome II criteria (7 items) for pain associated with SOD as shown in Table 3. Liver function tests and abdominal ultrasound were repeated and were found to be normal in all patients as shown in Table 3. Initially all patients were considered to have Type III sphincter of Oddi dysfunction. ERCP and sphincter of Oddi manometry was performed on 7 patients as two patients refused to consent to any further invasive management (Fig. 1). During ERCP and sphincter of Oddi manometry one patient was found to have a small stone in the bile duct, which was extracted after performing an endoscopic sphincterotomy. The manometric findings of the other six patients are shown in table 4. Five out the six patients were found to have abnormal sphincter of Oddi motility as shown in Table 4 and were considered patients with true Type III sphincter of Oddi dysfunction. A classical sphincterotomy was performed to all six patients. After a median of 10 (6-18) months of follow-up patients were found to be satisfied with the results of sphincterotomy as they considered themselves to be free of pain (Fig. 1). Their VAS had decreased from a mean ± SD of 7.0 ± 2.2 to a mean ± SD of 1.8 ± 0.43 as shown in Fig. 2.

Table 1 Rome II Criteria for biliary pain and Modified Milwaukee Classification for sphincter of Oddi dysfunction

Rome II Criteria for biliary pain due to sphincter of Oddi dysfunction		
Episodes of severe pain located in the epigastrium and right upper quadrant and all the following		
Episodes lasting 30 minutes or more		
Symptoms have occurred on one or more occasions in the previous 12 months		
Pain is steady and interrupts daily activities or requires consultation		
No evidence of structural abnormalities to explain symptoms		
Modified Milwaukee Classification for sphincter of Oddi dysfunction		
Type I	**Type II**	**Type III**
Biliary type pain	Biliary type pain	Biliary type pain only
With the following	**One or two of the following**	
Anormal LFTs	Anormal LFTs	
ALP > 2 times normal on 2 occasions	ALP > 2 times normal on 2 occasions	
Dilated bile duct	Dilated bile duct	
(> 12 mm) on US	(> 12 mm) on US	

Table 2 Patient characteristics

Item	
Age in years*	39.4 ± 9.0
Female : Male	37 : 3
Pain (%)	40 (100)
Visual Analogue Scale*	8.2 ± 1.2
Other symptoms (%)	
Epigastric discomfort	36 (90)
Intolerance to fatty meals	34 (85)
Distension	30 (75)
Nausea	25 (62.5)
Heart burn	23 (57.5)
Sweating	18 (45)
Vomiting	17 (42.5)
Regurge	16 (40)
Belching	10 (25)

* Data presented as mean ± SD

Table 3 Pain characteristics, liver function and ultrasound findings in patients with post-cholecystectomy pain(9 patients)

Item	
Patients with Rome II criteria pain (%)	
Six items	4 (44.44)
Four items	3 (33.33)
Three items	2 (22.22)
VAS*	6.5 ± 2.2
Pain details	
Site (%)	
Right upper quadrant	7 (77.78)
Epigastrium	1 (11.11)
Both	1 (11.11)
Degree (%)	
Moderate	5 (55.56)
Severe	4 (44.44)
Duration (%)	
< 30 minutes	4 (44.44)
> 30 minutes	5 (55.56)
Character (%)	
Steady	7 (77.78)
Interrupts activity or leads to consultation	8 (88.89)
Liver function tests*	
Bilirubin (mg/dl)	0.5 ± 0.2
AST (U/L)	15.8 ± 4.5
ALT (U/L)	16.7 ± 4.6
ALP (U/L)	167.3 ± 45.2
Ultrasound findings*	
Bile duct diameter (mm)	4.8 ± 2.5

* Data presented as mean ± SD

Table 4 Sphincter of Oddi manometry in patients with post-cholecytectomy pain (6 patients)

No.	Bile duct	Sphincter of Oddi			
	pressure	Basal pressure	Phasic amplitude	Phasic frequency	Phasic duration
	Normal values				
	< 12 mm/Hg	< 40 mm/Hg	< 220 mm/Hg	< 8 / min	< 10 sec
1	15.3	17.2	86.8	3	8.7
2	7	89.6	163.3	2	8
3	75	80	116.9	2	8
4	13.8	14.3	105.5	5	8.1
5	8.4	35.2	262	5	8.1
6	5.46	23.5	175	3	8.5

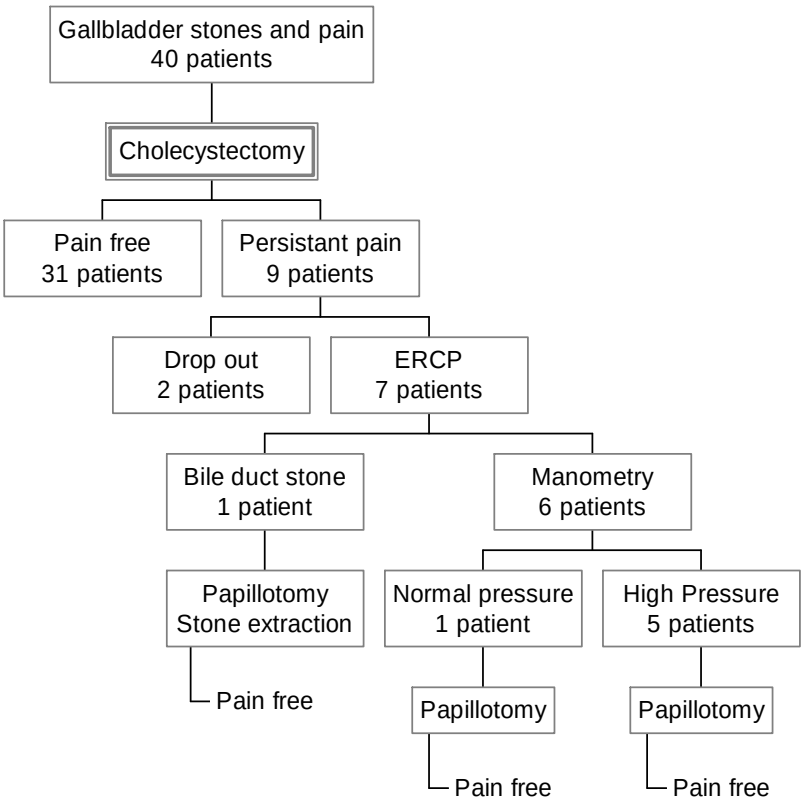

Fig. 1 Study Flow Chart

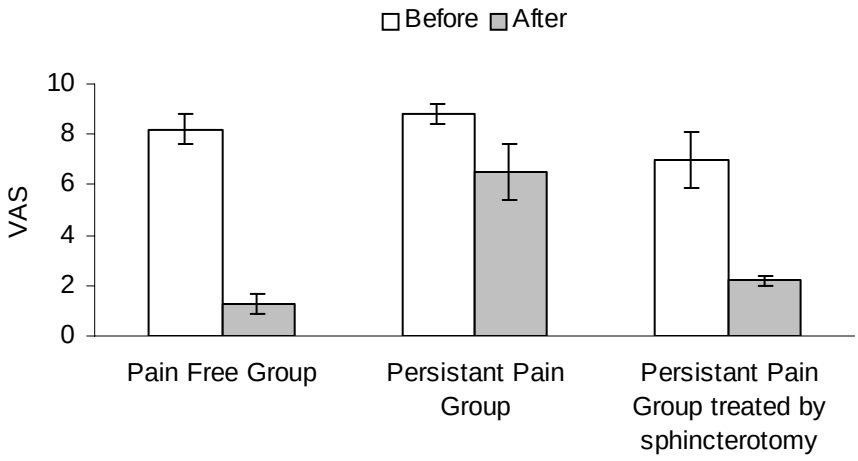

Fig. 2 Visual Analogue Scale change

DISCUSSION

Patients undergoing cholecystectomy definitely get rid of their gallstones but not necessarily of their pain. In the current study, cholecystectomy lead to pain relief in 77.5% of patients which is in accordance with the results of a recent systematic review[7] were the pooled pain relief for elective cholecystectomy, whether open or laparoscopic, was 72%. However, patients undergoing surgery for acute cholecystectomy benefit significantly more from their surgery as 86% are pain free after surgery. Results of associated symptoms, collectively referred to as dyspeptic symptoms, are heterogeneous as reported relief rates range from 46% to 89%.

Whereas the indication for emergency cholecystectomy is to treat or prevent potentially fatal peritonitis, thousands of elective cholecystectomies are performed on a daily basis, in order to prevent or alleviate pain. A comparison of pain before and after cholecystectomy makes it difficult to attribute improvement exclusively to the surgical procedure, which puts pressure on us, surgeons, to re-examine the rational of elective cholecystectomy. A proper evaluation of the effectiveness of cholecystectomy in terms of pain relief rate requires a randomized placebo-controlled trial. However, this raises the ethical dilemmas incorporated in all surgical randomized controlled trials asking for sham operations.[8] Second best would be a trial comparing early elective cholecystectomy to watchful waiting with backup cholecystectomy. Concern still remains, however, about the blinding of patients and investigators to the procedure performed not to mention the significant placebo effect of surgery.[9]

A less radical approach would be to try to predict what group of patients would benefit best or least from cholecystectomy. In this study, out of the nine preoperative associated symptoms with pain; vomiting was found to be the only independent predictor of post-cholecystectomy pain. However, there is a lack of consistency in the literature regarding outcome predictors for pain after cholecystectomy, which includes predominance of dyspeptic symptoms, operative risk, physical and mental health status, duration of symptoms.[10] This variation could be reflecting variation in patient population and methodology used rather than true predictors of post-cholecystectomy.

The differential diagnosis of post-cholecystectomy pain is poorly defined in patients whose pain is not of biliary origin, although, intestinal dysmotility,[11] visceral hyperalgesia,[12] and pseudovisceral neuropathic causes of post-cholecysetcomy pain[13-19] have been described. The term neuropathic pain is widely used and includes pain originating from the spine, peripheral nerves, abdominal wall, or postoperative neuromas.

Most patients with post-choecystectomy pain will have a biliary cause for their pain, however, they often have no diagnostic findings on routine investigation. Apart from overlooked pathology such as missed stones or peptic ulcers SOD bears the main responsibility for persistence of pain after cholecystectomy. The true extent of SOD is difficult to know as most studies on SOD available are performed on the group of patients who complain after cholecystectomy and not on the main cohort of patients with gallstones who undergo cholecystectomy as is the case with this study.[20] Five patients (12.5%) were found to have manometric abnormalities, however, only two (5%) had elevated basal sphincter pressure above 40 mmHg, sure sign of SOD, which is close to the 1% found by an earlier study on 454 patients.[21] Although, these figures are relatively small, considering, the large number of patients undergoing cholecystectomy every year there is already a large cohort of

patients who are not satisfied with their surgery and where SOD is the main cause for their dissatisfaction. In the USA 500 000 cholecystectomies[22] are performed yearly which means that at least 5000 patients could be complaining of pain every year after surgery as a result of SOD.

Patients with SOD respond to sphincterotomy in a varied fashion depending on the presence of associated structural changes or biochemical derangement (see Table 1). There is a general consensus that patients with SOD Type I respond universally to sphincterotomy. However, much debate remains with SOD Type II and Type III (current study population). Patients with SOD Type III, although having similar manometric features to type II, respond less favorably to sphincterotomy especially in the long-term.[23,24] Regardless of SOD type, sphincterotomy in patients with high sphincter pressure (> 40 mmHg) is effective, but no better than placebo in patients with normal basal pressure.[25,26] That is why the subgroup of patients, in our study, with abnormal manometry apart from high basal sphincter pressure should be followed-up to make sure that their response is sustainable and not a mere placebo effect.

This study has demonstrated and supported others in their findings that a substantial number of patients will continue to suffer from pain after cholecystectomy. A larger study with enough power is required to verify the association of vomiting with post-cholecystectomy pain. Sphincterotomy, in the first year, effectively abolishes post-cholecystectomy pain in patients with abnormal sphincter of Oddi motitlity.

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