Available online at www.sciencedirect.com

ScienceDirect

The Surgeon, Journal of the Royal Colleges of Surgeons of Edinburgh and Ireland

www.thesurgeon.net

A systematic review of the aetiology and management of post cholecystectomy syndrome

Jennifer Isherwood [a,*], *Kathryn Oakland* [b], *Achal Khanna* [a]

[a] *Department of General Surgery, Milton Keynes Hospital, United Kingdom*
[b] *Department of Gastroenterology, Oxford University Hospitals, United Kingdom*

ARTICLE INFO

Article history:
Received 5 January 2018
Received in revised form
20 February 2018
Accepted 7 April 2018
Available online xxx

Keywords:
Aetiology
Management
Differential diagnosis
Cause
Post-cholecystectomy syndrome

ABSTRACT

Background: 10% of patients who undergo a cholecystectomy go on to develop post-cholecystectomy syndrome (PCS). The majority of these patients may suffer from extra-biliary or unrelated organic disorders that may have been present before cholecystectomy. The numerous aetiological causes of PCS result in a wide spectrum of management options, each with varying success in abating symptoms. This systematic review aims to provide a summary of the causative aetiologies of post cholecystectomy syndrome, their incidences and efficacy of available management options.

Methods: The Medline, Embase and Cochrane databases were searched for studies patients who developed PCS symptoms following laparoscopic cholecystectomy, published between 1990 and 2016. The aetiology, incidence and management options were extracted, with separate collation of randomised control trials and non-randomised studies that reported intervention. Outcomes included recurrent symptoms following intervention, unscheduled primary and secondary care attendances and complications.

Results: Twenty-one studies were included (15 case series, 2 cohort studies, 1 case control, 3 RCTs). Five studies described medical treatment (nifedipine, cisapride, opiates); seven studies described endoscopic or surgical intervention. Early presentation of PCS (<3 years post-cholecystectomy) was more likely to be gastric in origin, and later presentations were found to be more likely due to retained stones. Sphincter of Oddi dysfunction (SOD) accounted for a third of cases in an unselected population with PCS.

Conclusions: Causes of post cholecystectomy syndrome are varied and many can be attributed to extra-biliary causes, which may be present prior to surgery. Early symptoms may warrant early upper gastrointestinal endoscopy. Delayed presentations are more likely to be associated with retained biliary stones. A large proportion of patients will have no cause identified. Treatment options for this latter group are limited.

* *Corresponding author*. Department of Surgery, Milton Keynes Hospital Trust, Standing Way, Milton Keynes, MK8 5LD, United Kingdom.
E-mail address: jisherwood@doctors.org.uk (J. Isherwood).

https://doi.org/10.1016/j.surge.2018.04.001

Please cite this article in press as: Isherwood J, et al., A systematic review of the aetiology and management of post cholecystectomy syndrome, The Surgeon (2018), https://doi.org/10.1016/j.surge.2018.04.001

Introduction

Symptoms attributable to gallstone disease result in 60,000 cholecystectomies per annum in the UK.[1] Improvements in surgical techniques and advances in post-operative care have resulted in just over 50% of cholecystectomies being performed as day-cases, a rise from 16% in 2008–09.[2,3] The majority of patients recover uneventfully. 10% of patients may develop post-cholecystectomy syndrome (PCS) weeks to month's later.[4]

Post cholecystectomy syndrome was first described in 1947 by Womack and Crider.[5] It refers to the persistence of gastrointestinal symptoms following cholecystectomy and may occur in 5–47% of patients.[6–8] The aetiology can be broadly divided into biliary, extra-biliary, organic and functional.[9]

It has been hypothesised that the majority of patients who develop post cholecystectomy syndrome may actually suffer from extra-biliary or organic disorders, such as gastroesophageal reflux disease or acute and chronic pancreatitis.[10] The difficulty lies in establishing whether these disorders were present before cholecystectomy and were subsequently exacerbated by the post-operative changes in biliary kinetics, or whether they are new symptoms secondary to the procedure. Inappropriate operations may also predispose to the development of PCS.

Retained stones, de novo ductal stone formation, strictures and sphincter of Oddi dysfunction (SOD) may all present as PCS and can all be attributed to biliary aetiology post-surgery.[11] The Rome III committee concluded that PCS pain could be categorized by character and location of symptoms,[12] and thus assist characterisation.

Due to the different causes of PCS there are a number of management options available. These can be categorized into medical, endoscopic and surgical. The management of choice is largely dependent on the aetiology and premorbid state of the patient. Although guidelines exist for the management of the underlying cause of post cholecystectomy syndrome e.g. retained or de novo stone, there are no published guidelines on how to investigate post cholecystectomy syndrome of unknown cause for the underlying aetiology.

This systematic review aims to describe the causative aetiologies of post-cholecystectomy syndrome. Their incidence, therapeutic interventions, patient outcomes, resolution of symptoms and adverse are also described.

Materials and methods

This systematic review was registered with the PROSPERO database of systematic reviews (CRD42016035916) and reported in accordance with the PRISMA guidelines.[53]

A systematic search of Medline, Embase and Cochrane databases was conducted. The search strategy comprised the keywords and MeSH terms: 'Post Cholecystectomy Syndrome', 'aetiology' and 'management' for the time period 1990–2016. Search strategies for each database are included in the supplement. The inclusion criteria were as follows; studies reporting 10 cases or more, reporting PCS in adults (defined as 18 years and over) following laparoscopic cholecystectomy, published in English from 1990 onwards. A hand search of bibliographies was conducted to identify any additional articles.

Open surgery operations were excluded to reduce heterogeneity of the included studies. The first laparoscopic cholecystectomy was performed by Professor Müher in 1986.[13] Studies of laparoscopic cholecystectomy published prior to 1990 were therefore excluded, as outcomes in these preliminary studies were likely to be biased by operator experience.

All abstracts were independently reviewed by two of the authors. Any disputed abstracts were further discussed and put to the senior author for arbitration. The full texts of eligible abstracts were reviewed and screened for study eligibility independently by two authors. All study types; randomised control trials (RCTs), case–control, cohort and case series were eligible for inclusion. Results from case series were excluded from any pooled analysis relating to intervention, as they carry high risk of bias.[49] Case series data on aetiology were included on a descriptive basis. Where there was insufficient data to make a decision about eligibility study authors were contacted for additional information.

Two authors independently extracted the following data from each study:

- Aetiology – defined as the named cause of symptoms as described in each paper, reported for each participant
- Symptoms – defined as the reported nature of the symptom, timing of symptoms reported against time from initial cholecystectomy
- Treatment – frequency of medical, endoscopic or surgical intervention

Primary outcomes were the number of participants with a described aetiology and the type and timing of recurrent symptoms after cholecystectomy. Secondary outcomes included the number and type of complications related to the intervention, number of participants reporting recurrent symptoms following intervention, number of attendances at primary or secondary care services after intervention and all-cause mortality.

Studies that reported a case–control or cohort study design without methodological concordance were discussed with the senior author and analysed as case series if appropriate.

Statistical analysis

Results of randomised controlled trials were converted to risk ratios (RR) plus 95% confidence intervals (CI) for dichotomous data and mean difference (MD) plus 95% CI for continuous data using Revman (Cochrane Collaboration, Denmark). Results of cohort and case control studies were converted to odds ratios (OR) plus 95% CI for dichotomous data and mean difference (MD) plus 95% CI for continuous data and pooled using random effects meta-analysis if appropriate. Where studies reported standard error, this was converted to standard deviation.

Risk of bias

- Risk of bias in RCTs was assessed using the Cochrane risk of bias tool[14]

Please cite this article in press as: Isherwood J, et al., A systematic review of the aetiology and management of post cholecystectomy syndrome, The Surgeon (2018), https://doi.org/10.1016/j.surge.2018.04.001

- Case control and cohort studies were assessed using the Newcastle–Ottawa Scale[15]

Results

The search identified 1077 articles (Fig. 1). Duplicate articles were removed, 104, and the remaining titles and abstracts were reviewed. 876 articles were excluded following title and abstract screen and 97 potentially eligible references were identified for full paper review. On full text review, 69 were excluded and we were unable to obtain the full paper for 7 references by inter library loan despite a national search, leaving 21 articles for data extraction (15 case series, 2 cohort studies, 1 case control and 3 RCTs).

Study characteristics

All of the studies recruited participants from a single centre. They were published from a range of countries; three from India[18,24,26] and USA[10,28,32] respectively, two from the UK[23,34] and one from China,[33] Thailand,[31] Austria,[29] Hungary,[27] Romania,[25] Ireland,[22] Denmark,[6] Australia,[21] Italy,[20] France,[19] Norway,[17] Sweden[30] and Germany,[16] providing good geographical diversity. The studies were conducted between 1990 and 2014. The study characteristics are shown in Table 1.

Thirteen studies described an intervention or treatment; five studies (three RCTs,[16–18] one retrospective cohort[19] and 1 retrospective case series[31]) described medical treatments; two RCT's compared cisapride versus placebo,[16,17] one RCT compared nifedipine versus placebo,[18] one cohort study compared opiate use versus non-opiate use prior to onset of pain,[19] and one case control compared combinations of antispasmodics, laxatives, antacids and cisapride.[31] Seven studies (one prospective cohort[20] and six case series[27,10,30,32–34]) described endoscopic or surgical intervention. One prospective cohort[20] and five case series[27,30,32–34] included endoscopic sphincterotomy as an intervention. Endoscopic sphincterotomy was compared with balloon dilation or surgical

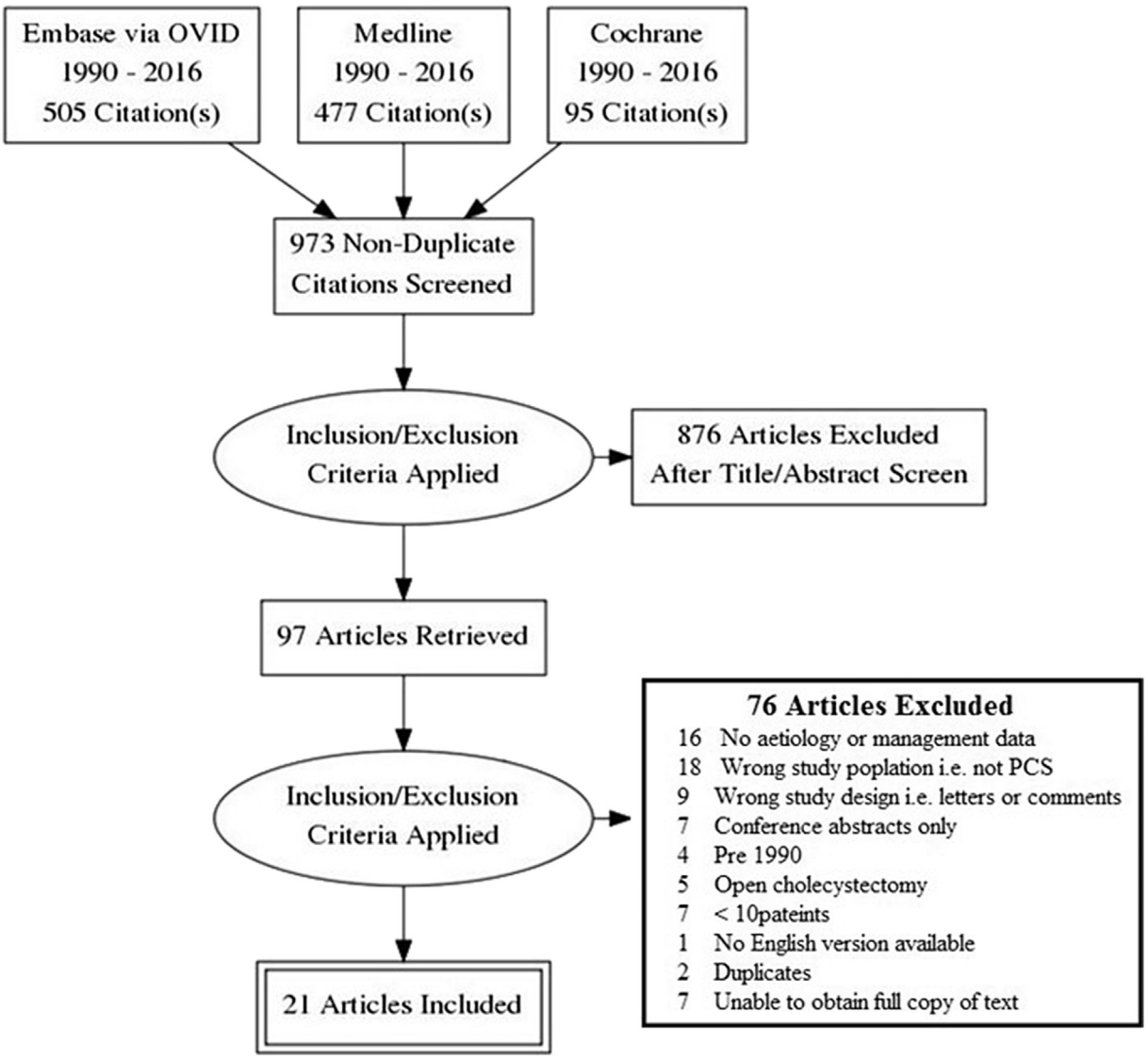

Fig. 1 – PRISMA flow chart for study selection.

Please cite this article in press as: Isherwood J, et al., A systematic review of the aetiology and management of post cholecystectomy syndrome, The Surgeon (2018), https://doi.org/10.1016/j.surge.2018.04.001

Table 1 – Study characteristics.

Study [year]	Country	Study methods	Total participants	Participant eligibility criteria	M:F	Age ± ge (range), years	Duration of study	Intervention(s)
Bouzo 1990[16]	Germany	RCT (cross-over)	20	Colic-like pain, meteorism, flatulence, dyspepsia	6:14	52.4	8 weeks	Cisapride versus placebo
Farup 1991[17]	Norway	RCT (cross-over)	19	Recurrent abdominal pain or discomfort in the right upper quadrant of the abdomen in relation to meals of ≥3 months duration	0:19	56 (44–71)	10 weeks	Cisapride versus placebo
Khuroo 1992[18]	India	RCT (cross-over)	28	≥3 episodes of pain resembling biliary pain in preceding 3 months, elevated serum ALP at least twice during documented pain & sphincter of Oddi findings suggestive of spasm	3:25	35 ± 1.5	26 weeks	Nifedipine versus placebo
Druart-Blazy 2005[19]	France	Retrospective cohort	37	Pain, abnormal liver biochemistry or ultrasound abnormalities and suspected Sphincter of Oddi dysfunction	7:30	56	mean 3.5 years	Opiates prior to onset of pain versus non opiates
Cicala 2002[20]	Italy	Prospective Cohort	140	Sphincter of Oddi dysfunction (defined using Rome Criteria)	12:18	50 (23–66)	10–13 months	Endoscopic Sphincterotomy versus conservative
Bennett 2009[21]	Australia	Retrospective Case control	72	Biliary-like pain consistent with Sphincter of Oddi dysfunction (Rome Criteria)	8:64	45 ± 12	NR	None
Bisgaard 2005[6]	Denmark	Prospective Case series	150	Biliary symptoms resembling pre-operative symptoms	21:129	41 (20–79)	2 years	None
Caldwell 1995[22]	Ireland	Prospective Case series	22	All cholecystectomy patients	3:19	42 (24–85)	6 months	None
Carlson 1992[23]	UK	Retrospective Case series	384	Abdominal pain	24:126	54.8 (no detail)	NR	None
Dilawari 1990[24]	India	Presumed Retrospective Case series	122	Post cholecystectomy syndrome (no detail)	34:88	46.5 (18–80)	NR	None
Filip 2008[25]	Romania	Presumed Prospective Case series	80	Abdominal pain, rigors, jaundice or dyspepsia	32:48	56.2 ± 6.3 (35–80)	NR	None
Kochhar 1993[26]	India	Presumed Retrospective Case series	18	Epigastric or right hypochondrium pain, flatulent dyspepsia	4:14	(18–61)	NR	None
Madacsy 2006[27]	Hungary	Prospective Case series	85	Suspected Sphincter of Oddi dysfunction (Geenen classification)[52]	NR	NR	12 months	Endoscopic sphincterotomy
Philips 2014[10]	USA	Retrospective Case series	12	Remnant cystic duct lithiasis	5:7	38.3 (24–57)	NR	ERCP versus Surgery
Quallich 2002[28]	USA	Prospective Case series	83	Suspected Sphincter of Oddi dysfunction (no detail)	10:50	NR	NR	None

Please cite this article in press as: Isherwood J, et al., A systematic review of the aetiology and management of post cholecystectomy syndrome, The Surgeon (2018), https://doi.org/10.1016/j.surge.2018.04.001

Table 1 – (*continued*)

Study [year]	Country	Study methods	Total participants	Participant eligibility criteria	M:F	Age ± ge (range), years	Duration of study	Intervention(s)
Rogy 1991[29]	Austria	Retrospective Case series	322	Re-operation after cholecystectomy (no detail)	95:227	61	NR	None
Rolny 1993[30]	Sweden	Presumed Retrospective Case series	17	Group I SOD (Geenen classification)[52]	2:15	62 (37–80)	Mean 28 months	Endoscopic sphincterotomy versus Surgical sphincterotomy
Soontrapornchai 1997[31]	Thailand	Presumed Retrospective Case series	27	Recurrent pre-operative symptoms	NR	NR	NR	antispasmodics, laxatives, cisapride, antacids
Topazian 2004[32]	USA	Retrospective Case series	74	Chronic abdominal pain at least 1 year after cholecystectomy	7:67	46 (22–79)	Mean 36 months	Endoscopic sphincterotomy
Zhou 2003[33]	China	Case series	386	History of PCS (no detail)	155:231	(19–85)	NR	Endoscopic sphincterotomy versus balloon dilatation
Fullarton 1992[34]	UK	Case series	40	Case: Group II SOD (Geenen classification)[52] Control: CBD stones or no pancreaticobiliary disease	8: 32	55.5	mean 24 months	Endoscopic sphincterotomy

NR; not reported.

sphincterotomy in two of these case studies.[30,33] One case series compared ERCP with surgical intervention[27] (open bile duct exploration).

All studies included male and female participants, although most included a higher ratio of females. Only one study recorded BMI.[10] Some studies reported only patient weights, without a clear indication of habitus, therefore limiting inter-participant comparison. The ages of study participants ranged from 41 to 62 years.

The method of patient identification for inclusion varied considerably but mostly consisted of self-report of symptoms to the research team during clinical consultations in the prospective studies, or review of notes in the retrospective studies. The criteria for inclusion as a case of PCS differed between studies. Seven studies included participants if they had features consistent with SOD, Cicala et al.[20] and Bennett et al.[21] using the Rome Criteria, Fullarton and Murray,[34] Madacsy et al.[27] and Rolny et al.[30] using the Geenen Classification. Four studies reported no detail on the criteria that constituted PCS.[22,24,29,33] All studies varied in the timeframe in which symptoms were captured, both in regard to the duration of time since laparoscopic cholecystectomy and length of participant follow up. Although pain characteristics were described in most studies, all failed to define how they determined if the pain was a continuation from the pre-operative period, exacerbated following a period of improved symptoms or of new onset.

Aetiology

One RCT,[18] one cohort[19] and 12 case series reported the cause of PCS in their study population (Table 2). In the first three years after cholecystectomy, gastric pathologies including peptic ulcer disease, hiatus hernia and gastro-oesophageal reflux disease were the most common causes of PCS, found in 11–100% cases. In the longer-term (more than three years post-cholecystectomy) retained ductal stones within the biliary tree were the most common cause, reported in 4–40% participants. Sphincter of Oddi dysfunction (SOD) accounted for 1.8–31% of cases in an unselected population with PCS.[18,25,32,33] In population pre-selected with likely SOD[19,21,27,28] only 25–47% cases had true SOD confirmed on liver biochemistry, ERCP or manometry as per the Rome or Milwaukee Criteria.[35–37] In these studies 4.1–50% cases had no cause of their symptoms identified.[19,21,27,28] The number of reported aetiological diagnosis did not necessarily correspond with the number of patients recruited to the study, the discrepancy has been reported as unknown in Table 2.

Medical management

The three RCTs that investigated medical management assessed cisapride, nifedipine or placebo.[16–18] Bouzo[16] randomised 20 participants to receive 10 mg cisapride, three-times daily for four weeks or placebo, Farup et al.[17] randomised 19

Please cite this article in press as: Isherwood J, et al., A systematic review of the aetiology and management of post cholecystectomy syndrome, The Surgeon (2018), https://doi.org/10.1016/j.surge.2018.04.001

Table 2 – Reported final diagnoses of patients presenting with post-cholecystectomy syndrome.

Study	Total Patients diagnosis recorded for	Time since operation (years)	Abdominal – extra biliary			Biliary–organic
			Peptic ulcer disease, GORD or HH (%)	Pancreatitis N (%)	Hepatitis N (%)	CBD stone/ microlithiasis N (%)
Caldwell[22]	22	0.5	7 (100)	excluded	excluded	excluded
Khuroo[18]	153	>0.5	excluded	3	excluded	32 (21)
Bisgaard[6]	16	1	5 (31)	excluded	excluded	0
Soontrapornchai[31]	22	1–2	3 (11)	excluded	1 (4)	0
Kochhar[26]	18	0–3	10 (56)	excluded	excluded	2 (11)
Topazian[32]	74	Mean 3	2 (5)	excluded	excluded	3 (4)
Filip[25]	80	0–5	excluded	6 (7.5)	excluded	24 (30)
Rogy[30]	35	Median 9	excluded	3 (9)	1 (3)	14 (40)
Dilawari[24]	105	0–20	excluded	5 (5)	excluded	30 (29)
Zhou[33]	341	unknown	6 (1.6)	excluded	excluded	243 (65)
Druart-Blazy[19]	147	0.25–32	excluded	excluded	excluded	44 (30)
Bennett[21]	72	unknown	excluded	excluded	excluded	excluded
Madacsy[27]	85	unknown	excluded	excluded	excluded	15 (18)
Quallich[28]	60	unknown	excluded	excluded	excluded	3 (5)

a Other diagnoses included biliary acariasis, chronic wound breakdown, cystitis, musculoskeletal pain, adhesions, colitis, haematological, coeliac sprue, hilar lymphadenopathy, pre-ampullary diverticulum, liver and spleen congestion from thalassaemia, *Campylobacter jejuni*.

b Depicts post-operative causes not detailed within the text. Unknown causes account for any discrepancy noted between the total number of aetiologies listed in the paper, and the reported total number of participants for which a diagnosis was recorded for, also listed in the table.

participants to receive 20 mg cisapride twice-daily or placebo and Khuroo et al.[18] randomised 28 patients to 12 weeks of nifedipine at maximally tolerated dose between 5 and 20 mg or placebo.

In the cross-over RCT by Bouzo[16] fewer patients experienced recurrent episodes of PCS symptoms at four weeks of treatment with cisapride (RR 0.41, 95% CI 0.22 to 0.77, 20 participants). Farup et al.[17] assessed the efficacy of cisapride using patient reported pain scores and biliary drainage, but did not report discrete values for these outcomes, only median differences. The authors reported a trend towards increased symptom frequency, with mean daily pain scores increasing in the cisapride group in the latter two weeks of treatment compared with the placebo group. However this was not statistically significant. Neither study reported adverse events, or the number of unscheduled post-intervention visits to primary or secondary care.

Khuroo et al.[18] reported that when receiving nifedipine, participants had a trend towards fewer episodes of pain (MD −1.6, 95% CI −3.27 to 0.07, 28 participants), lower pain scores (MD −10.1, 95% CI −14.8 to −5.39, 28 participants) and fewer visits to the emergency room (MD −1.1, 95% CI −1.94 to −0.26, 28 participants). The study did not report adverse events.

The heterogeneous nature of the RCTs precluded meta-analysis.

Druart-Blazy et al.[19] examined a group of 37 patients with suspected Sphincter of Oddi dysfunction, comparing 13 participants who received regular opiates before the onset of pain with 23 who received no opiate analgesia. Participants receiving opiates had more episodes of recurrent symptoms (OR 3.15, 95% CI 0.45 to 21.95, 36 participants) over the follow-up period of 3.5 years, although the authors did not state whether patients continued their treatment regime for the duration of the study. The study did not report adverse events.

Endoscopic/surgical management

Cicala et al.[20] conducted sub-group analysis of a prospective cohort study of 30 patients with a diagnosis of sphincter of Oddi dysfunction (Rome Criteria I and II). Of these patients, 22 patients were found to have a prolonged hepatic-hila-duodenal transit time and were subsequently offered sphincterotomy. 14 patients elected to undergo endoscopic sphincterotomy, and were compared to the remaining 8 patients who were managed conservatively. Significantly fewer patients that underwent sphincterotomy experienced recurrent symptoms by 13 months (OR 0.01, 95% CI 0.0 to 0.18, 22 participants). All of the patients that were managed conservatively (n = 8) experienced recurrent symptoms. This study did not report adverse outcomes or unscheduled visits to primary or secondary care post-intervention.

Risk of bias

None of the RCTs provided sufficient detail to determine the risk of bias of their methods of sequence generation or allocation concealment (Table 3). Bouzo[16] and Farup et al.[17] stated that they performed double-blind RCTs. Khuroo et al.[18] also stated this, but when participants received the placebo drug investigators were not blinded, whereas both were blinded when participants received the study medication. This may have led to a potential source of bias. Only Khuroo et al.[18] reported the use of a protocol that could be used to assess bias in selective outcome reporting. Bouzo[16] were deemed to be at high risk of other bias as there was no wash-out period included in this cross-over trial. Farup et al.[17] and Khuroo et al.[18] both incorporated a washout period of two weeks between placebo and the study drug.

Please cite this article in press as: Isherwood J, et al., A systematic review of the aetiology and management of post cholecystectomy syndrome, The Surgeon (2018), https://doi.org/10.1016/j.surge.2018.04.001

Biliary–organic	Biliary–functional			Post-operative		Other[a]	Unknown
Benign/malignant stricture N (%)	Cholangitis N (%)	SO stenosis N (%)	SOD/biliary dyskinesia N (%)	Cystic duct remnant N (%)	Insufficient cholecystectomy N (%)		
excluded	excluded	excluded	excluded	excluded	excluded	3 (18)	
5 (3)	30 (20)	5	48 (31)	excluded	excluded	20 (13)	15 (10)
excluded	excluded	excluded	excluded	excluded	excluded	3	
excluded	excluded	excluded	excluded	excluded	excluded	3	15 ()
excluded	excluded	excluded	excluded	excluded	excluded	excluded	6 (33)
excluded	excluded	excluded	39 (27)	excluded	excluded	14 (31)	24 (43.5)
8 (10)	excluded	excluded	7 (9)	3 (4)	2 (2.5)	30 (38)	0
excluded	excluded	6 (11)	excluded	4 (11)	7 (20)		
31 (30)	excluded	excluded	excluded	excluded	excluded	5 (5)	34 (32)
61 (16.6)	excluded	5 (1.3)	7 (1.8)	4 (1)	Excluded	15 (4.0)	30 (8)
14 (9.5)	excluded	excluded	37 (25)	28 (19)[b]		11 (7.4)	6 (4.1)
excluded	excluded	18 (25)	33 (46)	excluded	excluded	excluded	21 (29)
excluded	excluded	excluded	40 (47)	excluded	excluded	excluded	30 (35)
excluded	excluded	excluded	25 (45)	excluded	excluded	excluded	30 (50)

The cohort studies by Druart-Blazy et al.[19] and Cicala et al.[20] scored 6 and 5, respectively on the Newcastle–Ottawa risk of bias scale. Neither controlled for group differences at baseline and all failed to score for comparability. Notably nine patients in the non-opiate group in the study by Druart-Blazy et al.[19] had an endoscopic sphincterotomy versus none in opiate group. As the cohorts were not matched at baseline, it is likely that the opiate group had more severe symptoms, necessitating their opiate use. In the study by Cicala et al.[20] patients were allocated to conservative treatment over sphincterotomy if they refused the intervention. This would create a self-selecting group with significant comparability bias.

The case–control study by Bennett et al.[21] looked for association between psychosocial variables and SOD, and scored 7 on the Newcastle–Ottawa risk of bias scale. The study group's baseline characteristics (age, representation across SOD classifications) were all similar suggesting appropriate controls were made for comparability.

Discussion

This systematic review collates the findings of nearly three decades of research on PCS. A key finding of this review is the spectrum of aetiologies that contribute to PCS. In the first three years post cholecystectomy the most frequent diagnoses are peptic ulcer disease, GORD and hiatal hernias. Beyond three years, the most common diagnoses relate to ductal stones and microlithiasis although nearly a third of cases will not have a conclusive diagnosis. The frequency of SOD is low, accounting for fewer than 50% PCS symptoms even in populations that have had other causes of PCS excluded. The literature exploring management of post

Table 3 – Risk of bias of included studies.

RCT	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other
Bouzo	Unclear	unclear	Low risk	Low risk	Low risk	unclear	High Risk
Farup	Unclear	unclear	Low risk	Low risk	Low risk	unclear	Low risk
Khuroo	Unclear	unclear	Low risk	High risk	Low risk	Low risk	Low risk
Cohort and case–control studies	Representativeness (1)	Selection of non-exposed (1)	Ascertainment of exposure (1)	Outcome of interest not present at start of study (1)	Comparability (2)	Assessment of outcome (1)	Follow up long enough and adequate (2)
Druart-Blazy	1	1	1	1	0 + 0	1	1
Cicala	1	1	1	1	0 + 0	0	1
Bennett	1	1	1	1	1 + 0	1	1

The Cochrane risk of bias score was used for the 3 RCTs included and the Newcastle–Ottawa score for the cohort and case control studies. The score allocated for each component of the relevant validated scoring systems can be seen demonstrating which part of the study methodology was open to potential bias.

Please cite this article in press as: Isherwood J, et al., A systematic review of the aetiology and management of post cholecystectomy syndrome, The Surgeon (2018), https://doi.org/10.1016/j.surge.2018.04.001

cholecystectomy syndrome is scarce and heterogeneous, and the studies that do exist are limited by small numbers of participants or flawed methodology.

The definition of post cholecystectomy syndrome is broad and variable. The term encompasses a selection of non-specific symptoms, which may or may not be related to or exacerbated by the surgical removal of the gallbladder. Definitions vary regarding the timing of symptoms after cholecystectomy and consensus is lacking. Timing of symptoms is important as arguably the longer the delay between surgery and the development of further symptoms, the less likely it is that these can be attributed to cholecystectomy. We have demonstrated that within three years of surgery, PCS symptoms are mostly caused by non-biliary pathologies. Beyond three years, biliary-related pathologies do account for most symptoms, but these are not related to cholecystectomy. Therefore if a patient presents with biliary symptoms post-cholecystectomy the term PCS should be used to re-start the diagnostic process as opposed to being a diagnosis it its own right. Ultimately the term PCS may become redundant.

In the studies collated in this review, it was unclear whether the pain was new in onset, followed surgery, or was persistent from the pre-operative period. The latter could suggest misdiagnosis of the original symptoms. This dilemma was highlighted by Rogy et al.,[29] who suggested that the most common cause for PCS was overlooked extra-biliary disorders.

Describing the most prevalent causes of PCS is useful to guide the diagnostic process for patients presenting with symptoms post cholecystectomy, and ultimately hasten the identification and treatment of the cause. Notably the most common causes are easily identifiable on endoscopy or routine imaging. We found that beyond three years post cholecystectomy the types of aetiology tended to change. Aetiologies moved from gastric causes towards an increased incidence of biliary lithiasis or pathologies that were in themselves risk factors for stone formation, such as biliary strictures and stenosis. This temporal pattern in aetiology has also been demonstrated by Skalicky,[50] who reported that PCS patients may present with 'early atypical symptoms' of PCS or late symptoms as much as 3–5 years following surgery, with the greater proportion of reported PCS occurring in the latter group.[38] Other studies describe retained biliary stones, sphincter of Oddi dysfunction and biliary stenosis as the most frequent causes of PCS[24,39,40] although we found that these aetiologies were most prevalent several years after cholecystectomy. These findings are explicable by the changes in biliary physiology following removal of the gallbladder. The loss of the reservoir function of the gallbladder is partly compensated for by dilation of the biliary tree, which predisposes to biliary stasis, the formation of stones and possible infection.[41] Post cholecystectomy patients have also been shown to have an increased CBD pressure, which may partly contribute to the development of PCS.[42]

In this systematic review most studies used a range of blood results, radiology and endoscopy to investigate and diagnose the cause of PCS. It is beyond the scope of this paper to synthesize the efficacy and sensitivity of diagnostic methods but several studies did attempt to assess this. Filip et al.[25] reported elevated serum bilirubin and alkaline phosphatase (ALP) in combination with abdominal ultrasound accurately predicted PCS in 90% cases. In the present review we have found that up to 50% patients had PCS symptoms despite normal investigations though.

Several studies have tried to identify predictive factors for PCS. Bisgaard et al.[6] found that the incidence of PCS was higher in patients who had experienced intense acute post-operative pain. This has been shown in other studies of chronic pain following surgery.[43] However, patient's risk of experiencing acute post-operative pain could not be predicted by their pain threshold pre-operatively, as assessed by a nociceptive stimulus i.e. cold pressor test.[6]

Stefaniak et al.[51] proposed that PCS had a psychosocial influence and those without a social network for support and increased remuneration were more likely to somatise symptoms. Bennett went on to describe groupings of psychosocial and gender factors which together differentiated PCS patients with sphincter of Oddi dyskinesia (but not stenosis) from PCS patients with normal sphincter of Oddi motor activity, suggesting an association with functional PCS and social status.

Studies examining the management of PCS are few in number. We identified three studies of pharmacological intervention, all examining cisapride or nifedipine. In 2000 the Medicines Control Agency withdrew the licence for cisapride in the UK following a review by the Committee on Safety of Medicines that reported rare but serious side effects, including long QT syndrome and other cardiac arrhythmias, some of which proved fatal.[44] Calcium channel antagonists inhibit sphincter of Oddi contraction.[45] Studies of sublingual nifedipine at endoscopic manometry demonstrate a reduction in basal Sphincter of Oddi pressure and fewer phasic contractions.[46] The RCT by Khuroo et al.[18] demonstrated lower pain scores and fewer unscheduled visits to secondary care with regular nifedipine. This was a small trial (28 participants), and the use of nifedipine in PCS warrants further research. Additionally whether nifedipine has a different risk and side effect profile in a population with normal blood pressures requires further assessment.

Sphincter of Oddi pressures can also be attenuated using endoscopic sphincterotomy. Endoscopic sphincterotomy is thought to be the treatment of choice for the management of SOD when basal pressures are elevated (>40 mmHg),[47] and can assist with retrieval of bile duct stones. In the current review we found no randomised evidence supporting its efficacy. Evidence was confined to a cohort study of 22 participants, finding that endoscopic sphincterotomy was associated with a reduction in recurrent PCS symptoms. This study did not report adverse events however, which is important given risks of this procedure: pancreatitis (5%), haemorrhage (2%) and cholangitis (1%).[48] The other study identified was a case series, which reported improvement in symptoms,[27,32] and procedure related complication rates of 5.7%,[33] consistent with the literature.

There are several limitations to this systematic review. The broad definition of PCS makes the identification of eligible studies difficult. Furthermore the heterogeneity of study populations precludes meta-analysis, significantly hindering the power and generalizability of any conclusions. The quality of studies was mostly poor and underpowered. Modes of investigation also varied greatly between the studies, making synthesis of aetiological data less reliable. To mitigate this we reclassified many of the authors' classifications into broad

Please cite this article in press as: Isherwood J, et al., A systematic review of the aetiology and management of post cholecystectomy syndrome, The Surgeon (2018), https://doi.org/10.1016/j.surge.2018.04.001

groups. The culmination of these limitations makes the derivation of any definitive conclusions that can aid clinical decision making extremely difficult. The search strategy was limited to full English papers and we would recommend that any future revisions of this systematic review should search and include relevant papers from publications of all languages.

This systematic review acts as a caution. Highlighting the lack of a universally agreed clinical definition for post cholecystectomy syndrome and the paucity of robust studies to help define or better understand this poorly understood syndrome. If this syndrome is to remain in medical vocabulary there is an imminent need for studies with a robust methodology and adequately powered to clarify the remit of this syndrome and ensure consistency in its use and applicability.

Conclusion

Post cholecystectomy syndrome is used to describe a collection of symptoms experienced by patients following cholecystectomy, many of which can be attributed to causes beyond the biliary system. The symptoms experienced are not collectively representative of a single disease or abnormality so referencing them as a syndrome may be inaccurate. Whether some of the symptoms are truly a result of gallbladder removal is questionable. In the immediate period following laparoscopic cholecystectomy many patients presenting with pain will have GORD or peptic ulcer disease. Physicians should exclude these causes before pursuing specialised investigations of the biliary system. In the later period, ductal stones become more common, but a third of patients will have no cause identified. Treatment options for this latter group of patients are limited.

Author contributions

Miss Isherwood and Mr Khanna designed the hypothesis.

All authors were involved in review of abstracts and full papers, as an independent reviewer or arbitrator.

Miss Isherwood and Miss Oakland extracted and interpreted the data.

Miss Isherwood drafted the manuscript and Miss Oakland and Mr Khanna provided critical revisions.

Disclosures

The authors have no conflicts of interest or financial ties to disclose.

Ethical approval statement

For this type of study formal consent is not required.

Informed consent statement

Does not apply.

Acknowledgements

The Authors have no acknowledgements to make.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.surge.2018.04.001.

REFERENCES

1. NHS Institute for Innovation and Improvement. *Cholecystectomy services redesign*. London. 2012.
2. NHS Improving Quality. *NHS better care, better value indicators (incorporating opportunity locator)*. London. 2015.
3. NHS Institute for Innovation and Improvement. *Cholecystectomy services redesign: reducing length of stay in hospitals*. London. 2012.
4. Jensen SW. *Post cholecyestectomy syndrome*. [Online]. Available from: http://www.emedicine.com/MED/topic2740.htm.
5. Womack NA, Crider R. The persistence of symptoms following cholecystectomy. *Ann Surg* 1947;**126**:31–55.
6. Bisgaard T, Rosenberg J, Kehlet H. From acute to chronic pain after laparoscopic cholecystectomy; a prospective follow up analysis. *Scand J Gastroenterol* 2005;**40**:1358–64.
7. Russello D, Di AS, Scala R, Favetta A, Emmi S, Guastella T, et al. Does cholecystectomy always resolve biliary disease? *Minerva Chir* 1997;**52**:1435–9.
8. Anand AC, Sharma R, Kapur BML. Analysis of symptomatic patients after cholecystectomy; is the term post-cholecystectomy syndrome an anachronism? *Trop Gastroenterol* 1995;**17**:126–31.
9. Drossman DA. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology* 2006;**130**:1377–90.
10. Phillips MR, Joseph M, Dellon ES, Grimm I, Farrell TM, Rupp CC. Surgical and endoscopic management of remnant cystic duct lithiasis after cholecystectomy – a case series. *J Gastroenterol Surg* 2014;**18**:1278–83.
11. Zhu J, Zang Z. Laparoscopic remnant cholecystectomy and transcystic common bile duct exploration for gallbladder/cystic duct remnant with stones and choledocholithiasis after cholecystectomy. *J Laparoendosc Adv Surg Tech* 2015;**25**(1).
12. Behar J, Corazziari E, Guelrud M. Functional gallbladder and sphincter of Oddi disorders. *Gastroenterology* 2006;**130**:1498–509.
13. Reynolds Jr W. The first laparoscopic cholecystectomy. *J Soc Laparoendosc Surg* 2001;**5**(1):89–94.
14. Higgins JGS. *Cochrane handbook for systematic reviews of interventions (Part 3). Cochrane book series*. 2008. p. 392–432.
15. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;**25**(9):603–5.
16. Bouzo H. Cisapride in the postcholecystectomy syndrome. A double blind, placebo-controlled, crossover study. *Curr Ther Res* 1990;**47**(3):566.
17. Farup P, Tjora S, Tholfsen J. Effect of cisapride on symptoms and bilary drainage in patients with postcholecystectomy syndrome. *Scand J Gastroenterol* 1991;**26**:945.
18. Khuroo M, Zargar S, Yattoo G. Efficacy of nifedipine therapy in patients with sphincter of Oddi dysfunction; a prospective, double blind, randomized, placebo-controlled, cross over trial. *Br J Clin Pharmacol* 1992;**33**:477–85.

Please cite this article in press as: Isherwood J, et al., A systematic review of the aetiology and management of post cholecystectomy syndrome, The Surgeon (2018), https://doi.org/10.1016/j.surge.2018.04.001

19. Druart-Blazy A, Pariente A, Berthelemy P, Arotçarena R. The underestimated roles of opiates in patients with suspected sphincter of Oddi dysfunction after cholecystectomy. *Gastroenterol Clin Biol* 2005;**29**:1220–3.
20. Cicala M, Habib FI, Vavassori P, Pallotta N, Schillaci O, Costamagna G, et al. Outcome of endoscopic sphincterotomy in post cholecystectomy patients with sphincter of Oddi dysfunction as predicted by manometry and quantitative choledochoscintigraphy. *Gut* 2002;**50**:665.
21. Bennett E, Evans P, Dowsett J, Kellow J. Sphincter of Oddi dysfunction: psychosocial distress correlates with manometric dyskinesia but not stenosis. *World J Gastroenterol* 2009;**15**(48):6080–5.
22. Caldwell MT, McDermott M, Jazrawi S, O'Dowd G, Byrne PJ, Walsh TN, et al. Helicobacter Pylori infection increases following cholecystectomy. *Ir J Med Sci* 1995;**164**(1):52.
23. Carlson GL, Rhodes M, Stock S, Lendrum R, Lavelle MI, Venables CW. Role of endoscopic retrograde cholangiopancreatography in the investigation of pain after cholecystectomy. *Br J Surg* 1992;**79**:1342.
24. Dilawari JB, Chawla YK, Singhal AK, Kataria S. Postcholecystectomy syndrome in Northern India. Study on the diagnosis and therapeutic role of ERCP. *Gastroenterol Japan* 1990;**25**(3):394–9.
25. Filip M, Saftoiu A, Popescu C, Gheonea DI, Iordache S, Sandulescu L, et al. Postcholecystectomy syndrome – an algorithmic approach. *J Gastrointest Liver Dis* 2009;**18**:67–71.
26. Kochhar R, Malik AK, Nijhawan R, Goenka MK, Mehta SK. H. Pylori in postcholecystectomy symptoms. *J Clin Gatroenterol* 1993;**17**(3):269.
27. Madácsy L, Fejes R, Kurucsai G, Joó I, Székely A, Bertalan V, et al. Characterization of functional bilary pain and dyspeptic symptoms in patients with sphincter of Oddi dysfunction: effect of papillotomy. *World J Gastroenterol* 2006;**12**(42):6850–6.
28. Quallich LG, Stern MA, Rich M, Chey WD, Barnett JL, Elta GH. Bile duct crystals do not contribute to sphincter of Oddi dysfunction. *Gastrointest Endosc* 2002;**65**(2):163.
29. Rogy MA, Függer R, Herbst F, Schulz F. Reoperation after cholecystectomy. The role of the cystic duct stump. *HPB Surg* 1991;**4**:129–35.
30. Rolny P, Geenan J, Hogan W. Post cholecystectomy patients with "objective signs" of partial outflow obstruction: clinical characteristics, sphincter of oddi manometry findings and results of therapy. *Gastroinstest Endosc* 1993;**39**(6):779.
31. Soontrapornchai P, Maipang T, Ovartlarnporn B. Postcholecystectomy syndrome after laparoscopic cholecystectomy. *Asian J Surg* 1997;**20**(4):315.
32. Topazian M, Hong-Curtis J, Li J, Wells C. Improved predictors of outcome in postcholecystectomy pain. *J Clin Gastroenterol* 2004;**38**(8):692.
33. Zhou PH, Liu FL, Yao LQ, Qin X. Endoscopic diagnosis and treatment of post-cholecystectomy syndrome. *Hepatobilary Pancreat Dis Int* 2003;**2**(1):117–20.
34. Fullarton M, Murray WR. Evaluation of endoscopic sphincterotomy in spincter of oddi dysfunction. *Endocsopy* 1992;**24**:199–202.
35. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* 2006;**130**(5):1480–91.
36. Petersen BT. An evidence-based review of sphincter of Oddi dysfunction: part 1, presentations with "objective" biliary findings (types I and II). *Gastrointest Endosc* 2004;**59**:525–34.
37. Petersen BT. Sphincter of Oddi dysfunction, part 2: evidence-based review of the presentations, with "objective" pancreatic findings (types I and II) and of presumptive type III. *Gastrointest Endosc* 2004;**59**:670–87.
38. Bodvall B. The postcholecystectomy syndrome. *Clin Gastroenterol* 1973;**53**:1149–60.
39. Useche E, Salazar S, Vetencourt R, Castillo J, Guzmán S. The effectiveness of endoscopic retrograde cholangiopancreatography in the etiological diagnosis of post cholecystectomy syndrome. *GEN* 1993;**47**(3):157–61.
40. Murshid K. The postcholecystectomy syndrome: a review. *Saudi J Gastroenterol* 1996;**2**(3):124–37.
41. Sousa AE, Rodríguez JG, Sánchez JI, Gayoso RG, Ghanimé GS, Rodríguez HP. Agenesis of the gallbladder. Statistic review of the Spanish literature and presentation of a new case. *Rev Esp Enferm Apar Dig* 1989;**75**(2):135.
42. Tanaka M, Ikeda S, Nakayama F. Change in bile duct pressure responses after cholecystectomy: loss of gallbladder as a pressure reservoir. *Gastroenterology* 1984;**87**(5):1154–9.
43. Perkins F, Kehlet H. Chronic pain as an outcome of surgery: review of predictive factors. *Anesthesiology* 2000;**93**:1123–33.
44. Ferriman A. UK licence for cisapride suspended. [Online]. 2000;**321**:259. Available from: https://doi.org/10.1136/bmj.321.7256.259.
45. Sand J, Arvola P, Nordack I. Calcium channel antagonists and inhibition of human sphincter of Oddi contractions. *Scand J Gastroenterol* 2005;**40**(12):1394–7.
46. Guelrud M, Mendoza S, Rossiter G, Ramirez L, Barkin J. Effect of nifedipine on sphincter of Oddi motor activity: studies in healthy volunteers and patients with biliary dykinesia. *Gastroenterology* 1988;**95**(4):1050–5.
47. Craig A, Toouli J. Sphincterotomy for biliary sphincter of Oddi dysfunction. *Cochrane Database Syst Rev* 2001;(1). Art. No.: CD001509.
48. Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, et al. Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996;**335**:909–19.
49. Grimes, Schulz. Descriptive studies: what they can and cannot do. *Lancet* 2002;**359**:145–9.
50. Skalicky M. Dynamic changes of echogenicity and the size of the papilla of vater before and after cholecystectomy. *J Int Med Res* 2011;**39**:1051–62.
51. Stefaniak T, Vingerhoets AJ, Babinska D, Trus M, Glowacki J, Dymecki D, et al. Psychological factors influencing results of cholecystectomy. *Scand J Gastroenterol* 2004;**39**(2):127–13252.
52. Geenen JE, Hogan WJ, Dodds WJ, Toouli J, Venu RP. The efficacy of endoscopic sphincterotomy after cholecystectomy after cholecystectomy in patients with sphincter of Oddi dysfunction. *N Engl J Med* 1989;**320**:82–7.
53. PRISMA, Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;**151**:264–9. w264.

Please cite this article in press as: Isherwood J, et al., A systematic review of the aetiology and management of post cholecystectomy syndrome, The Surgeon (2018), https://doi.org/10.1016/j.surge.2018.04.001