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GENERAL & SELECTED POPULATIONS SECTION

Are Invasive Procedures Effective for Chronic Pain? A Systematic Review

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Abstract

Objective. To assess the evidence for the safety and efficacy of invasive procedures for reducing chronic pain and improving function and health-related quality of life compared with sham (placebo) procedures. **Design.** Systematic review with meta-analysis. **Methods.** Studies were identified by searching multiple electronic databases, examining reference lists, and communicating with experts. Randomized controlled trials comparing invasive procedures with identical but otherwise sham procedures for chronic pain conditions were selected. Three authors independently extracted and described study characteristics and assessed Cochrane risk of bias. Two subsets of data on back and knee pain, respectively, were pooled using random-effects meta-analysis. Overall quality of the literature was assessed through Grading of Recommendations, Assessment, Development, and Evaluation. **Results.** Twenty-five trials (2,000 participants) were included in the review assessing the effect of invasive procedures over sham. Conditions included low back (N = 7 trials), arthritis (4), angina (4), abdominal pain (3), endometriosis (3), biliary colic (2), and migraine (2). Thirteen trials (52%) reported an adequate concealment of allocation. Fourteen studies (56%) reported on adverse events. Of these, the risk of any adverse event was significantly higher for invasive procedures (12%) than sham procedures (4%; risk difference = 0.05, 95% confidence interval [CI] = 0.01 to 0.09, $P = 0.01$, $I^2 = 65\%$). In the two meta-analysis subsets, the standardized mean difference for reduction of low back pain in seven studies (N = 445) was 0.18 (95% CI = –0.14 to 0.51, $P = 0.26$, $I^2 = 62\%$), and for knee pain in three studies (N = 496) it was 0.04 (95% CI = –0.11 to 0.19, $P = 0.63$, $I^2 = 36\%$). The relative contribution of within-group improvement in sham treatments accounted for 87% of the effect compared with active treatment across all conditions. **Conclusions.** There is little evidence for the specific efficacy beyond sham for invasive procedures in chronic pain. A moderate amount of evidence does not support the use of invasive procedures as compared with sham procedures for patients with chronic back or knee pain. Given their high cost and safety concerns, more rigorous studies are required before invasive procedures are routinely used for patients with chronic pain.

Key Words: Surgery; Placebo; Sham; Pain; Systematic Review; Meta-analysis

Introduction

Chronic pain is a major worldwide problem. In the United States, it is estimated that more than 100 million people suffer from chronic pain, with costs between $560 and $635 billion dollars per year [1]. The estimated prevalence of pain lasting at least three months is 14.6% [2]. The prevalence of chronic musculoskeletal pain conditions and frequent headaches is 43% [3]. Data from the 2012 National Health Interview Study estimated the prevalence of chronic daily pain to be 25.3 million people or 11.2% of the population [4]. These numbers do not describe the full impact that chronic pain has on productivity, quality of life, and human suffering.

To treat pain, the use of opioids has increased dramatically over the last several decades, with 9.6 to 11.5 million adults or approximately 3%–4% of the adult US population having been prescribed long-term opioid therapy [5]. Opioids have limited effectiveness for chronic pain and are accompanied by substantial risk of adverse outcomes including addiction, overdose, and deaths. Deaths from opioids now exceed deaths from motor vehicle accidents [6]. Thus, the need for nonpharmacological approaches for treating chronic pain has grown.

Invasive procedures (including surgery) might mitigate the need for chronic opioid and other pharmacological therapies and be viable options for chronic pain treatment. Procedures that completely replace damaged or arthritic joints or change major anatomical structures can produce long-term reduction in pain and improvement in function [7]. However, invasive procedures are increasingly being used for pain where the anatomical causes for the pain are not so clear.

The development of minimally invasive procedures has expanded the use of such interventions for treating a variety of chronic pain conditions such as low back pain [8], arthritis [9], and endometriosis [10]. In 2014, more than $45 billion was spent in the United States on surgical treatments for chronic low back pain (LBP). Arthroplasty costs for chronic knee pain topped $41 billion [11]. Invasive procedures are considered effective and are standard care for these two conditions. However, many types of invasive procedures are marketed, used, and paid for without evidence from rigorous study designs involving randomization, allocation concealment and blinding, or placebo controls. In the absence of these controls for common sources of bias, studies on invasive procedures may be giving a false impression of their true efficacy. Individual efficacy studies of invasive procedures have been published for LBP [12,13] and osteoarthritis of the knee [14], and a recent meta-analysis estimated the magnitude of the effects of sham surgery on subjective and objective outcomes [15]. However, no comprehensive systematic review of the current evidence on the safety and efficacy of invasive procedures compared with placebo treatment in chronic pain has been done.

It is the purpose of this study to identify and evaluate the current evidence for invasive procedures compared with their identical sham procedures in the treatment of chronic pain and assess the impact on reducing pain, medication use, disability, adverse events, and enhancing health-related quality of life for patients with various chronic pain conditions.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for reporting this systematic review with meta-analyses.

Study Eligibility Criteria

Randomized controlled trials (RCTs) that compared any invasive procedure, including classical surgery, with a parallel sham procedure for patients with chronic pain conditions were eligible. Invasive procedures were defined as when an instrument was inserted into the body (either endoscopically or percutaneously) for the purposes of manipulating tissue or changing anatomy. Procedures used only as a method to deliver another active treatment such as a drug (e.g., steroids), cells, implantation of an electrical device, or new joint were excluded. To be eligible, all procedures needed to be compared with an identical yet sham procedure that used the same invasive approach, instruments, and ritual but eliminated the hypothesized active component of tissue manipulation. Chronic pain conditions were defined as those conditions where pain lasted more than three months [7,16]. Other outcomes related to function and health-related quality of life were captured when reported. Only studies with observation periods of one or more months after treatment were eligible.

Identification and Selection of Studies

The search strategy was adapted from a previously published systematic review and meta-analysis conducted by the authors investigating nonspecific components in sham-controlled surgical trials for all conditions [17]. An updated search was conducted for the purposes of this paper through January 2018 across PubMed, EMBASE, CINAHL, Central (Cochrane Library), PILOTS, PsycInfo, DoD Biomedical Research, and clinicaltrials.gov to capture any recent relevant literature. Search terms included ("Diagnostic Techniques, Surgical" OR "Orthopedic Procedures" OR "Specialties, Surgical" OR "Surgical Procedures, Operative" OR "surgery" [Subheading] or surgery) AND ("Placebos" OR "Placebo Effect" or sham surg* or placebo surg* or mock surg* or simulated surg* or placebo proc* or sham proc* or mock proc* or simulated proc*). All searches were restricted to humans and RCT study design [17]. In addition, reference lists were examined, and experts in the field were contacted to ensure comprehensiveness of the included

studies. Four investigators (CC, KM, KL, LC) screened titles and abstracts independently and in duplicate using a structured form, and studies on chronic pain conditions were selected for analysis. Any disagreements in selection or classification were resolved through discussion and consensus and approved by the first author (WJ).

Data Collection and Study Appraisal

We used the Mobius Analytics Systematic Review System (Mobius Analytics Inc., Ottawa, Ontario, Canada) for data entry and execution of the review. All studies meeting the predefined inclusion criteria were assessed for methodological quality independently and in duplicate using the Cochrane risk of bias tool [18]. Data were extracted to capture study characteristics and pain outcomes at all time points. Additional outcomes related to function, medication use, health-related quality of life, and adverse events were also extracted. Study appraisal and data extraction were performed by three investigators (CC, KM, LC). These investigators are all experienced in systematic review methods, including data extraction and extracted data in duplicate. In addition, 20% of the studies were checked by the primary author (WJ). All discrepancies were tracked and resolved by discussion, with final decisions made by the primary author.

Data Synthesis and Analysis

Studies were grouped according to chronic pain condition and the procedure reported in the study. Where data were available for a reduction in pain intensity, disability, health-related quality of life, adverse events, dropouts, and/or medication use, the sample size, mean, and standard deviation for each treatment group at each time point were extracted in duplicate (CC, KM). For continuous data, standardized mean differences (SMDs) were computed as the difference between groups in pre–post change scores by using Comprehensive Meta-Analysis, version 3.3.070 (Biostat, Englewood, NJ, USA). When standard deviations for change scores were not reported, they were calculated from pre and post standard deviations [19], using $r = 0.5$ for the product–moment correlation. For studies with dichotomous outcomes, either the relative risk between the percentage of responders in the sham and active treatment groups (responder ratio) or the risk difference between groups (for adverse events and study dropouts) was calculated with Cochrane Collaboration's Review Manager (RevMan; version 5.2.7). This was done regardless of whether the studies were pooled for analysis or not.

A forest plot was created for each study that had data capable of supporting an effect size analysis to facilitate a visual comparison of results across studies and conditions.

Because of the variety of conditions and treatments, a meta-analysis was not done for the entire study sample. However, the authors judged meta-analysis feasible when

1) there were more than three studies within a single chronic pain condition with data available in the papers; 2) the interventions and outcomes were similar enough to allow for a clinically meaningful estimate of the reduction in pain intensity; and 3) when the comparison was made to the intervention's own sham. This approach meets current standards for meta-analysis [20,21]. Low back pain and osteoarthritis of the knee met these criteria. Meta-analyses of SMDs, relative risks, and risk differences were then performed with the generic inverse model of RevMan for low back and knee pain using random effects models. Statistical heterogeneity was examined by Cochrane's Q test and I^2, with low, moderate, and high I^2 values of 25%, 50%, and 75%, respectively. Egger's test was used to assess funnel plot asymmetry as a measure of publication bias [22]. Pooled effect sizes for the pain-related outcome of primary interest in back and knee pain were translated into the visual analog scale (VAS; 0–100) for ease of clinical interpretation using a standard deviation of 25 points [23]. A P value of less than 0.05 was set as the level of significance.

The overall quality of the body of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation approach based on the following criteria: risk of bias, inconsistency, indirectness, imprecision, magnitude of the estimates of effects, and publication bias [24]. Two authors (CC, KM) independently performed this exercise and then met with the primary author (WJ) to review and come to consensus.

Results

Study Selection

We identified 7,362 citations based on the original search executed [17] and updated through January 2018. Twenty-five studies (in 28 publications) published between 1959 and 2013, involving a total of 2,000 patients with specific chronic pain conditions, met eligibility criteria for the systematic review (Figure 1). No studies met the eligibility criteria from 2014 through January 2018.

Characteristics of Included Studies

Characteristics of included studies are summarized in Table 1. Of the 25 studies on chronic pain conditions, low back pain (N = 7 studies) was the most frequent diagnosis reported [12,13,25–29], followed by knee osteoarthritis (N = 4) [14,30–32], angina from coronary artery disease (N = 4) [33–37], abdominal pain (N = 3) [38–40], endometriosis (N = 3) [41–45], biliary pain (N = 2) [46,47], and migraine (N = 2) [48,49]. The total number of enrolled patients per study ranged from 10 [30] to 298 (Table 1) [37].

The procedures used included arthroscopic surgery or irrigation [14,30–32], heart catheterization with laser treatment or septal repair [35–37,48], endoscopic
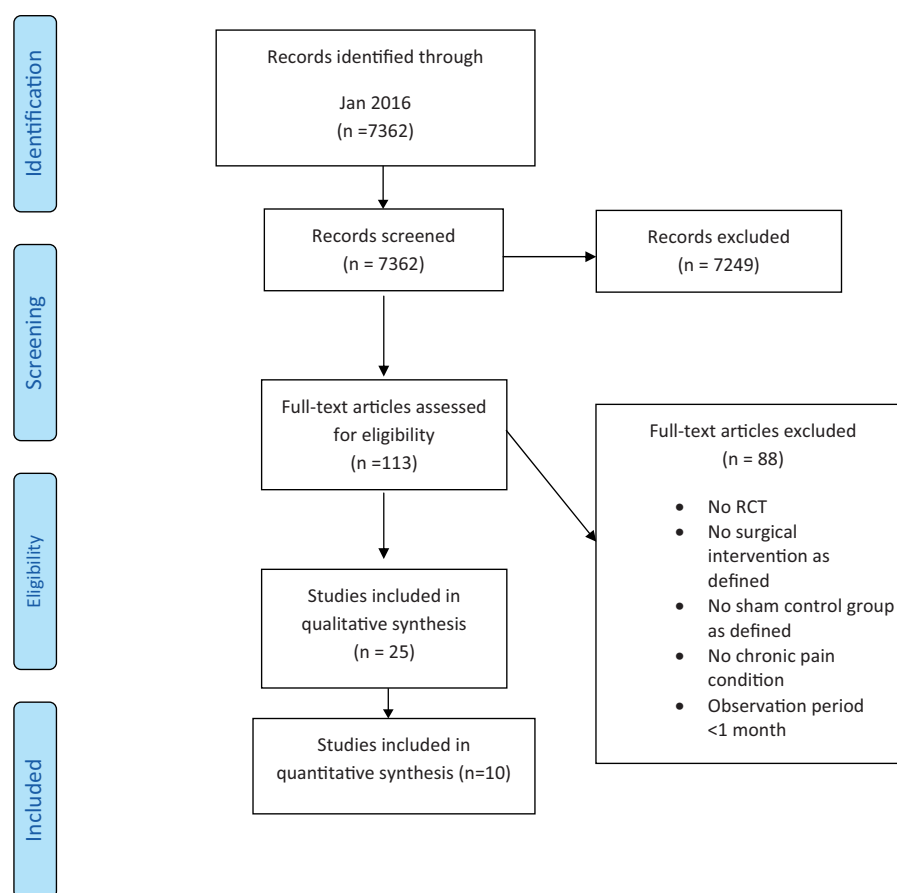
Figure 1. PRISMA flow diagram. RCT = randomized controlled trial.

sphincterectomy [39,46,47], percutaneous or open neurectomy (mechanical or via radiofrequency) [25,26,28,29,40,49], laparoscopic surgery or laser treatment [38,43–45], vertebroblasty [12,13], intradisc delivery of electrothermal energy [27], and surgical ligation of internal mammary arteries [33,34]. All control groups used a parallel sham procedure mimicking the active procedure. Sham percutaneous and endoscopic procedures typically involved skin incisions only or insertion and removal of a needle or a scope without further tissue manipulation (Table 1).

In addition to pain as an outcome, more than half of the studies reported at least one secondary outcome, including function-related outcomes (disability; N = 6), health-related quality of life parameters (global, physical, mental; N = 11), and medication use (N = 3). Seventeen studies reported a dichotomous (responder) outcome.

Risk of Bias in Included Studies

Overall, the risk of bias was moderate to low. Of the 25 studies included in the systematic review, 17 studies (68%) reported an adequate method for generating the allocation sequence; however, only 13 (52%) had adequate concealment of allocation. Blinding of patients and outcome assessors was adequate in 21 (84%) studies, and incomplete data were adequately addressed in 18

(72%). Blinding of surgeons could not be done. Seventeen (68%) were free from suggestion of selective outcome reporting, and 19 (76%) were judged to be free of other sources of bias.

Adverse Events

Of the 25 studies included in this analysis, five (20.0%) reported that no adverse events or complications occurred, nine (36.0%) described the adverse events and in which study arm they occurred, five (20.0%) described the adverse events but did not distinguish in which study arm they occurred, two (8.0%) described the adverse events insufficiently, and four (16.0%) did not report on or mention adverse events. In the 14 studies providing sufficient data, the risk of any adverse event was significantly higher in the active groups (12%) than in the sham groups (4%; risk difference = 0.05, 95% confidence interval [CI] = 0.01 to 0.09, $P = 0.01$, $I^2 = 65\%$). On average, the number of study dropouts did not differ between the active and sham groups (risk difference = 0.01, 95% CI = –0.01 to 0.03, $P = 0.38$, $I^2 = 9\%$) (Supplementary Data).

Study Results and Analysis

The findings for all studies are summarized in Table 1, and calculated SMDs are shown in Figure 2A. Four

Table 1. Characteristics of included studies

Source	Condition	Total No., Treatment/Control	Active Treatment	Sham Treatment	Selected Cochrane ROB Items	Pain and Related Outcome(s)
Low back pain						
van Kleef et al., 1999 [25]	Chronic low back pain	T 15/C 16	Radiofrequency lumbar facet denervation	Electrodes were introduced, but no radiofrequency lesion was made	Concealment: unclear; Blinding; adequate	Pain intensity 1–3 mo: SMD: 0.86 (0.13, 1.60); Medication use 1–3 mo: SMD: 0.59 (–0.13, 1.31); Global QoL 1–3 mo: SMD: 0.34 (–0.37, 1.05); # adverse events: RD: 0.00 (–0.12, 0.12)
Leclaire et al., 2001 [26]	Low back pain (>3 mo)	T 36/C 34	Percutaneous radiofrequency articular denervation	Same procedure without denervation	Concealment: adequate; Blinding; adequate	Pain intensity 1–3 mo: SMD: –0.29 (–0.78, 0.19); Disability 1–3 mo: SMD: 0.18 (–0.30, 0.67); # adverse events: RD: 0.00 (–0.05, 0.05)
Freeman et al., 2005 [27]	Chronic discogenic low back pain	T 38/C 19	Delivering of electrothermal energy via catheter	Identical positioning of catheter without delivering electrothermal energy	Concealment: unclear; Blinding; adequate	Pain intensity 6 mo: SMD: –0.46 (–1.02, 0.10); Disability 6 mo: SMD: 0.20 (–0.36, 0.75); QoL Physical 6 mo: SMD: –0.13 (–0.68, 0.42) Mental QoL 6 mo: SMD: 0.04 (–0.52, 0.59); # adverse events: RD: 0.05 (–0.09, 0.19)
Nath et al., 2008 [28]	Chronic low back pain	T 20/C 20	Percutaneous radiofrequency neurotomy	Identical procedure except no current was used	Concealment: unclear; Blinding; adequate	Pain intensity 6 mo: SMD: 0.56 (–0.07, 1.20); Medication use 6 mo: SMD: 0.68 (0.04, 1.33); Global QoL 6 mo: SMD: 1.04 (0.37, 1.71); # adverse events: 0.00 (–0.09, 0.09)
Buchbinder et al., 2009 [12]	Painful osteoporotic vertebral fractures	T 38/C 40	Vertebroplasty	Simulated vertebroplasty with insertion of the needle until lamina and odor of cement	Concealment: adequate; Blinding; adequate	Pain intension 1–3 mo: SMD: 0.22 (–0.24, 0.68), 6 mo: 0.04 (–0.43, 0.50); Disability 3 mo: SMD: –0.21 (–0.68, 0.25), 6 mo: 0.00 (–0.46, 0.46); Global QoL 1–3 mo: SMD: 0.17 (–0.34, 0.69), 6 mo: 0.17 (–0.34, 0.69); # adverse events: RD: 0.13 (–0.09, 0.34)
Kallmes et al., 2009 [13]	Painful osteoporotic vertebral fractures	T 68/C 63	Vertebroplasty	Simulated procedure with odor of cement	Concealment: adequate; Blinding; adequate	Pain intensity 1–3 mo: SMD: 0.15 (–0.19, 0.50); Disability 3 mo: SMD: 0.06 (–0.28, 0.40); Global QoL 1–3 mo: SMD: 0.15 (–0.19, 0.49); # adverse events: RD: 0.00 (–0.04, 0.04)

(continued)

Table 1. continued

Source	Condition	Total No., Treatment/Control	Active Treatment	Sham Treatment	Selected Cochrane ROB Items	Pain and Related Outcome(s)
Patel et al., 2012 [29]	Chronic sacroiliac joint pain	T 34/C 17	Lateral branch neurotomy using cooled radiofrequency	Identical procedure without delivery of radio-frequency energy	Concealment: unclear Blinding: adequate	Pain intensity 1–3 mo: SMD: 0.61 (0.02, 1.21) Disability 3 mo: SMD: 0.90 (0.26, 1.53) Global QoL 1–3 mo: SMD: 0.35 (−0.28, 0.96) # adverse events: RD: 0.00 (−0.09, 0.09)
Arthritis						
Moseley et al., 1996 [30]	Arthritis	lavage: 3/debridement: 2/C 5	Arthroscopic debridement or arthroscopic lavage	Skin incisions but no placement of instruments into the knee	Concealment: unclear Blinding: adequate	Patients who felt the operation was worthwhile
Moseley et al., 2002 [14]	Arthritis	Lavage: 61/ Debridement: 59/C 60	Arthroscopic debridement or arthroscopic lavage	Skin incisions but no placement of instruments into the knee	Concealment: adequate Blinding: adequate	Pain intensity 1–3 mo: SMD: −0.23 (−0.55, 0.09), 6 mo: −0.27 (−0.59, 0.05), 12 mo: 0.17 (−0.22, 0.56)
Bradley et al., 2002 [31]	Arthritis	T 89/C 91	Arthroscopic knee irradiation	Needle was advanced to, but not through, the joint capsule	Concealment: unclear Blinding: adequate	Pain intensity 1–3 mo: SMD: −0.12 (−0.42, 0.17), 6 mo: −0.15 (−0.44, 0.15), 12 mo: −0.05 (−0.34, 0.24) Medication usage 1–3 mo: SMD: −0.47 (−0.77, −0.17), 6 mo: −0.35 (−0.65, −0.05) Global QoL: 6 mo: SMD: 0.34 (0.04, 0.64), 12 mo: 0.38 (0.08, 0.68)
Silvonen et al., 2013 [32]	Arthritis	T 70/C 76	Arthroscopic partial meniscectomy	Simulation of arthroscopic meniscectomy	Concealment: adequate Blinding: adequate	Knee pain after exercise 1–3 mo: SMD: 0.25 (−0.08, 0.58), 6 mo: 0.14 (−0.19, 0.45), 12 mo: −0.04 (−0.37, 0.28) Global QoL 12 mo: SMD: 0.11 (−0.22, 0.43) # adverse events: RD: 0.01 (−0.02, 0.05)
Angina						
Cobb et al., 1959 [33]	Angina pectoris	T 8/C 9	Ligation of the internal mammary arteries	Skin incision with exposure of the internal mammary arteries with no ligation	Concealment: unclear Blinding: adequate	Patients with subjective improvement in angina >40% 12 mo: RR: 1.13 (0.51, 2.49) # adverse events: RD: 0.01 (−0.29, 0.32)
Dimond et al., 1960 [34]	Angina pectoris	not stated	Ligation of internal mammary arteries	Skin incision with exposure of the internal mammary arteries with no ligation	Concealment: unclear Blinding: adequate	Patients with ≥50% subjective improvement 12 mo: RR: 0.74 (0.48, 1.14)
Salem et al., 2004 [36] Salem et al., 2005 [35]	Aangina pectoris	T 40/C 42	Percutaneous myocardial laser revascularization plus optimal medical therapy	Sham procedure involving the laser catheter being inserted but not activated plus optimal medical therapy	Concealment: adequate Blinding: adequate	Patients with improvement by ≥1 CCS class 6 mo: RR: 1.75 (1.09, 2.80), 12 mo: 1.71 (1.07, 2.72)
Leon et al., 2005 [37]	Angina pectoris	T 196/C 102	Diagnostic catheterization and direct myocardial revascularization via laser catheterization	Diagnostic catheterization, and the laser was turned on outside the body	Concealment: unclear Blinding: adequate	Exercise duration pain 6 mo: SMD: 0.06 (−0.18, 0.30), 12 mo: 0.06 (−0.16, 0.32) Physical QoL 6 mo: −0.16 (−0.47, 0.15), 12 mo: 0.01 (−0.42, 0.21) Mental QoL 6 mo: 0.01 (−0.30, 0.33), 12 mo: 0.14 (−0.17, 0.46)

(continued)

Table 1. continued

Source	Condition	Total No., Treatment/Control	Active Treatment	Sham Treatment	Selected Cochrane ROB Items	Pain and Related Outcome(s)
Abdominal pain						
Swank et al., 2003 [38]	Chronic abdominal pain and adhesions	T 52/C 48	Laparoscopic adhesion lysis	Diagnostic laparoscopy only	Concealment: adequate Blinding: adequate	Pain intensity 1–3 mo: SMD: −0.28 (−0.68, 0.11), 6 mo: 0.13 (−0.26, 0.53), 12 mo: 0.17 (−0.22, 0.56) # adverse events: RD: 0.12 (0.02, 0.21)
Core et al., 2012 [39]	Painful pancreatic sphincter dysfunction	T 11/C 9	Endoscopic sphincterotomy	Sham endoscopy (not described)	Concealment: adequate Blinding: high risk	Patients with two or more distinct episodes of acute pancreatitis at follow-up evaluation 24 mo: RR: 0.82 (0.53, 1.26)
Boelens et al., 2013 [40]	Painful anterior cutaneous nerve Entrapment syndrome	T 22/C 22	Neurectomy of the intercostal nerve endings at the level of the abdominal wall	Sham surgery with exposure of intercostal nerve endings with no further surgical procedure	Concealment: adequate Blinding: adequate	Patients ≥50% improvement in pain 1–3 mo: RR: 4.0 (1.59, 10.06)
Endometriosis						
Sutton et al., 1994 [42] Sutton et al., 1997 [41]	Endometriosis	T 32/C 31	Laparoscopic laser treatment	Diagnostic laparoscopy	Concealment: unclear Blinding: adequate	Patients with any improvement in pain 1–3 mo: RR: 1.16 (0.72, 1.87), 6 mo: RR: 2.77 (1.37, 5.60) # adverse events: RD: 0.00 (−0.06, 0.06)
Abbott et al., 2004 [43]	Endometriosis	T 20/C 19	Laparoscopic excision	Diagnostic laparoscopy	Concealment: adequate Blinding: adequate	Pain dysmenorrhea intensity 6 mo: SMD: 0.10 (−0.53, 0.73) Global QoL 6 mo: SMD: 0.11 (−0.52, 0.74) Physical QoL 6 mo: SMD: −0.08 (−0.84, 0.67) Mental QoL 6 mo: SMD: 0.27 (−0.36, 0.91) # adverse events: RD: 0.10 (−0.05, 0.25)
Jarrell et al., 2005 [44] Jarrell et al., 2007 [45]	Endometriosis	T 8/C 7	Laparoscopic biopsy and excision	Diagnostic laparoscopy	Concealment: adequate Blinding: adequate	(data not usable)
Cholia (biliary cholic/pain)						
Geenen et al., 1989 [46]	Cholia	T 23/C 24	Endoscopic sphincterotomy	Sham sphincterotomy was performed with activation of the electrocautery unit in the duodenal lumen	Concealment: unclear Blinding: adequate	Patients reporting good or fair clinical improvement at 12 mo: RR: 2.24 (1.12, 4.46)
Toouli et al., 2000 [47]	Cholia	T 37/C 42	Endoscopic sphincterotomy	Endoscopy with noise simulation of sphincterotomy	Concealment: unclear Blinding: unclear	Patients with improvement in abdominal pain at 24 mo: RR: 1.45 (0.94, 1.91)

(continued)

Table 1. continued

Source	Condition	Total No., Treatment/Control	Active Treatment	Sham Treatment	Selected Cochrane ROB Items	Pain and Related Outcome(s)
Migraine						
Dowson et al., 2008 [48]	Migraine with aura	T 74/C 73	Patent foramen ovale closure with the starflex septal repair implant	Skin incision in the groin only	Concealment: adequate Blinding: adequate	Frequency of migraine attacks 6 mo: SMD: 0.24 (−0.08, 0.57) Disability 6 mo: SMD: 0.03 (−0.29, 0.35) # adverse events: RD: 0.18 (0.07, 0.28)
Guyuron et al., 2009 [49]	Migraine headache	T 49/C 26	Endoscopic removal of muscles and nerves in the predominant trigger sites	Exposure of the muscles and nerves through a similar incision, but the integrity of the structures was maintained	Concealment: adequate Blinding: adequate	Pain intensity 12 mo: SMD: 0.51 (0.03, 1.00) Physical QoL 12 mo: SMD: −0.32 (−0.80, 0.16) Mental QoL 12 mo: SMD: 0.58 (0.09, 1.06) # adverse events: RD: 0.35 (0.21, 0.49)

Standardized mean differences were computed as the difference between groups in pre–post change scores by using Comprehensive Meta-Analysis, version 3.3.070 (Biostat, Englewood, NJ, USA). When standard deviations for change scores were not reported, they were calculated from pre and post standard deviations [19], using $r = 0.5$ for the product–moment correlation. For studies with dichotomous outcomes, either the relative risk between the percentage of responders in the sham and active treatment groups (responder ratio) or the risk difference between groups (for adverse events) was calculated with Cochrane Collaboration's Review Manager (RevMan; version 5.2.7). A negative effect size favors sham treatment over active treatment in all cases, but for number adverse events risk difference, a positive effect indicates that there were fewer reported in the sham than the active.

Adapted and updated from: Jonas WB, Crawford C, Colloca L, et al. To what extent are surgery and invasive procedures effective beyond a placebo response? A systematic review with meta-analysis of randomised, sham controlled trials. BMJ Open 2015;5(12):e009655 [17].

C = sham control; CCS = Canadian Cardiovascular Society; QoL = quality of life; RD = risk difference; RR = responder ratio; SMD = standardized mean difference; T = real treatment.

studies were published on patients with angina pectoris where the procedure consisted of laser revascularization or internal mammary artery ligation compared with an identical yet sham control procedure. Outcomes varied across studies and mostly consisted of subjective improvement as stated by the patient or physician. Concealment was unclear in three of these studies. Three studies were included on abdominal pain where patients underwent various procedures. These studies had small sample sizes, and results were inconsistent. Three studies were on patients with endometriosis treated with laparoscopic excision (N = 2) or laser ablation (N = 1) and compared with the same but sham treatment. Sample sizes were small, and outcomes varied from study to study, making interpretation unclear. Two studies involved biliary pain treated with endoscopic sphincterotomy or a sham treatment. Patient improvement was noted after 12–24 months post-treatment. Two migraine studies used either patent foramen closure or muscle removal compared with sham procedures and recorded frequency of migraine attacks or pain intensity after six months. Both reported improvement over sham treatment for the active treatments.

There were at least three studies sufficient for pooling with meta-analysis in both low back pain and knee pain from osteoarthritis. Seven studies with 445 participants were included in the meta-analysis for back pain. The overall pooled SMD for reduction of low back pain was 0.18 (95% CI = −0.14 to 0.51, $P = 0.26$, $I^2 = 62\%$). Translated into the VAS pain score using a 0–100 point scale, this equates to a 4.5-point reduction in pain. Three studies involving 496 participants were included for knee pain due to osteoarthritis. The SMD was 0.04 (95% CI = −0.11 to 0.19, $P = 0.63$, $I^2 = 36\%$) for this condition, equating to a one-point VAS score reduction (Figure 2B). The proportion of improvement due to sham treatment in low back pain was 73%. In osteoarthritis, the average improvement in the sham surgery group was greater than after real surgery. On average, when compared with their own identical controls across all studies, pain reduction in the sham groups accounted for 87% of the improvement seen with active treatments (Figure 3). There did not appear to be evidence for substantial publication bias (Egger's test $P = 0.17$).

Secondary Outcomes

Several studies reported on secondary outcomes such as disability, medication use, and quality of life. Six studies measured disability-related outcomes from three to six months postsurgery. Looking at all studies, the reduction in disability postprocedure did not differ between the two groups at three months or at six months in the majority of studies (SMD range = −0.21 to 0.20) (Table 1). Only three studies measured medication use from three to six months postprocedure. They reported conflicting results for reduction in medication use between groups at
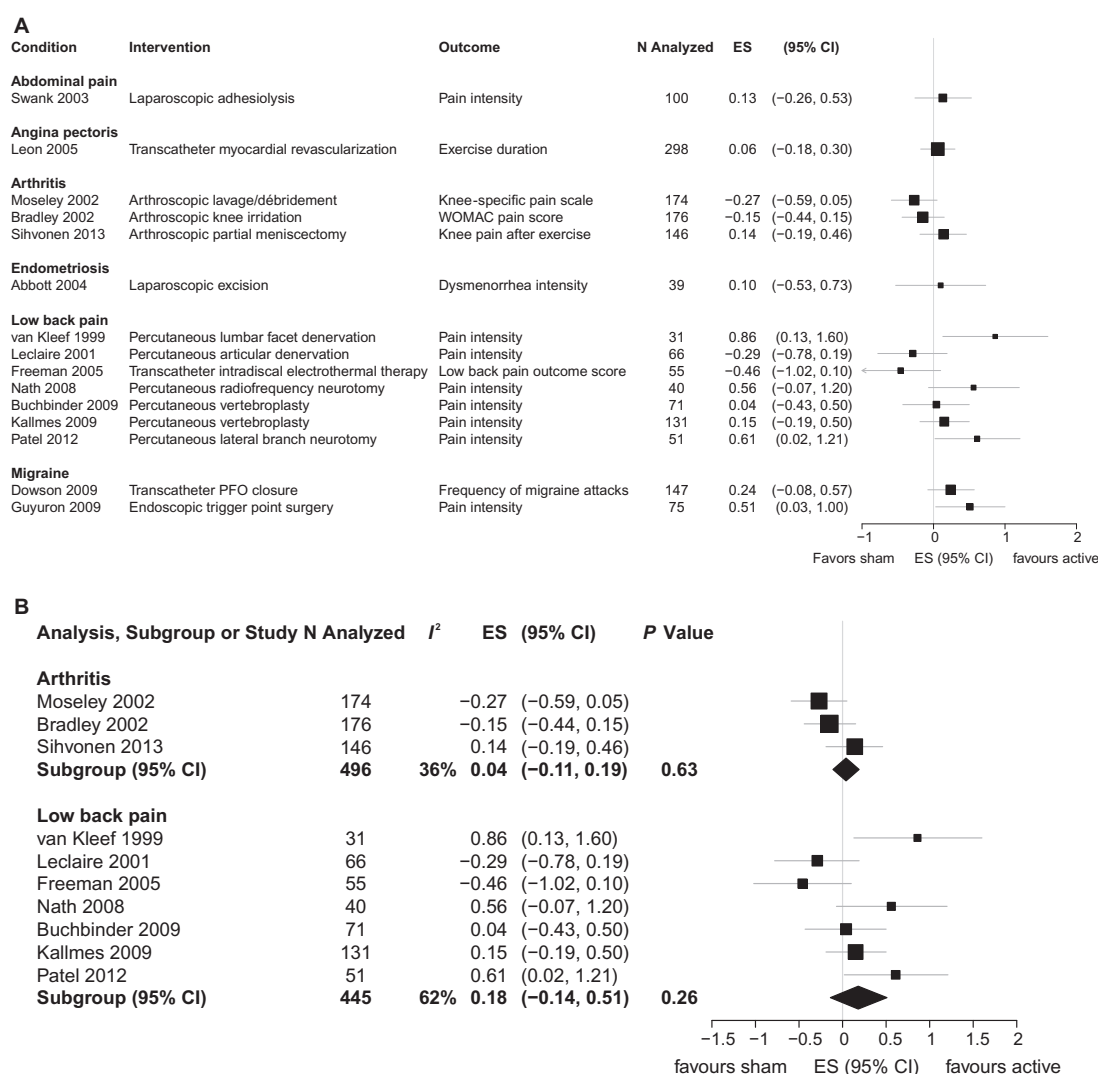
A

Condition	Intervention	Outcome	N Analyzed	ES	(95% CI)
Abdominal pain					
Swank 2003	Laparoscopic adhesiolysis	Pain intensity	100	0.13	(−0.26, 0.53)
Angina pectoris					
Leon 2005	Transcatheter myocardial revascularization	Exercise duration	298	0.06	(−0.18, 0.30)
Arthritis					
Moseley 2002	Arthroscopic lavage/débridement	Knee-specific pain scale	174	−0.27	(−0.59, 0.05)
Bradley 2002	Arthroscopic knee irridation	WOMAC pain score	176	−0.15	(−0.44, 0.15)
Sihvonen 2013	Arthroscopic partial meniscectomy	Knee pain after exercise	146	0.14	(−0.19, 0.46)
Endometriosis					
Abbott 2004	Laparoscopic excision	Dysmenorrhea intensity	39	0.10	(−0.53, 0.73)
Low back pain					
van Kleef 1999	Percutaneous lumbar facet denervation	Pain intensity	31	0.86	(0.13, 1.60)
Leclaire 2001	Percutaneous articular denervation	Pain intensity	66	−0.29	(−0.78, 0.19)
Freeman 2005	Transcatheter intradiscal electrothermal therapy	Low back pain outcome score	55	−0.46	(−1.02, 0.10)
Nath 2008	Percutaneous radiofrequency neurotomy	Pain intensity	40	0.56	(−0.07, 1.20)
Buchbinder 2009	Percutaneous vertebroplasty	Pain intensity	71	0.04	(−0.43, 0.50)
Kallmes 2009	Percutaneous vertebroplasty	Pain intensity	131	0.15	(−0.19, 0.50)
Patel 2012	Percutaneous lateral branch neurotomy	Pain intensity	51	0.61	(0.02, 1.21)
Migraine					
Dowson 2009	Transcatheter PFO closure	Frequency of migraine attacks	147	0.24	(−0.08, 0.57)
Guyuron 2009	Endoscopic trigger point surgery	Pain intensity	75	0.51	(0.03, 1.00)

Favors sham   ES (95% CI)   favours active

B

Analysis, Subgroup or Study	N Analyzed	I^2	ES	(95% CI)	P Value
Arthritis					
Moseley 2002	174		−0.27	(−0.59, 0.05)	
Bradley 2002	176		−0.15	(−0.44, 0.15)	
Sihvonen 2013	146		0.14	(−0.19, 0.46)	
Subgroup (95% CI)	**496**	**36%**	**0.04**	**(−0.11, 0.19)**	**0.63**
Low back pain					
van Kleef 1999	31		0.86	(0.13, 1.60)	
Leclaire 2001	66		−0.29	(−0.78, 0.19)	
Freeman 2005	55		−0.46	(−1.02, 0.10)	
Nath 2008	40		0.56	(−0.07, 1.20)	
Buchbinder 2009	71		0.04	(−0.43, 0.50)	
Kallmes 2009	131		0.15	(−0.19, 0.50)	
Patel 2012	51		0.61	(0.02, 1.21)	
Subgroup (95% CI)	**445**	**62%**	**0.18**	**(−0.14, 0.51)**	**0.26**

favours sham   ES (95% CI)   favours active

Figure 2. A) Individual between-group effects of invasive treatments compared with sham procedures. B) Meta-analysis for arthritis and low back pain. CI = confidence interval; ES = effect size.
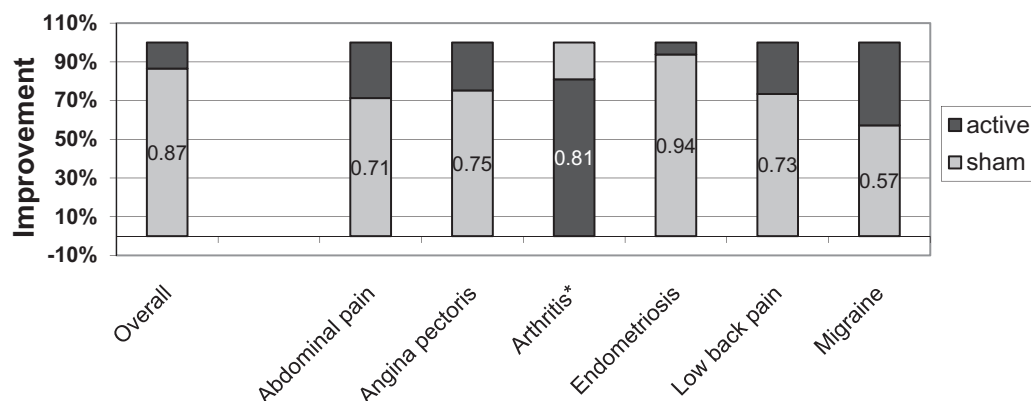

Figure 3. Relative contribution of within-group improvement in sham treatments to improvement in active treatment. *For arthritis, the improvement was larger for the sham treatments than for the active treatments.

either time point (SMD range = −0.47 to 0.68). Eleven studies reported on health-related quality of life using either a global score, physical or mental, or a combination,

primarily measured with the SF-36 or SF-12. Of those reporting on global health, the studies appear to favor active treatment over sham fairly consistently; over time,

however, the majority reported small SMDs. When assessing physical quality of life, the SMDs seem to favor the sham over the active treatments overall, whiched showed small SMDs. Mental quality of life showed no to small effects across studies (Table 1).

Discussion

There is currently insufficient evidence to support the specific efficacy of invasive procedures for the treatment of chronic pain. Very few studies have been done on any one condition, treatments and pain measures differed, and outcomes were inconsistent between studies. Quantitative pooling of outcomes for seven studies on low back pain and three on knee osteoarthritis showed no difference in pain at six months compared with sham procedures. At least for back pain and knee pain, sham surgical procedures explain the majority of the benefit, with confidence in these estimates being strong.

This study has several limitations. First, there are few studies in any one pain condition, resulting in substantial clinical heterogeneity across populations and interventions. A sufficient number of studies with reasonably low heterogeneity were present only for back and knee pain. Second, many types of invasive procedures for pain have not been subjected to sham-controlled studies, so our results may not apply to those procedures and conditions. Finally, none of the studies were double-blind, precluding full rigor in the evaluation of these procedures for chronic pain.

Our findings raise several questions for clinicians, researchers, and policy makers. First, can we justify widespread use of these procedures without rigorous testing? Without such testing, the true efficacy of invasive procedures for chronic pain will remain unknown [50,51]. The risks of surgical and invasive procedures are not minor and appear to be higher with real compared with sham procedures. Risks in both groups include anesthesia, permanent injury to the body, psychologic stress, and time, cost, and productivity losses [52]. Without more rigorous examination, large numbers of patients are exposed to risky and possibly unnecessary procedures. Furthermore, new procedures will be invented and applied with the belief that they are specific and necessary without knowing whether this is true [53]. It is currently felt to be unethical to deliver new drug treatments without testing them for their specific effects against placebo comparison arms [54]. Why should it be different with invasive procedures?

However, is it even possible to properly test invasive procedures against sham comparisons? Blinding of patients, who are both recipients of the interventions and assessors of subjective outcomes, is challenging. Mimicking a complex, invasive procedure such as surgery or insertion of a scope or a needle requires an elaborate sham procedure. Double-blinding is not possible as the surgeon knows which procedure is applied. In addition, there is significant controversy over the ethics of using sham procedures, even with carefully informed patients, further restricting the number of such studies being done [55,56]. Placebo controls are controversial in general, and recommending sham surgery procedures even more so [57]. As patients report between 60% and 70% reduction in pain after invasive procedures, why not just compare them with proven treatments?

Would doing sham surgical studies change practice? The answer seems to be "sometimes." When sham internal mammary studies of angina were published in the 1960s, the use of this procedure rapidly dropped off and was replaced by coronary bypass grafting, which has never been tested against sham bypass. However, only marginal changes have occurred in the use of vertebroplasty for low back pain after two studies reported no benefit of real over sham procedures [58]. When these studies were published, the accompanying editorial rationalized their continued use under the guise of "patient-centered" care and "informed choice" [59]. However, passing choice for interventions over to patients, especially when the evidence is controversial, should not be used as a substitute for evidence-based professional recommendations. A recent study of PCI stenting for angina showed no difference in pain or function compared with sham PCI, but the impact on this practice has yet to be determined [60].

The medical profession needs more nonpharmacological approaches for chronic pain, so it is unfortunate that the current evidence does not support the efficacy of invasive procedures for this problem. The implications of continuing to use these procedures without knowing whether they provide specific benefit are in urgent need of further research and discussion. In the meantime, it seems prudent that invasive procedures for chronic pain be avoided unless done as part of a clinical research study.

Acknowledgments

Supplementary Data

Supplementary data may be found online at http://pain-medicine.oxfordjournals.org.

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