

Preoperative opioid use and the outcome of thoracoscopic splanchnicectomy in chronic pancreatitis: a systematic review

Yama Issa · Usama Ahmed Ali · Stefan A. W. Bouwense ·
Hjalmar C. van Santvoort · Harry van Goor

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Abstract

Background Thoracoscopic splanchnicectomy (TS) is a minimally invasive intervention to relieve pain in patients with chronic pancreatitis (CP) with equivocal results. Preoperative opioid use seems to impair TS outcome but this has not been investigated in a systematic matter.

Methods We searched PubMed, EMBASE, and The Cochrane Library for studies on the outcome of TS in CP patients. Studies with ≥ 5 patients and a follow-up of ≥ 12 months were included. Success was defined as the proportion of patients free of opioids or who had a reduction of ≥ 4 points on a pain scale. The effect of opioid use on the success rate of TS was analyzed by uni- and multivariate regression.

Results Sixteen studies with 484 patients were included in our review. The mean (\pm SD) age of the patients was 44 ± 4.3 years and 66 % were male. Median follow-up period was 21 months (IQR 14–35). Median preoperative opioid use was 85 % (IQR 54–100 %). After TS, a median of 49 % (IQR 22–75 %) of patients were free of opioids at end of follow-up. The median success rate was 62 % (IQR 48–86 %). Mean success rate in studies in which ≤ 50 % of the patients used opioids preoperatively was 81 %

(SD ± 21) compared to 60 % (SD ± 15) for other studies ($p = 0.049$). Higher age, male gender, and lower rates of preoperative opioid use were associated with a higher success rate ($p = 0.003$, 0.047, and 0.017, respectively). Multivariate regression, including age, gender, preoperative opioid use, and duration of follow-up, identified age and preoperative opioid use as independent predictors of success after TS (both $p = 0.002$).

Conclusion Preoperative opioid use is associated with a worse outcome after TS in CP patients. To optimize outcome, use of TS may be considered at an earlier stage in the treatment of patients with CP before prolonged opioid therapy.

Keywords Chronic pancreatitis · Pain · Opioid · Thoracoscopic splanchnicectomy · Review · Meta-analysis

Chronic pancreatitis (CP) is a progressive inflammatory disease of the pancreas. Pain is the most dominant and disabling symptom and often leads to recurrent hospital admissions and multiple endoscopic or surgical interventions and pain, with a major negative impact on the quality of life and social functioning [1, 2].

The treatment of pain in CP is complex and can be divided in medical (e.g., enzyme replacement and non-opioid and opioid analgesics), endoscopic, and surgical therapy. Many patients with CP undergo surgical intervention for pain in the course of their disease, because medical and endoscopic therapies often fail to alleviate pain symptoms for a long period of time [3, 4]. Pancreatic resection and drainage procedures are considered the mainstay surgical therapy for CP. However, many patients are not suitable candidates for these interventions since they

Y. Issa (✉) · U. A. Ali
Department of Surgery, Academic Medical Center,
P.O. Box 22660, 1100 DD Amsterdam, The Netherlands
e-mail: y.issa@amc.uva.nl

U. A. Ali · H. C. van Santvoort
Department of Surgery, University Medical Center Utrecht,
Utrecht, The Netherlands

S. A. W. Bouwense · H. van Goor
Department of Surgery, Radboud University Nijmegen Medical
Center, Nijmegen, The Netherlands

lack an inflammatory mass or dilated pancreatic duct that could be treated surgically. Moreover, these surgical interventions are associated with considerable morbidity and mortality and often lead to deterioration of pancreatic function.

In 1994, thoracoscopic splanchnicectomy (TS) was first described as minimally invasive therapy for pain in CP [5]. With this procedure, the nociceptive input of the pancreas is interrupted by denervating the splanchnic nerves at the level of the thorax before they enter the sympathetic cord. Several studies have been published that show good short-term pain relief but worse outcome over time [6, 7]. This may explain the limited use of TS.

There are different theories about the failure of TS over time, including technical failure to divide all relevant nerve branches, progressive involvement of the posterior abdominal wall by the inflammatory mass of the pancreas, and activation of silent receptors with afferents in other nerves such as the vagal nerve. Furthermore, some studies showed that previous pancreatic surgical or endoscopic interventions and use of opioids were associated with a reduced success rate after TS [8, 9]. Evidence has emerged that prolonged use of opioids may result in sensitization of peripheral nerves, leading to a permanent hyperalgesic state that is very difficult to manage and reverse [10–12].

The effect of preoperative opioid use on the outcomes of surgical procedures for CP, and TS in particular, has not been explored in a systematic manner. We performed a systematic review to evaluate the effect of preoperative opioid use on the success of TS in terms of long-term pain relief.

Methods

Study selection

A systematic literature search of MEDLINE, EMBASE, and The Cochrane Library was performed for all studies on the outcome of TS used in patients with CP. The MEDLINE and EMBASE search terms were (“Sympathectomy” OR “Splanchnic Nerves” OR (“Splanchnic” AND “denervation”) OR splanchnicectomy) AND (chronic pancreatitis OR “Pancreatitis, Chronic”). The Cochrane search terms were (splanchnicectomy OR splanchnic) and (pancreatitis AND chronic) in Clinical Trials. We searched MeSH terms as well as free text words in the title, abstract, and keywords. All titles and abstracts of studies identified in the initial search were screened to select those that reported on patients with CP who underwent TS. Study selection and data extraction were conducted by two reviewers independently, and discrepancies were resolved by discussion. All cross references were screened for

potentially relevant studies not identified in the initial literature search.

Inclusion criteria were (1) consecutive cohort studies presenting results of unilateral or bilateral TS in patients with CP, (2) studies must have a follow-up of at least 12 months, and (3) studies must have reported preoperative opioid analgesia use and the rate of pain relief after TS. Exclusion criteria were (1) a small cohort (fewer than 5 patients); (2) approaches for TS other than thoracoscopic (e.g., a transhiatal or intra-abdominal approach); (3) series with mixed diseases, unless CP patients were presented and analyzed separately; (4) different publications by the same group using overlapping cohorts (only the most recent study was included); (5) studies in a language other than English, German, or Dutch; and (6) publications other than cohort studies (e.g., case reports, letters, editorials, experimental studies, book chapters).

Study outcomes

The primary outcome was the long-term success of TS, defined as the proportion of patients who at the end of follow-up were free of opioid analgesia or had a reduction of four or more points on the visual analog scale (VAS) or numerical rating scale (NRS) [12]. Secondary outcomes were the percentage of patients free of opioids and the percentage of patients free of pain. We investigated the effect of the following factors on our primary outcome: sex, age, preoperative use of opioids, duration of follow-up, prior interventions of the pancreas (e.g., endoscopic, surgical, nerve blockade), duration of disease or pain, and the underlying pancreatic morphology (e.g., dilated duct, enlarged pancreatic head).

Data extraction

The following variables were extracted, when available: gender, age, number of patients with CP who underwent TS, follow-up (in months), preoperative and postoperative opioid use, study design, whether free of opioids at the time of follow-up, VAS or NRS pain score before and after TS, the difference in pain scores before and after TS, previous celiac blockades, and endoscopic or surgical interventions. The duration of disease or pain and morphology were not reported systematically and in enough detail to be extracted from the data and to use for proper analysis; thus, these potential predictive factors were discarded from data extraction and data analysis.

Data and statistical analysis

Dichotomous data are presented as events and percentages. Continuous data are presented as mean [\pm standard

deviation (SD)] or median [interquartile range (IQR)], as appropriate. Studies were initially stratified into those in which 25, 50, and 75 % of the patients used opioids. Because few studies met these criteria, studies were stratified into those with 50 % or fewer patients with preoperative opioid use and those with more than 50 %. The success rate is presented and compared between these two groups by means of the χ^2 test. Additionally, factors potentially associated with the study's outcome in univariable analysis ($p < 0.20$) were included in a multivariable analysis using a backward stepwise model. Statistical significance was considered $p < 0.05$. All analyses were performed using SPSS ver. 19.0. The study search, selection, and reporting were adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [13].

Results

We screened a total of 220 articles and selected 53 potentially relevant articles. Of these 53 papers, 37 were excluded. Reasons for exclusion were there were fewer than five patients ($n = 5$) [14–18]; different publications by the same group using overlapping cohorts ($n = 6$) [11, 19–23]; the study had a mixed population of patients (e.g., CP and pancreas carcinoma) without any possibility of separating the results ($n = 3$) [24–26]; the study was in a language other than English, German, or Dutch ($n = 3$) [27–29]; the study used a transhiatal or intra-abdominal approach for TS ($n = 15$) [30–43]; and the publication was not a cohort study (e.g., it was a case report, letter, editorial, experimental study, book chapter) ($n = 5$) [44–48]. The results of the literature search are summarized in Fig. 1.

Sixteen studies were finally included in this systematic review (Table 1) [6–8, 12, 21, 49–60]. Fourteen studies (88 %) were prospective cohort studies and two were retrospective cohort studies. All studies reported either the proportion of patients who at the end of follow-up were free of opioid analgesia or the proportion of patients who had a reduction of four or more points on the VAS or NRS regardless of postoperative opioid use.

The selected studies included a total of 484 patients with CP who underwent TS as treatment for pain. The median number of patients per study was 21 (IQR 14–47), with the number of patients per study ranging from 8 to 75. The mean age of all patients was 44 years ($SD \pm 4.3$) and 66 % were male. The median follow-up of the studies was 21 months (IQR 14–35). The median preoperative opioid use was 85 % (IQR 54–100). In four studies fewer than 50 % of the patients used opioids before TS [8, 53–55].

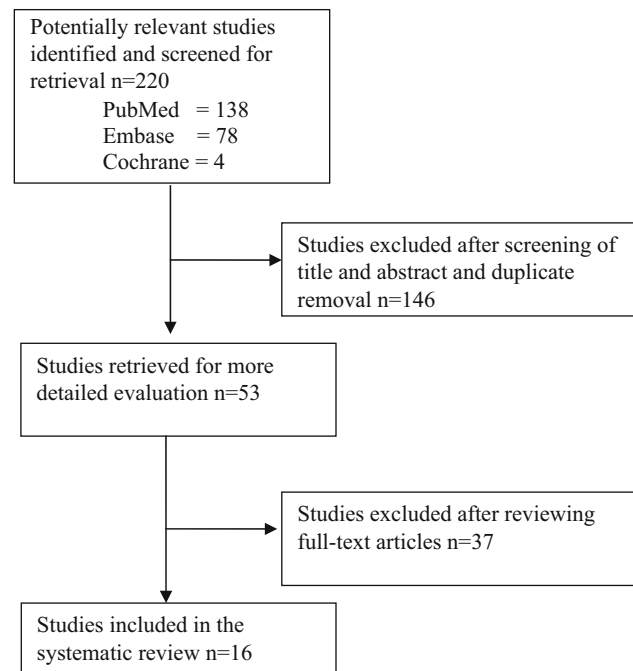


Fig. 1 Study flowchart

Characteristics of all included studies are presented in Table 1.

At the end of follow-up, a median of 49 % (IQR 22–75) of patients was free of opioid analgesics. The mean decrease in VAS/NRS from before to after TS was 4.3 ($SD \pm 1.84$) points. The median success rate was 62 % (IQR 48–86). The mean success rate of the studies with 50 % or less of the patients using preoperative opioids was significantly higher than that of the studies with more than 50 % of patients using preoperative opioids [81 % ($SD \pm 21$) vs. 60 % ($SD \pm 15$) ($p = 0.049$)] (Fig. 2).

In univariable analysis, increased age, male gender, and lower rates of preoperative opioid use were associated with a higher success rate ($p = 0.003, 0.047, 0.017$, respectively) (Table 2; Figs. 3, 4). These factors and length of follow-up ($p = 0.17$) were included in the multivariable analysis. Multivariable regression revealed age and preoperative opioid use as independent predictors of success after TS. Higher rates of preoperative opioid use and younger age were thus independently associated with a worse outcome after TS (Table 3).

Discussion

In this study we reviewed the outcome of TS in patients with CP. The results support the hypothesis that preoperative opioid use reduces the success rate of TS, as evidenced by the strong association between a high rate of

Table 1 Study characteristics

Study [ref]	Country	Years	Design	No. patients	Age (mean)	Male (%)	Follow-up (months)	Previous operation	Previous endoscopic intervention	Celiac blockade	Preoperative opioid use (%)	Free of opioids (%) ^a	Pain relief after TS (mean)	Success rate (%)
Andrén-Sandberg et al. [59]	Sweden	1996	P	14	48	58	16	N = 7	NR	NR	100	79	4	79
Bradley et al. [49]	USA	1998	P	16	42.9	69	23	N = 15	NR	NR	100	20	4.15	50
Buscher et al. [57]	Netherlands	2002	P	44	41	59	36	N = 47	12	12	82	12	6.5	46
Buscher et al. [6]	Netherlands	2008	P	75	46	60	54	N = 28	9	2	88	55	35	55
Davis et al. [50]	USA	2008	P	54	43.4	33	12	N = 2.7 ^b	N = 2.7 ^b	NR	70	14 ^c	2.6	68
Hammond et al. [51]	USA	2004	P	20	43	40	15	N = 19	NR	N = 59	95	17	3	60
Howard et al. [7]	USA	2002	P	55	38.5	35	32	N = 6	32	NR	100	44	1.3	41
Ihse et al. [52]	Sweden	1999	P	21	48	67	43	N = 20	NR	NR	67	62	5	90
Kusano et al. [53]	Japan	1997	R	9	42.3	75	14	NR	NR	N = 2	22	88	7.7	88
Leksowski et al. [60]	Poland	2005	P	42	36.4	80	38	N = 8	NR	N = 2	100	47	4.3	47
Maher et al. [21]	USA	1996	P	15	41	27	17	NR	NR	N = 15	73	53	4.1	46
Makarewicz et al. [54]	Poland	2003	P	32	51.5	66	12	NR	NR	NR	45	7 ^d	4.4	94
Moodley et al. [55]	South Africa	1999	P	17	47	100	12	N = 0	NR	NR	0	94	6.1	94
Noppen et al. [56]	Belgium	1998	R	8	49.1	71	23	N = 1	NR	NR	100	28	NR	63
Stefaniak et al. [8]	Poland	2008	P	48	NR	NR	18	NR	NR	NR	50	50	1.5	50
Tarnowski et al. [58]	Poland	2004	P	14	NR	93	24	NR	NR	N = 2	100	69	6.55	79

Operations include pancreatic resection and drainage procedures, papiloplasty, biliodigestive bypass, pseudocyst drainage, cholecystectomy, explorative laparotomy, gastric resections and reconstructions

^a At the time of follow-up

^b Mean number of diagnostic and interventional endoscopies per patient

^c 70 % of the patients

^d After 3 months of follow-up

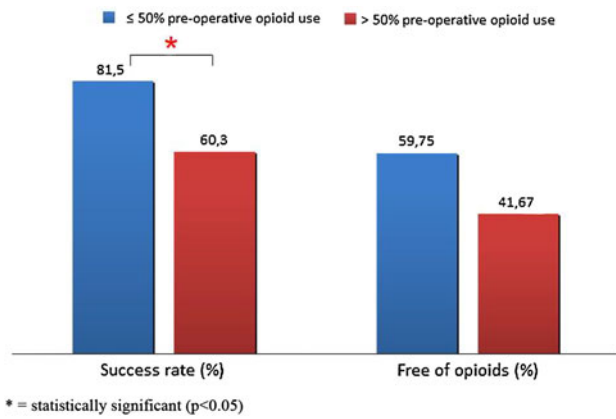


Fig. 2 Influence of preoperative opioid use on success rate and proportion of opioid-free patients after TS

Table 2 Univariable analysis of risk factors associated with success rate after TS

Risk factors	Regression coefficients (95 % CI)	p value
Age	3.322 (1.336 to 5.308)	0.003
Male gender	0.468 (0.006 to 0.929)	0.047
Preoperative opioid use	-0.361 (-0.645 to -0.076)	0.017
Follow-up duration	-0.531 (-1.333 to 0.271)	0.177
Previous operation	-0.437 (-1.451 to 0.578)	0.350
Previous endoscopy	-0.479 (-4.350 to 3.393)	0.361
Previous celiac block	-0.128 (-1.054 to 0.798)	0.737

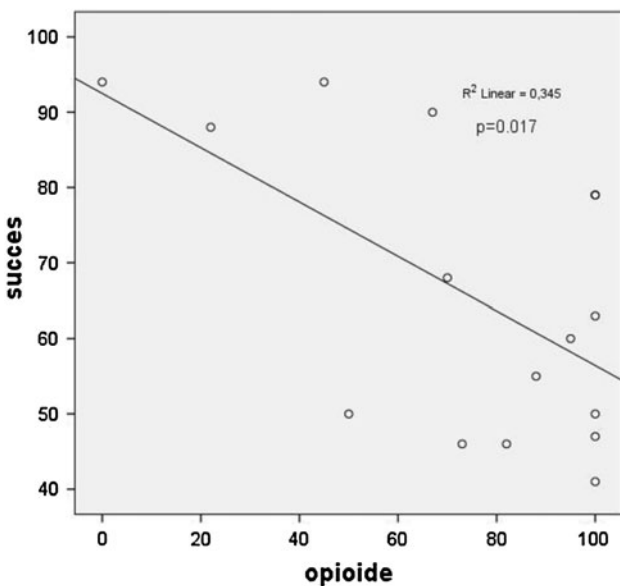


Fig. 3 Correlation of preoperative opioid use and success rate after TS

preoperative opioid use and a low rate of long-term pain relief. Results indicate that TS should be considered before patients with CP start using opioids for their pain.

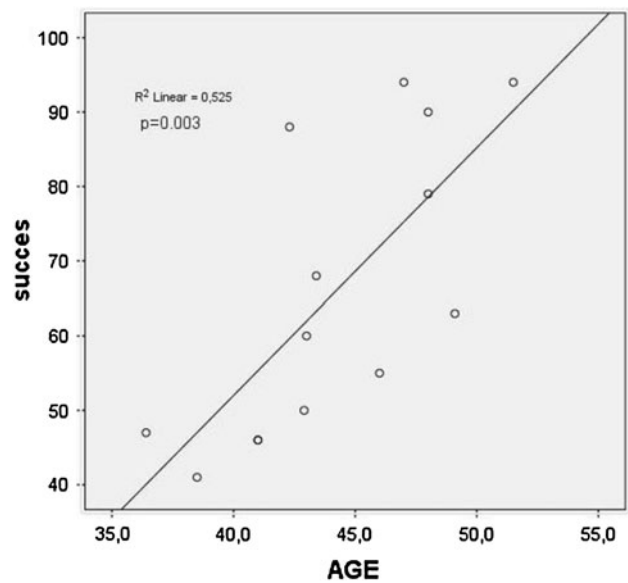


Fig. 4 Correlation of age and success rate after TS

Table 3 Multivariable analysis of risk factors associated with success rate after TS

Risk factors	Regression coefficients (95 % CI)	p value
Age	2.557 (1.191 to 3.923)	0.002
Preoperative opioid use	-0.348 (-0.532 to -0.164)	0.002

Two cohort studies showed that preoperative treatment with opioid analgesics is a significant predictor of early recurrence of pain ailments after TS [6, 8]. The negative effect of opioid use is also in line with the findings of studies on the effect of opioids in pancreatic surgery for CP [61–63]. Preoperative opioid use was a predisposing factor of failure to achieve complete long-term pain relief after pancreatic drainage and resection procedures, with an odds ratio of 30 [61]. We recently found an independent association between preoperative daily opioid use and persistent severe pain after pancreatic surgery in a large multicenter cross-sectional cohort study of 223 consecutive CP patients with a median follow-up of 62 months [62]. Alexakis et al. [63] analyzed the outcome of pancreatic resection for CP in 112 patients with and without preoperative opioid use. Patients who used opioids had symptom onset at a younger age, longer symptom duration, more hospitalizations, a higher frequency of diabetes mellitus, a higher pain score, and more restrictions to daily activity. Twenty-one (46 %) patients with opioid use had a total pancreatectomy compared with 9 (14 %) without opioid use; the opioid users also had a higher frequency of postoperative bleeding and early reoperation. Interestingly, similar negative results with respect to preinterventional opioid use were obtained in patients who underwent

endoscopic therapy for CP [64]. Patients who responded to endoscopic therapy were more likely to be older at the start of endoscopic therapy, had less constant pain, required fewer daily narcotics, and had a shorter interval between diagnosis of CP and start of endoscopic therapy. These findings point out that opioid use reduces the success of all types of interventions to treat CP pain.

A potential explanation for the lower rate of success is opioid-induced hyperalgesia, in which opioids cause peripheral and central sensitization and patients become more sensitive to certain pain stimuli. This is thought to result from neuroplastic changes in the peripheral and central nervous systems that lead to sensitization of the sensory pathways [65, 66]. Clinically, opioid-induced hyperalgesia is difficult to distinguish from opioid dependency, which may also explain the lower success rates of TS and other pain interventions. Opioid use may be a reflection of longstanding pancreatic pathology, a longer history of pancreatitis, multiple failed previous interventions, and continuous pain treated by opioids [5, 7, 62, 63]. In such patients it is difficult to assess the independent effect of opioid use on treatment success. Previous surgical intervention and pancreatic pathology have been investigated as predictive factors for treatment failure after TS [5, 7, 22]. Howard et al. [7] showed that TS appears to work best in patients who had no prior operative or endoscopic intervention. These patients also required lower amounts of daily opioid analgesics and had fewer additional procedures for pain control in the 24-month follow-up period [7]. Cuschieri et al. [5] reported that the best results were observed in patients with minimal-change pancreatitis. These data support the hypothesis that patients with mild pathology, in the early phase of their disease, and without opioid use might benefit most from TS. Unfortunately, data were not sufficiently reported to analyze the influence of previous pancreatic intervention, duration of the disease, or pathology on the outcome of TS.

We also found that a higher age was associated with a better outcome of TS. Interpreting this finding without further information about the etiology of the patients and the duration of disease prior to intervention is difficult. Such data were not available from the published studies. Perhaps patients with hereditary pancreatitis tend to do worse than patients with other etiologies (e.g., late-onset idiopathic CP) who develop pancreatitis at a later age. Patients who develop CP at a younger age will have had a longer duration of disease and pain, which also could explain the higher risk of developing hyperalgesia. These theories, however, cannot be proven without further data.

A limitation of our study is the use of aggregate data, which decreases the power of the study. However, obtaining individual patient data, which would have

allowed more power and more uniform definitions, was not feasible. Nevertheless, analysis of data from 484 pooled patients with a long follow-up showed clear and strong associations, providing robust evidence of the negative effects of preoperative opioid use on the outcome of TS.

TS is currently considered a treatment of “last resort” for CP, performed only sporadically for patients with severe pain who failed to respond to previous medical, endoscopic, and surgical interventions. Our results suggest that TS is more successful when patients have not yet used opioids. A minimally invasive procedure such as TS seems a good alternative to major pancreatic surgery early in the disease course and would be more acceptable to patients. Moreover, TS is suitable for virtually all patients with CP, regardless of the presence of morphological changes that are needed to target surgical or endoscopic treatment. Therefore, early TS might offer a unique opportunity to treat minimal-change CP (i.e., small-duct CP), a group of patients with currently very few treatment options.

Although large, well-designed studies are needed to further establish the role of early TS in patients with CP, results of this review should help clinicians better define patients who will likely benefit from splanchnicectomy.

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