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Randomized sham-controlled trials in endoscopy: a systematic review and meta-analysis of adverse events

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Abstract

Background and Aims—Sham procedures in endoscopy are used with the intention of controlling for placebo response, potentially allowing more precise evaluation of treatment effect. Nevertheless, this type of study may impose significant risk without potential benefit for those in the sham group. The aim of the current study is to systematically review and analyze the endoscopic literature to assess the safety of sham controls.

Methods—MEDLINE and Embase databases were searched for endoscopic sham procedures for all dates through July 2017. Only randomized controlled trials comparing an endoscopic therapy with a sham were included. Primary outcome was adverse events (AE) categorized as mild, moderate, or severe. Results were combined using a random-effects model. Heterogeneity was assessed with I-squared, and publication bias was assessed with the Egger test and funnel plots.

Results—Data were extracted from 34 publications (1987–2017; 100% full-text), with a total of 2,492 procedures (1,355 treatment/1,137 sham). Sham procedures involved upper endoscopy (31 studies) and ERCP (3 studies). Treatment arms included procedures with the following indications: weight loss (38.2%), GI bleeding (26.5%), GERD (20.6%), sphincter of Oddi dysfunction (SOD) (8.8%), and dysphagia (6.2%). Overall percentage of severe adverse events

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Popov V: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; study supervision

Thompson CC: study concept and design; critical revision of the manuscript for important intellectual content; study supervision

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(SAE) in the sham group was 1.7% (19/1137). Of these, the most common SAE in sham groups were need for surgery/intensive care unit (ICU) stay (35.3%), post-ERCP pancreatitis (23.5%), and perforation (11.8%). There was no significant difference in the odds of developing a severe adverse event between the treatment group and the sham group (OR, 1.3; 95% CI, 0.7 – 2.3]).

Conclusion—The frequency of adverse events in endoscopic sham procedures is substantial, and subjects patients to considerable morbidity. These results raise a serious ethical dilemma regarding the use of sham-controlled trials.

INTRODUCTION

Sham-controlled trials have become increasingly common in endoscopic research. Sham procedures are used with the intention of controlling for placebo response, potentially allowing more precise evaluation of treatment effect. Moreover, it may increase the scientific validity of an RCT^{1–3}. Often, the use of sham-controlled trials, opposed to non-sham controls, is a requirement for device approval or procedure reimbursement.

Sham-controlled trials may be of additional benefit to the patients involved. Assignment to the control group may allow subjects involved in such research to receive standard medical treatment at no cost. These patients may be eligible to undergo the intervention at a later date should it prove to be beneficial, and, conversely, provides the hindsight to avoid the intervention if found to be harmful.

However, sham procedures pose an indisputable ethical dilemma^{4,5}. Opponents of sham procedures argue that this type of study may impose significant risk without potential benefit for those in the sham group. Sham endoscopic interventions are not completely innocuous, and may result in more than minimal risks to participants. Furthermore, participation in this research may constitute an unacceptable violation of the rights of research subjects, with the potential for unforeseeable risks, and without benefits for those in the sham group.

The aim of the current study was to systematically review and analyze the endoscopic literature to assess the safety of sham controls.

METHODS

Literature Search

Before initiating the literature search, the search strategy, study inclusion and exclusion criteria, primary and secondary outcomes, and planned statistical analyses were defined and are described below.

MEDLINE and Embase databases were searched for endoscopic sham procedures from inception through July 2017 using the Ovid interface. Studies in English with greater than 5 adult participants were included. Animal trials were excluded. A search strategy using a combination of subject headings and text words was constructed to find articles that included endoscopic trials in which there was a sham control arm.

Review of titles/abstracts, full review of potentially relevant studies, and data abstraction were performed independently and in parallel by 2 authors (V.P. and A.S.). Only randomized controlled trials comparing an endoscopic therapy to a sham were included. The lists of full manuscripts meeting inclusion criteria from the 2 reviewers (V.P. and A.S.) were compared, and any disagreements were resolved by discussion and consensus, with a senior author (C.T.) serving as the final arbiter if consensus was not achieved.

Study Selection

Study Design and Population—We included all randomized controlled trials (RCTs) comparing an endoscopic intervention to an endoscopic sham control arm. Although no consensus definition exists for a sham procedure in endoscopy, an adopted definition from the Oxford English Dictionary was used in this analysis⁶. We defined an endoscopic sham procedure as one performed on a control group subject to expose him or her to similar incidental effects as those experienced by study group subjects on whom the investigational endoscopic intervention is performed. All observational studies and randomized controlled trials that did not include an endoscopic sham arm were excluded. Additionally, studies describing interventional therapy without providing data on adverse events were excluded.

Intervention—The study therapy was defined as either upper endoscopy, colonoscopy, or endoscopic retrograde cholangiopancreatography (ERCP) performed in both the treatment and sham arms, with a difference in intervention performed in the former group. These interventions included but were not limited to endoscopic bariatric therapies, Barrett's ablation procedures, reflux procedures, treatment of gastrointestinal hemorrhage, and procedures to treat sphincter of Oddi dysfunction.

Comparison—Odds ratios (ORs) and risk ratios (RRs) in the outcome parameter after the endoscopic procedure were pooled together, weighted and compared. Additionally, 95% confidence intervals (CIs), event rate, heterogeneity, and variance between sham and treatment groups when comparing mild, moderate, and severe adverse events were evaluated.

Outcomes—The primary outcome was adverse events categorized as mild (heartburn, sore throat, transient epigastric pain, or bloating), moderate (dysphagia, vomiting, desaturation, stenosis, ulceration, severe reflux, post-ERCP pancreatitis, or hospitalization), or severe (bleeding requiring intervention, aspiration pneumonia, perforation, sepsis, organ failure, or other adverse event requiring surgery or any of the above adverse events requiring ICU stay). These predefined outcomes were chosen as they characterize the clinically relevant spectrum of adverse events incurred by undergoing endoscopic procedures. The results are reported as pooled adverse events and subgroup analyses based on categories. The secondary outcome was to determine the added risk incurred by subjects randomized to the sham arm, followed by crossover to treatment, in studies with a partial cross-over design.

Data Extraction—A data collection sheet was created to record information on study characteristics and outcomes. Data were extracted by 2 authors (A.S. and V. P.)

independently and then compared. Any disagreements were resolved by discussion with the senior author (C.T.).

Data Analysis—For all of our studies, we calculated the pooled ORs and RRs for mild, moderate, and severe adverse events for both the sham and treatment groups, in addition to the 95% confidence interval, event rate, and *P* value. We pooled the results of the RCTs to assess the magnitude of the effect.

Risk-of-bias assessment of the RCTs was done using the Cochrane Collaboration Risk-of-Bias tool⁷. We extracted data regarding quality based on several domains: sequence generation, allocation concealment, blinding of participants and outcome assessment, incomplete data, and selective reporting.

Results were combined using a random-effects analysis due to our initial assumption of variation among the individual studies. Heterogeneity among the individual studies was assessed by the Cochrane Q-test and the I^2 statistic. Heterogeneity was defined as significant if I^2 was greater than 50%. A funnel plot was constructed to evaluate for publication bias for the main outcomes. The funnel plot was inspected visually for asymmetry. Egger testing was also performed. In this study, acuity of illness and year of study were thought to be possible sources of heterogeneity. If substantial heterogeneity was found for the primary outcomes, sensitivity analysis was performed by acuity of illness as evidenced by indication and type of the intervention. Patients undergoing urgent procedures for upper GI/variceal bleeding were considered to be of poorer health status than other populations undergoing non-urgent procedures. Additionally, studies were analyzed by year (2005 vs >2005). All analyses were done using Comprehensive Meta-Analysis software, version 2.0 (Biostat, Inc Englewood, NJ, USA) unless specified otherwise.

RESULTS

Study Selection

We identified 889 citations that matched our initial search criteria, and another 7 citations from other sources. After removal of duplicates, 416 articles remained and were reviewed (Figure 1). After abstract review, 53 studies were identified. After full manuscript review and discussion, thirteen additional studies were excluded given the intervention was not endoscopic in nature. Authors with insufficient information regarding adverse events were contacted, and those in which information remained unavailable were also excluded^{8–12}. Two final studies were excluded on the basis of including fewer than three participants in the sham arm. After review, 34 publications between 1987 and 2017 were included from which data were extracted. All of these publications were full-text.

Study characteristics

Characteristics and outcomes of individual trials are described in Table 1. All 34 studies were randomized controlled trials. Trials were conducted in several countries, including the United States, Spain, Italy, Netherlands, Australia, Belgium, Germany, Sweden, and Singapore. Trials ranged from one to 15 centers, enrolling between 18 and 332 patients per trial. A total of 2,492 endoscopic procedures were performed, 1,355 from the treatment arms

and 1,137 from the sham arms. Sham procedures involved upper endoscopy and ERCP in 31 and 3 studies, respectively, and consisted of sedation or general anesthesia, a minimum of one endoscopic procedure, and additional interventions including but not limited to mucosal fluid injection, installation of large fluid boluses into the stomach, overtube placement, and Bougie advancement with frequent rotation (Table 1).

Treatment arms within the selected randomized controlled trials (RCTs) included procedures with the following indications: weight loss (38.2%), GI bleeding (26.5%), GERD (20.6%), SOD (8.8%), and dysphagia (6.2%). Average age in the treatment and sham groups were 48.1 and 48.3 years, respectively. Furthermore, 50.6% and 50.3% of patients were female in the treatment and sham groups, respectively.

Primary outcome

Adverse events by category (mild, moderate severe) for both the sham and treatment groups are shown in Table 2. Total number of all adverse events was 1,257 (50.4%). There were no deaths attributed to the study or sham procedure. The pooled ORs and RRs, 95% confidence intervals, heterogeneity, and variance between sham and treatment groups when comparing mild, moderate, and severe adverse events are shown in Table 3. The OR (95% confidence interval [CI]) of developing an adverse event categorized as mild, moderate, or severe were 2.7 (95% CI, 1.2–5.6), 3.8 (95% CI, 1.6–9.1), and 1.3 (95% CI, 0.7–2.4), respectively.

The forest plot showing event rate of all adverse events for sham procedures is shown in Figure 2A. Total number of mild, moderate, and severe adverse events in sham groups was 240, 63, and 19, respectively. The overall percentage of SAE in the sham group was 1.7% (19/1137). Of these, the most common SAEs were needed for surgery/ICU stay (35.3%), post-ERCP pancreatitis (23.5%), and perforation (11.8%). The forest plot showing event rate of all adverse events for treatment procedures is shown in Figure 2B. Total number of mild, moderate, and severe adverse events in the treatment group was 603, 299, and 33, respectively. The overall percentage of SAE in the treatment group was 2.4% (33/1112). Of these, the most common SAEs were need for surgery/ICU stay (38.7%), perforation (16.1%), and bleeding (9.7%) were most common. Event rate, pooled odds ratio, 95% confidence intervals, heterogeneity, and variance between these groups are shown in Table 1. There was no significant difference in the odds of developing a severe adverse event between the treatment group and the sham group (OR 1.3 [0.7, 2.3]). The pooled OR [95% confidence interval] of developing an adverse event was 0.5 [0.3, 0.8] in the sham group compared with the treatment group. The forest plot comparing pooled ORs of adverse events for sham and treatment groups is shown in Figure 3.

Sensitivity analyses were performed to investigate heterogeneity in mild and moderate pooled event rates for both sham and treatment arms. Acuity of intervention (ie, urgent versus non-urgent) had a significant impact on between study variability for sham pooled event rates for mild (R-squared = 0.37) and severe (R-squared = 0.86) but could not explain the heterogeneity found in the treatment group. Additionally, a significantly increased event rate was found in studies performed >2005 versus ≤2005 (pooled mean = 0.16 vs 0.06, *P* value <0.001). The heterogeneity in pooled moderate AE could be explained by acuity and year of study, with a combined R-squared of 0.70.

Secondary outcome

Six studies reported adverse event data for subjects randomized to the sham arm, followed by cross-over to treatment^{13–18}. In partial cross-over design studies, the estimated average pooled increased risk of developing a non-severe event after being randomized to the sham arm was risk ratio = 1.33 (95% CI, 1.14 – 1.56), $p < 0.001$, I-squared = 6.74, Tau-squared = 0.003, compared with those randomized to the treatment group.

Quality Assessment and Publication Bias

A funnel plot was created to evaluate for publication bias. Visual inspection of the funnel plots revealed no obvious asymmetry to suggest publication bias, and there was no evidence of publication bias by the Egger test (Egger regression intercept = -1.3 , $p = 0.23$) (Figure 4). Biases for individual studies and overall quality are shown in Table 4.

DISCUSSION

Sham-controlled trials have become increasingly more common in endoscopic research. This is in part due to the fact that endoscopic procedures are often amenable to sham designs, as there are no obvious incisions incurred during the procedure making it relatively easy to maintain blinding. Nevertheless, the use of sham procedures in human research raises ethical concerns, given the potential to harm subjects despite not receiving the desired intervention. Additionally, some endoscopic sham procedures are intended to induce symptoms that are suggestive of the patient having had the procedure, potentially carrying increased risk.

Many endoscopic trials often involve partial cross-over designs, which allow patients in the sham arm to receive the study procedure after unblinding. This is intended to have several positive effects including giving a sense of fairness to patients, increasing enrollment, and keeping patients who feel they have received the sham procedure engaged throughout the trial. Unlike with double cross-over pharmaceutical trials, the treatment group does not undergo a sham procedure following the unblinding process in the majority of these trials. This disparity creates potential for increased risk in those randomized to the sham arm, as many will typically undergo an additional procedure.

To our knowledge, this is the only meta-analysis to date investigating the adverse effects endured by the sham arm during endoscopic randomized controlled studies (RCTs). In the 34 trials that met inclusion criteria for this meta-analysis, there were a total number of 321 adverse events in the sham arm (240 mild, 63 moderate, and 18 severe). These numbers do not reflect adverse events incurred in the cross-over portion of the study where patients would receive the therapy under investigation. The most common severe adverse events in sham group were not insignificant, including six patients who required surgery/ICU stay, 4 patients who developed post-ERCP pancreatitis, and 2 patients who developed a perforation from the sham procedure itself, despite not undergoing the intervention planned for the treatment arm. Although pooled odds ratio of adverse events was 2 times greater in the treatment group than the control group, the risk of having an adverse event in the sham group was not trivial. In fact, there was no significant difference in SAE between groups

(OR 1.3; 95% CI, 0.7 – 2.3). Thus, the risk of a sham procedure outweighs the absolute lack of clinical benefit, and may, in fact, exceed acceptable research risk.

Furthermore, subjects are not merely randomized to the study intervention or sham arm. Many subjects after sham procedures subsequently undergo a study intervention, as part of a partial cross-over design. This is intended to retain patients in the control arm and limit loss to follow-up. Unfortunately, numerous studies do not report the results of this partial cross-over. In our analysis, only six of 34 studies report cross-over outcomes. These subjects are not only exposed to the risk of the sham procedure, but also to the risk of the study intervention. The pooled additional risk incurred from being initially randomized to the sham arm and then receiving a cross-over intervention was significant (RR=1.33; 95% CI, 1.14, 1.56; $p<0.001$), compared with patients initially randomized to the study intervention. Thus, in partial cross-over designs, patients initially randomized to the sham group again incur disproportionately increased risk.

Additionally, sensitivity analysis was performed to clarify heterogeneity where present. We found that procedural acuity had an effect on heterogeneity in the sham group. This finding brings into question the ethics of withholding all treatment (for the purposes of research) in patients requiring urgent care. Furthermore, studies performed after 2005 contained more adverse events than older studies. This observation could be multi-factorial in origin. The nature of the sham procedure itself may be becoming more aggressive, as seen in obesity and GERD studies that require Bougie placement and manipulation (Table 1). Additionally, more meticulous reporting of adverse events may partially explain this finding. Regardless, the safety of endoscopic sham procedures does not appear to have improved over the last 30 years.

The results of this meta-analysis raise a serious ethical dilemma regarding the use of sham-controlled trials, opposed to non-sham randomized controls, as a requirement for endoscopic device approval or procedure reimbursement. Many have advocated that the risk of sham interventions may not be acceptable or reasonable in relation to the added knowledge provided due to the sham procedure itself^{4,19}. Moreover, inclusion of a sham arm may lead to the risk of exploitation of participants for the sake of scientific knowledge, and may not be relevant to real world clinical practice²⁰.

There are many different types of RCT design that involve random allocation to different groups of therapy. Subjects can be randomized to criterion standard, alternative therapies, no therapy with observation, or placebo/sham. Originally, placebo-controlled trials were designed for medication studies and introduced no increased risk to subjects beyond lack of an alternative therapy. Sham trials are similar to placebo controls except that they introduce a procedure in place of a sugar pill, therefore subjecting the sham arm to the risk associated with the sham procedure. Justification for this is predicated on the risk of a sham procedure not exceeding the threshold of acceptable research risk. Objections to this type of trial by ethicists and proceduralists are due to a variety of reasons^{21,22}. First, there is substantial risk in an RCT that the intervention arm may not be effective, and could carry unknown morbidity. Having the control arm be a sham procedure additionally removes the possibility of being allocated to an arm with known benefit. This exposes trial patients to prolonged

periods of time in which no subject may receive effective therapy, while incurring risk of the study procedure and/or the sham procedure. Second, the risk posed to the sham arm by the placebo intervention itself, knowing there is no clinical benefit, is of dubious ethical justification. Third, the use of *active* misleading aimed at making subjects believe that they are receiving the actual intervention, when they are in fact not, is of ethical concern^{21,22}. Finally, some sham controls with partial cross-over design decrease scientific validity by introducing perverse incentives. For example, in the ESSENTIAL trial, subjects were randomized to an endoscopic obesity therapy or a sham procedure, with a partial cross-over for patients initially allocated to the sham arm²³. The only subjects eligible for the cross-over study were those who did not lose weight. Subjects that lost weight were not considered eligible for cross-over. As a result, patients that were close to this cut-off reported deliberate increase in food consumption to avoid exclusion from the cross-over procedure. This can artificially decrease the effectiveness of an intervention. It may also diminish scientific validity by introducing systematic bias against the study therapy. Similar to this, an inverse placebo effect can be seen in subjects that do not believe they received an intervention, thereby minimizing the difference between the sham and treatment arm.

There are, however, some potential advantages to sham-controlled trials. A comparison of the experimental intervention with a sham arm facilitates blinding of the patient, investigator, and other study personnel, thereby providing the ability to discern between specific effects of the intervention and other potential biases^{3,24–29}. Additionally, inclusion of a sham group has been postulated to provide knowledge that will prevent the introduction of insufficiently proven, potentially risky, interventions into clinical practice and thereby prevent unnecessary, and often expensive, costs to the health care system^{27,30}.

In the present review, patients randomized to undergo a sham procedure still endured the risk of undergoing sedation and an endoscopy or ERCP, often in conjunction with a second procedure that carried additional hazard. The risk of severe adverse events inherent to upper endoscopic examination under sedation is approximately one per thousand procedures³¹, with a mortality rate estimated to be as high as three per ten thousand cases³². These events are mostly related to cardiovascular events, although perforation also occurs. This does not include the risk of additional sham manipulations, which may involve dilation, ablation, and other interventions. Particularly, ERCP carries additional risk from adverse events specific to pancreatobiliary instrumentation, including pancreatitis, sepsis, and hemorrhage or retroperitoneal duodenal perforation after therapeutic procedures. In our analysis, and consistent with previous literature, post-ERCP pancreatitis was the most common etiology leading to a severe adverse event observed in patients undergoing ERCP. It is well known that this adverse event can be associated with significant morbidity and cost to the healthcare system. Studies investigating novel obesity and GERD treatments report placement of large Bougies up to 54F being advanced into the esophagus and rotated at regular intervals to simulate the study intervention, device placement and maneuvering^{23,33}. This carries the risk of mucosal abrasion, bleeding, aspiration, and perforation. Other study designs require numerous sham procedures, as many as ten per subject in some trials, where a placebo was injected into esophageal mucosa as a sham in a variceal bleeding study^{34,35}. This exposes the subject to numerous sedation events, in addition to withholding actual treatment for as long as 24 months.

Based on the results of this study, investigators should reconsider use of sham-controlled trial designs for endoscopic interventions, while maintaining an emphasis on sound RCT designs. If the decision is made to proceed with a sham arm, it must be clear exactly what clinically relevant information will be provided by the study design, above that which could be provided by a standard RCT design. Additionally, investigators must take every precaution to minimize the risks associated with the sham procedure, and ensure that the patients are fully aware of the additional risks imposed by potentially having both a sham procedure and subsequently the study treatment.

There are several strengths of this meta-analysis. To our knowledge, this is the first study to systematically review and analyze the endoscopic literature to assess the safety of sham controls. Thirty-four studies with over two thousand endoscopic procedures were included, thus limiting publication bias. Sound methodological design was employed, and only studies which provided sufficient information were included, with authors contacted individually for missing data. Additionally, all included trials were RCTs, which limited conceptual bias due to poor study design known to influence other types of studies. Finally, adverse events were analyzed by severity to provide a clinical context to the findings.

There are also limitations to our study. Reporting of adverse events varied, with some studies only reporting SAE. As a result, mild and moderate adverse events may have been underreported, suggesting there may have been additional adverse events in both groups that were not captured, and sham procedures may carry more risk than we identified in this meta-analysis. Nevertheless, we suspect that underreporting would have been similar between treatment and sham groups, and therefore unlikely to affect the pooled odds ratios. Additionally, identification or determination of adverse events can be subjective and introduce bias.

In conclusion, the results of this systematic review raise a considerable ethical dilemma regarding the use of sham-controlled trials, opposed to non-sham controls, as a requirement for endoscopic device approval or procedure reimbursement. The risk imposed on the sham group is not insignificant, and may be disproportionate to the treatment group when considering the commonly used partial cross-over design. Standard RCT designs with an appropriate control group should be preferred to this higher risk sham-control strategy.

Database: Ovid MEDLINE(R) <1946 to June Week 1 2017>, Embase <1974 to 2017 June 13>
Search Strategy:

- 1 endoscopy.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (277809)
- 2 limit 1 to english language (221870)
- 3 limit 2 to human (201266)
- 4 sham.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (163275)
- 5 limit 4 to english language (153439)
- 6 limit 5 to human (31896)
- 7 3 and 6 (207)
- 8 endoscopy.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (277809)

Database: Ovid MEDLINE(R) <1946 to June Week 1 2017>, Embase <1974 to 2017 June 13>
Search Strategy:

- 9 limit 8 to human (251214)
- 10 colonoscopy.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (97346)
- 11 limit 10 to english language (84927)
- 12 limit 11 to human (79304)
- 13 6 and 12 (41)
- 14 endoscopic.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (363400)
- 15 limit 14 to english language (300775)
- 16 limit 15 to human (275071)
- 17 6 and 16(309)
- 18 ercp.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (24174)
- 19 limit 18 to english language (20517)
- 20 limit 19 to human (18775)
- 21 6 and 20 (32)
- 22 limit 21 to "all adult (19 plus years)" [Limit not valid in Embase; records were retained] (30)
- 23 limit 22 to humans (30)
- 24 limit 23 to (clinical trial or randomized controlled trial) (14)
- 25 7 or 13 or 17 or 21 or 24 (427)
- 26 placebo.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (576716)
- 27 limit 26 to english language (538149)
- 28 limit 27 to human (483799)
- 29 3 and 12 and 16 and 20 and 28 (3)
- 30 3 and 28 (3772)
- 31 20 and 28 (450)
- 32 12 and 28 (1103)
- 33 16 and 28 (4176)
- 34 30 or 31 or 32 or 33 (7117)
- 35 remove duplicates from 25 (295)
- 36 remove duplicates from 25 (295)
- 37 endoscopy.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sy, tn, dm, mf, dv, kw, fx] (277809)
- 38 limit 37 to english language (221870)
- 39 limit 38 to human (201266)
- 40 sham.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sy, tn, dm, mf, dv, kw, fx] (163275)
- 41 limit 40 to english language (153439)
- 42 limit 41 to human (31896)
- 43 39 and 42 (207)
- 44 endoscopy.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sy, tn, dm, mf, dv, kw, fx] (277809)
- 45 limit 44 to human (251214)
- 46 colonoscopy.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sy, tn, dm, mf, dv, kw, fx] (97346)
- 47 limit 46 to english language (84927)
- 48 limit 47 to human (79304)
- 49 42 and 48 (41)
- 50 endoscopic.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sy, tn, dm, mf, dv, kw, fx] (363400)

Database: Ovid MEDLINE(R) <1946 to June Week 1 2017>, Embase <1974 to 2017 June 13>
Search Strategy:

- 51** limit 50 to english language (300775)
- 52** limit 51 to human (275071)
- 53** 42 and 52 (309)
- 54** ercp.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sy, tn, dm, mf, dv, kw, fx] (24174)
- 55** limit 54 to english language (20517)
- 56** limit 55 to human (18775)
- 57** 42 and 56 (32)
- 58** limit 57 to “all adult (19 plus years)” [Limit not valid in Embase; records were retained] (30)
- 59** limit 58 to humans (30)
- 60** limit 59 to (clinical trial or randomized controlled trial) (14)
- 61** 43 or 49 or 53 or 57 or 60 (427)
- 62** placebo.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sy, tn, dm, mf, dv, kw, fx] (576716)
- 63** limit 62 to english language (538149)
- 64** limit 63 to human (483799)
- 65** 39 and 48 and 52 and 56 and 64 (3)
- 66** 39 and 64 (3772)
- 67** 56 and 64 (450)
- 68** 48 and 64 (1103)
- 69** 52 and 64 (4176)
- 70** 66 or 67 or 68 or 69 (7117)
- 71** remove duplicates from 61 (295)
- 72** remove duplicates from 61 (295)
- 73** egd.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (7400)
- 74** limit 73 to english language (7196)
- 75** limit 74 to human (6184)
- 76** 6 and 75 (8)
- 77** enteroscopy.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (7342)
- 78** 6 and 77(1)
- 79** 6 and 77(1)
- 80** esophagoscopy.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (27352)
- 81** limit 80 to english language (20167)
- 82** limit 81 to human (18882)
- 83** 6 and 82 (30)
- 84** gastroscopy.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (40355)
- 85** 6 and 84 (27)
- 86** eus.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (21586)
- 87** 6 and 86 (20)
- 88** intragastric balloon.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (1131)
- 89** 6 and 88 (43)
- 90** BARRX.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (137)
- 91** 6 and 90 (2)
- 92** 61 or 76 or 79 or 83 or 85 or 87 or 89 or 91 (469)

Database: Ovid MEDLINE(R) <1946 to June Week 1 2017>, Embase <1974 to 2017 June 13>
Search Strategy:

- 93** 36 or 92 (469)
 - 94** manometry.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (47559)
 - 95** 6 and 94 (143)
 - 96** 93 or 95 (551)
 - 97** mucosal ablation.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (260)
 - 98** 6 and 97(0)
 - 99** radiofrequency ablation.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (41330)
 - 100** 6 and 99 (101)
 - 101** 96 or 100 (621)
 - 102** esd.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (9406)
 - 103** 6 and 102 (3)
 - 104** emr.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (14583)
 - 105** 6 and 104(11)
 - 106** radiofrequency ablation.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (41330)
 - 107** 6 and 106 (101)
 - 108** cryotherapy.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (26660)
 - 109** 6 and 108 (46)
 - 110** argon plasma coagulation.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (5116)
 - 111** 6 and 110(14)
 - 112** stent.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (208945)
 - 113** 6 and 112 (79)
 - 114** duodenal jejunal bypass liner.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (147)
 - 115** 6 and 114 (2)
 - 116** endobarrier.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (189)
 - 117** 6 and 116 (11)
 - 118** duodenal.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (141347)
 - 119** 6 and 118 (268)
 - 120** gastric.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (537887)
 - 121** 6 and 120 (886)
 - 122** esophageal.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, sy, tn, dm, mf, dv, kw, fx] (240209)
 - 123** 6 and 122 (223)
 - 124** 101 or 103 or 105 or 107 or 109 or 111 or 113 or 115 or 117 or 119 or 121 or 123 (1628)
 - 125** 101 or 103 or 105 or 107 or 109 or 111 or 113 or 115 or 117 or 119 or 121 or 123 (1628)
 - 126** remove duplicates from 125 (1168)
 - 127** 96 or 126 (1341)
 - 128** remove duplicates from 127 (1168)
-

Abbreviations

RCT Randomized controlled trial

AE	Adverse events
ERCP	Endoscopic retrograde cholangiopancreatography
OR	Odds ratio
ICU	Intensive care unit
GI	gastrointestinal
GERD	gastroesophageal reflux disease
CI	Confidence interval

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Figure 1.
PRISMA flow diagram of literature search results.

Figure 2. Forest plot showing mild, moderate, and severe adverse events for (A) sham and (B) treatment groups. *3 studies in (A)^{35,58,60} and 7 studies in (B)^{23,35,50,52,53,58,60} were

excluded from these figures because the number of events was higher than the total number of subjects or there were zero adverse events reported in both sham and treatment AE categories.

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Figure 3.

Forest plot showing pooled odds ratio of adverse events comparing sham and treatment groups. *10 studies in (B)^{23,34,35,37,45,50,52,53,58,60} were excluded from these figures because the number of events was higher than the total number of subjects or there were zero adverse events reported in both sham and treatment AE categories.

Figure 4.
Funnel plot demonstrating low chance of publication bias.

Table 1

Characteristics of studies included

Study	Study Procedure	Treatment intervention performed	Sham procedure	Origin of Study	N Treatment	N Sham
Fleischer, 1985 ³⁶	Endoscopy	ND:YAG laser therapy for varices	General or sedation	USA	10	10
Laine, 1987 ³⁷	Endoscopy	Multipolar electrocoagulation for bleeding ulcer	General or sedation; heater probe held in gut lumen	USA	21	23
Geenen, 1989 ³⁸	ERCP	Sphincterotomy	Biliary/pancreatic manometry; Sphincterotomy held in gut lumen	USA	23	24
Laine, 1989 ³⁹	Endoscopy	Heater probe for bleeding ulcer	General or sedation; heater probe held in gut lumen	USA	38	37
Rutgeerts, 1989 ⁴⁰	Endoscopy	Epinephrine injection	General anesthesia or sedation;	Belgium	25	25
Mathus-Vliegen, 1990 ⁴¹	Endoscopy	Intragastric balloon placement	General or sedation; Sham balloon	Netherlands	14	13
Fullarton, 1991 ⁴²	Endoscopy	Heater probe for bleeding ulcer	General or sedation; heater probe held in gut lumen	UK	20	23
Veteran's Affairs, 1991 ³⁵	Endoscopy	Sclerotherapy of varices	~10 EGDs with placebo mucosal injection	USA	143	138
Rutgeerts, 1993 ⁴³	Endoscopy	Alcohol injection of bleeding ulcer	General anesthesia or sedation	Belgium	25	25
Veteran's Affairs, 1994 ⁴⁴	Endoscopy	Sclerotherapy	1 EGD; Placebo mucosal injection	USA	122	131
Hartigan, 1997 ³⁴	Endoscopy	Sclerotherapy	~10 EGDs with placebo mucosal injection	USA	44	43
Scolapio, 2001 ⁴⁵	Endoscopy	Balloon dilation	Sedation, balloon catheter placed but not inflated	USA	43	40
Corley, 2003 ¹⁷	Endoscopy	Radiofrequency ablation	Stretta balloon inflation (repeated without injection)	USA	31	25
Mathus-Vliegen, 2003 ¹⁸	Endoscopy	Intragastric balloon placement	Sham balloon, 3 EGDs	Netherlands	11	17
Gorelick, 2004 ⁴⁶	ERCP	Botox injection	Sclerotherapy needle injection into bowel lumen	USA	12	14
Mathus-Vliegen, 2005 ⁴⁷	Endoscopy	Intragastric balloon placement	Sham balloon, 4 EGDs	Netherlands	12	21
Deviere, 2005 ¹⁶	Endoscopy	Enteryx	General anesthesia or sedation; Injection of co-polymer	Europe	31	30
Genco, 2006 ⁴⁸	Endoscopy	Intragastric balloon placement	2 EGDs	Italy	16	16
Schwartz, 2007 ⁴⁹	Endoscopy	EndoCinch	Sedation; overtube in place for 40 mins	Netherlands	18	15
Rothstein, 2006 ³³	Endoscopy	Plication of cardia	Plicator (45 Fr) placed over a wire and retroflexed	USA/Europe	72	72
Tarnoff, 2009 ⁵⁰	Endoscopy	Duodenojejunal bypass liner	General anesthesia or sedation	USA	20	4
Bajbouj, 2009 ¹⁴	Endoscopy	Argon plasma coagulation (APC)	General anesthesia or sedation; simulated APC	USA	11	10
Aziz, 2010 ⁵¹	Endoscopy	Stretta	Sedation	USA	24	12

Study	Study Procedure	Treatment intervention performed	Sham procedure	Origin of Study	N Treatment	N Sham
Rodrigues, 2010 ⁵²	Endoscopy	Duodenojejunal bypass liner	General anesthesia	Chile	12	3
Fockens, 2010 ¹³	Endoscopy	Gatekeeper prosthesis	General anesthesia or sedation; overtube placed	USA/Europe	75	43
Gersin, 2011 ⁵³	Endoscopy	Duodenojejunal bypass liner	Sedation	USA	21	24
Arts, 2012 ⁵⁴	Endoscopy	Sretta	General anesthesia or sedation	USA	9	11
Mathus-Vliegen, 2013 ⁵⁵	Endoscopy	Intragastric balloon placement	Sham balloon placed, multiple blood draws; 2 EGDs	Netherlands	16	21
Thompson, 2013 ⁵⁶	Endoscopy	Transoral gastrojejunal outlet reduction	General anesthesia; overtube placed for 30 min	USA	48	27
Mathus-Vliegen, 2014 ⁵⁷	Endoscopy	Intragastric balloon placement	Sham balloon placed, multiple blood draws	Netherlands	16	21
Eid, 2014 ⁵⁸	Endoscopy	Stomaphyx	General anesthesia; scope rotated for 30–40 min	USA	55	31
Cotton, 2014 ⁵⁹	ERCP	Sphincterotomy	Biliary/pancreatic manometry; pancreatic duct stent	USA	118	55
Hakansson, 2015 ⁶⁰	Endoscopy	Transoral incisionless fundoplication	General anesthesia; scope manipulation for 30 min	Sweden	22	22
Sullivan, 2017 ²³	Endoscopy	POSE TM	General anesthesia; 54 Fr Bougie placed and rotated every 15 mins × 3 times	USA	221	111

Table 2

Adverse events by study

Study	Study Procedure	Number of Adverse events in Treatment Group			Number of Adverse events in Sham Group		
		Mild	Moderate	Severe	Mild	Moderate	Severe
Fleischer, 1985 ³⁶	Endoscopy	0	0	3	0	0	2
Laine, 1987 ³⁷	Endoscopy	0	0	0	0	0	0
Geenen, 1989 ³⁸	ERCP	0	1	1	0	0	2
Laine, 1989 ³⁹	Endoscopy	0	7	1	0	0	0
Rutgeerts, 1989 ⁴⁰	Endoscopy	0	0	2	0	0	4
Mathus-Vliegen, 1990 ⁴¹	Endoscopy	1	1	0	5	0	0
Fullarton, 1991 ⁴²	Endoscopy	0	0	1	0	0	0
Veteran's Affairs, 1991 ³⁵	Endoscopy	107	106	0	25	4	1
Rutgeerts, 1993 ⁴³	Endoscopy	0	0	8	0	0	4
Veteran's Affairs, 1994 ⁴⁴	Endoscopy	0	0	0	0	0	0
Hartigan, 1997 ³⁴	Endoscopy	0	0	0	0	0	0
Scolapio, 2001 ⁴⁵	Endoscopy	0	0	0	0	0	0
Corley, 2003 ¹⁷	Endoscopy	4	5	0	1	0	1
Mathus-Vliegen, 2003 ¹⁸	Endoscopy	5	2	0	3	1	0
Gorelick, 2004 ⁴⁶	ERCP	0	2	1	0	6	0
Mathus-Vliegen, 2005 ⁴⁷	Endoscopy	7	3	0	5	0	0
Devriere, 2005 ¹⁶	Endoscopy	16	5	0	6	0	0
Genco, 2006 ⁴⁸	Endoscopy	13	0	0	4	0	0
Schwartz, 2007 ⁴⁹	Endoscopy	11	0	0	2	1	0
Rothstein, 2006 ³³	Endoscopy	39	6	2	12	3	0
Tarnoff, 2009 ⁵⁰	Endoscopy	16	5	0	0	0	0
Bajbouj, 2009 ¹⁴	Endoscopy	7	0	0	6	0	0
Aziz, 2010 ⁵¹	Endoscopy	12	3	0	4	0	0
Rodrigues, 2010 ⁵²	Endoscopy	12	6	0	0	0	0

Study	Study Procedure	Number of Adverse events in Treatment Group			Number of Adverse events in Sham Group		
		Mild	Moderate	Severe	Mild	Moderate	Severe
Fockens, 2010 ¹³	Endoscopy	23	2	4	9	3	0
Gersin, 2011 ⁵³	Endoscopy	14	7	3	0	0	0
Arts, 2012 ⁵⁴	Endoscopy	3	0	0	2	0	0
Mathus-Vliegen, 2013 ⁵⁵	Endoscopy	2	2	0	0	0	0
Thompson, 2013 ⁵⁶	Endoscopy	19	8	1	14	6	0
Mathus-Vliegen, 2014 ⁵⁷	Endoscopy	1	2	0	0	0	0
Eid, 2014 ⁵⁸	Endoscopy	62	16	2	29	4	2
Cotton, 2014 ⁵⁹	ERCP	0	15	2	0	10	2
Hakansson, 2015 ⁶⁰	Endoscopy	21	21	0	20	15	0
Sullivan, 2017 ²³	Endoscopy	208	74	2	93	10	1

Table 3

Pooled odds ratio and risk ratio, 95% confidence intervals, heterogeneity, and variance between sham and treatment groups when comparing mild, moderate, and severe adverse events.

Adverse events	Event Rate	95% Confidence Interval (CI)	I-squared	Tau-squared
Mild				
Sham	0.29	0.18–0.44	88.3	1.87
Treatment	0.24	0.14–0.37	89.7	2.64
Odds Ratio (OR)	OR = 2.7	1.4–5.4	75.3	1.45
Risk Ratio (RR)	RR = 1.5	1.2–1.9	79.0	0.10
Moderate				
Sham	0.05	0.03–0.09	64.4	1.25
Treatment	0.14	0.09–0.21	86.3	1.50
Odds Ratio (OR)	OR = 4.0	1.9–8.4	70.3	1.96
Risk Ratio (RR)	RR = 2.67	1.6–4.7	64.5	0.72
Severe				
Sham	0.04	0.03–0.06	14.7	0.21
Treatment	0.04	0.03–0.07	48.1	0.80
Odds Ratio (OR)	OR = 1.3	0.7–2.3	0	0
Risk Ratio (RR)	RR = 1.3	0.7–2.1	0	0

Table 4

Biases for individual studies and overall assessment of quality of manuscripts included.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting bias (reporting bias)	Overall quality
Fleischer, 1985 ³⁶	+	+	+	+	–	–	Mod
Laine, 1987 ³⁷	+	+	+	+	+	+	High
Geenen, 1989 ³⁸	+	+	+	+	+	+	High
Laine, 1989 ³⁹	+	+	+	+	+	+	High
Rutgeerts, 1989 ⁴⁰							
Mathus-Vliegen, 1990 ⁴¹	+	+	+	+	–	+	High
Fullarton, 1991 ⁴²	–	+	+	+	+	–	Mod
Veteran's Affairs, 1991 ³⁵	+	+	+	+	+	+	High
Rutgeerts, 1993 ⁴³	+	+	+	+	+	+	High
Veteran's Affairs, 1994 ⁴⁴	+	+	+	+	+	+	High
Hartigan, 1997 ³⁴	–	+	+	+	+	+	High
Scolapio, 2001 ⁴⁵	–	+	+	–	+	+	Mod
Corley, 2003 ¹⁷	+	+	+	+	+	+	High
Mathus-Vliegen, 2003 ¹⁸	–	+	+	+	–	+	Mod
Gorelick, 2004 ⁴⁶	–	+	+	+	+	+	High
Mathus-Vliegen, 2005 ⁴⁷	+	+	+	+	–	+	High
Devriere, 2005 ¹⁶	+	+	+	+	+	+	High
Genco, 2006 ⁴⁸	+	+	+	+	+	+	High
Schwartz, 2007 ⁴⁹	+	+	+	+	+	+	High
Rothstein, 2006 ³³	+	+	+	+	+	+	High
Tarnoff, 2009 ⁵⁰	+	+	+	+	+	+	High
Bajbouj, 2009 ¹⁴	+	–	+	+	+	+	High
Aziz, 2010 ⁵¹	+	+	+	+	+	+	High
Rodrigues, 2010 ⁵²	+	+	+	+	+	+	High

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Overall quality
Fockens, 2010 ¹³	–	+	+	+	+	+	High
Gersin, 2011 ⁵³	+	+	+	+	+	+	High
Arts, 2012 ⁵⁴	–	+	+	+	+	+	High
Mathus-Vliegen, 2013 ⁵⁵	–	+	+	+	+	+	High
Thompson, 2013 ⁵⁶	+	+	+	+	+	+	High
Mathus-Vliegen, 2014 ⁵⁷	–	+	+	+	+	+	High
Eid, 2014 ⁵⁸	+	+	+	+	+	+	High
Cotton, 2014 ⁵⁹	+	+	+	+	+	+	High
Hakansson, 2015 ⁶⁰	+	+	+	+	+	+	High
Sullivan, 2017 ²³	+	+	+	+	+	+	High