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Medical versus surgical treatment for refractory or recurrent peptic ulcer (Review)

Gurusamy KS, Pallari E

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[Intervention Review]

Medical versus surgical treatment for refractory or recurrent peptic ulcer

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ABSTRACT

Background

Refractory peptic ulcers are ulcers in the stomach or duodenum that do not heal after eight to 12 weeks of medical treatment or those that are associated with complications despite medical treatment. Recurrent peptic ulcers are peptic ulcers that recur after healing of the ulcer. Given the number of deaths due to peptic ulcer-related complications and the long-term complications of medical treatment (increased incidence of fracture), it is unclear whether medical or surgical intervention is the better treatment option in people with recurrent or refractory peptic ulcers.

Objectives

To assess the benefits and harms of medical versus surgical treatment for people with recurrent or refractory peptic ulcer.

Search methods

We searched the specialised register of the Cochrane Upper GI and Pancreatic Diseases group, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE, EMBASE, Science Citation Index Expanded, and trials registers until September 2015 to identify randomised trials and non-randomised studies, using search strategies. We also searched the references of included studies to identify further studies.

Selection criteria

We considered randomised controlled trials and non-randomised studies comparing medical treatment with surgical treatment in people with refractory or recurrent peptic ulcer, irrespective of language, blinding, or publication status for inclusion in the review.

Data collection and analysis

Two review authors independently identified trials and extracted data. We planned to calculate the risk ratio, mean difference, standardised mean difference, or hazard ratio with 95% confidence intervals using both fixed-effect and random-effects models with Review Manager 5 based on intention-to-treat analysis.

Main results

We included only one non-randomised study published 30 years ago in the review. This study included 77 participants who had gastric ulcer and in whom medical therapy (histamine H2 receptor blockers, antacids, and diet) had failed after an average duration of treatment of 29 months. The authors do not state whether these were recurrent or refractory ulcers. It appears that the participants did not have previous complications such as bleeding or perforation. Of the 77 included participants, 37 participants continued to have medical therapy while 40 participants received surgical therapy (antrectomy with or without vagotomy; subtotal gastrectomy with or without vagotomy; vagotomy; pyloroplasty and suture of the ulcer; suture or closure of ulcer without vagotomy or excision of the ulcer; proximal gastric or parietal cell vagotomy alone; suture or closure of the ulcer with proximal gastric or parietal cell vagotomy). Whether to use medical or surgical treatment was determined by participant's or treating physician's preference.

The study authors reported that two participants in the medical treatment group (2 out of 37; 5.4%) had gastric cancer, which was identified by repeated biopsy. They did not report the proportion of participants who had gastric cancer in the surgical treatment group. They also did not report the implications of the delayed diagnosis of gastric cancer in the medical treatment group. They did not report any other outcomes of interest for this review (that is health-related quality of life (using any validated scale), adverse events and serious adverse events, peptic ulcer bleeding, peptic ulcer perforation, abdominal pain, and long-term mortality).

Authors' conclusions

We found no studies that provide the relative benefits and harms of medical versus surgical treatment for recurrent or refractory peptic ulcers. Studies that evaluate the natural history of recurrent and refractory peptic ulcers are urgently required to determine whether randomised controlled trials comparing medical versus surgical management in patients with recurrent or refractory peptic ulcers or both are necessary. Such studies will also provide information for the design of such randomised controlled trials. A minimum follow-up of two to three years will allow the calculation of the incidence of complications and gastric cancer (in gastric ulcers only) in recurrent and refractory peptic ulcers. In addition to complications related to treatment and disease, health-related quality of life and loss of productivity should also be measured.

PLAIN LANGUAGE SUMMARY

Medical or operative treatment for ulcers in the stomach and upper small intestine resistant to medical treatment

Review question

In people who have stomach or upper small intestinal ulcers (peptic ulcers) that do not heal after eight to 12 weeks of medical treatment (refractory peptic ulcers) or comes back after healing (recurrent peptic ulcers), is medical or surgical treatment better?

Background

Approximately 1 in 100 to 1 in 800 people have peptic ulcers. The major causes of peptic ulcer are *Helicobacter pylori* infection, non-steroidal anti-inflammatory drug (NSAID) use, and smoking. People who have peptic ulcer have upper abdominal pain, which is sometimes accompanied by dyspepsia (that is fullness, bloating, loss of appetite after eating a small amount of food, or nausea). The most serious complications of peptic ulcers are bleeding from the ulcer and perforation of the peptic ulcer, which results in stomach or upper small intestinal contents or both leaking into the tummy. About 1 in 10 people with bleeding peptic ulcer and 1 in 4 people with perforated peptic ulcer die. Peptic ulcers cause approximately 3000 to 4500 deaths per year in the US.

Currently, medical management, usually with a group of drugs called proton pump inhibitors (such as omeprazole and lansoprazole), is the mainstay treatment for uncomplicated peptic ulcers. Recently concerns have arisen about the risk of fractures with long-term use of proton pump inhibitors. The alternative to medical treatment for refractory and recurrent peptic ulcer is surgical treatment to decrease the acid secretion in the stomach with the goal of curing the peptic ulcer. It is not known whether medical or surgical management is a better option for people with a refractory or recurrent peptic ulcer. We attempted to resolve this issue by searching the medical literature for studies comparing medical and surgical treatment in people with refractory or recurrent peptic ulcers.

Study characteristics

We found no randomised controlled trials, and identified only one non-randomised study published 30 years ago, on this topic. This study included 77 participants who had stomach ulcer and in whom medical therapy had failed after an average treatment duration of 29 months. Medical therapy included histamine H2 receptor blockers (medicines that block the action of the chemical histamine,

resulting in a decreased production of stomach acid, such as ranitidine), antacids, and diet. It must be highlighted that this form of medical treatment is not considered to be as effective as treatment with proton pump inhibitors. The authors do not state whether these were recurrent or refractory ulcers. Of the 77 included participants, 37 participants continued to have medical therapy, while 40 participants received surgical therapy. Whether to use medical or surgical treatment was determined by participant's or treating physician's preference. The evidence is current to September 2015.

Key results

The study authors reported that two participants in the medical treatment group (5%) had stomach cancer, which was identified after repeated examinations using a camera to look inside the body (an endoscope), in this case, the stomach and small intestine. They did not report the percentage of participants who had stomach cancer in the surgical treatment group. They also did not report the implications of the delayed diagnosis of stomach cancer in the medical treatment group. They did not report any other outcomes of interest (measures by which one treatment can be considered better than another) for this review (that is health-related quality of life, treatment-related complications, peptic ulcer-related complications, abdominal pain, and long-term deaths). There is thus no study that provides the relative benefits and harms of medical versus surgical treatment for recurrent or refractory peptic ulcers. Studies on this topic are urgently required.

Quality of the evidence

Since the only study that compared medical and surgical treatment in people with refractory or recurrent ulcers did not report any of the outcomes in a sufficiently detailed manner, we were not able to assess the quality of evidence in a formal way.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Medical treatments compared with surgery for refractory or recurrent peptic ulcer

Patient or population: adults with refractory or recurrent peptic ulcer
Settings: primary care (medical treatment) and secondary care (surgical treatment)
Intervention: medical treatment
Comparison: surgical treatment

We included only one non-randomised study published 30 years ago in this review. This study included 77 participants, of whom 37 participants continued to have medical therapy, while 40 participants received surgical therapy after an average duration of medical treatment with histamine H2 receptor blockers, antacids, and diet. Whether to use medical or surgical treatment was determined by participant's or treating physician's preference

The study authors reported that two participants in the medical treatment group (2 out of 37; 5.4%) had gastric cancer, which was identified by repeated biopsy. They did not report the proportion of participants who had gastric cancer in the surgical treatment group. They also did not report the implications of the delayed diagnosis of gastric cancer in the medical treatment group. They did not report any other outcomes of interest for this review (that is health-related quality of life (using any validated scale), adverse events and serious adverse events, peptic ulcer bleeding, peptic ulcer perforation, abdominal pain, and long-term mortality). We therefore could not derive the quality of the evidence

BACKGROUND

Description of the condition

See Appendix 1 for a glossary of terms used in this section.

Peptic ulcer includes gastric and duodenal ulcers (Malfertheiner 2009). Gastric and duodenal ulcers involve defects in the mucosal lining of the stomach and duodenum, respectively. The one-year-period prevalence of physician-diagnosed peptic ulcer disease (that is had peptic ulcer in a one-year period) varies between 0.12% and 1.5% (Sung 2009). The annual incidence of physician-diagnosed peptic ulcer disease is between 0.14% and 0.19% (Sung 2009). There has been a steady decline in the incidence and prevalence of peptic ulcer disease (Sung 2009). *Helicobacter pylori* (*H. pylori*) infection, non-steroidal anti-inflammatory drug (NSAID) use, and smoking are the major risk factors for peptic ulcer (Huang 2002; Kurata 1997). *H. pylori* induces and maintains inflammation of the gastric mucosa leading to gastric ulcers (Peek 1997). It increases acid secretion by increasing gastrin secretion (which, in turn, increases gastric acid secretion) and increases the acid secretion response of the stomach to gastrin (Malfertheiner 2011; Peek 1997). In addition, *H. pylori* also inhibits the inhibitory mechanisms that regulate the acid secretion, resulting in increased acid secretion (Malfertheiner 2011). Increased acid in the duodenum causes gastric metaplasia (replacement of duodenal epithelium with gastric epithelium), which is the defensive reaction of the body. However, gastric metaplasia predisposes infection of the duodenum with *H. pylori* leading to duodenal ulcers (Malfertheiner 2011). Increasing age and male gender are associated with increased incidence of peptic ulcer (Lin 2011; Malmi 2014).

The major symptom of uncomplicated peptic ulcer is upper abdominal pain, which may be associated with dyspeptic symptoms such as fullness, bloating, early satiety, and nausea (Malfertheiner 2011). In people with a duodenal ulcer, upper abdominal pain typically occurs on an empty stomach or during the night and is usually relieved by eating or by taking antacids (Malfertheiner 2011). Bleeding and perforation are the two major common complications of peptic ulcers (Hermansson 2009; Hernandez-Diaz 2013; Malmi 2014; Post 2006). The incidence rate of complications in people without uncomplicated peptic ulcers is 4.6 per 1000 person-years (Hernandez-Diaz 2013). The incidence of bleeding peptic ulcer in the general population varies between 0.27 and 1.06 per 1000 person-years, while that of perforated peptic ulcer in the general population is 0.03 to 0.30 per 1000 person-years (Lin 2011). *H. pylori* infection is a major risk factor for the development of complications (Hernandez-Diaz 2013). While the incidence of peptic ulcer complications has been decreasing in countries such as Sweden, Norway, and Finland (Ahsberg 2011; Hermansson 2009; Malmi 2014; Thorsen 2013), hospitalisation due to peptic ulcer has remained constant from 1996 in the US (Manuel 2007), while the incidence of complications of peptic ulcer has remained constant from 1980 in the Netherlands (Post

2006). Gastric outlet obstruction is another major complication of peptic ulcer (Barksdale 2002; Zittel 2000), but is not common in this era of *H. pylori* eradication and proton pump inhibitor treatment.

Upper gastrointestinal endoscopy (oesophageo-gastro-duodenoscopy, or OGD) is the main method of diagnosis of peptic ulcer. Currently, OGD is indicated in people with dyspepsia and 'alarm symptoms' (Ford 2008; Ikenberry 2007). Alarm symptoms include: family history of upper gastrointestinal malignancy, unintended weight loss, gastrointestinal bleeding, iron deficiency anaemia, progressive dysphagia (difficulty in swallowing), persistent vomiting, palpable mass or lymphadenopathy, and jaundice (Ikenberry 2007). In some guidelines, an older age group (ranging from 35 to 55 years, depending upon the geographical region) with new onset symptoms is an indication for OGD, even in the absence of alarm symptoms (Ford 2008; Ikenberry 2007). The main purpose of OGD is to rule out malignancy. While biopsy of gastric ulcers suspicious of malignancy based on features such as an associated mass lesion, elevated irregular ulcer borders, and abnormal adjacent mucosal folds is recommended, routine biopsy in gastric ulcers that are typical of NSAID-associated lesions, that is shallow flat antral ulcer with associated erosions, may not be necessary, although some malignant ulcers appear benign on endoscopic visualisation initially (ASGE Standards of Practice Committee 2010), so many endoscopists may perform a routine biopsy of all gastric ulcers (ASGE Standards of Practice Committee 2010). In addition to ruling out cancers, biopsies may also be performed to rule out *H. pylori* infection (ASGE Standards of Practice Committee 2010). Many endoscopists perform a routine surveillance (follow-up) endoscopy to ensure that the ulcer has healed and that it is benign (Breslin 1999). Routine biopsy is not recommended in duodenal ulcers, since duodenal ulcers are extremely unlikely to be malignant (ASGE Standards of Practice Committee 2010). For the same reason, routine endoscopic surveillance is not recommended in duodenal ulcers after resolution of symptoms with treatment (ASGE Standards of Practice Committee 2010).

Peptic ulcers can be classified in many ways. A simple classification is between gastric ulcers and duodenal ulcers. This is a clinically relevant type of classification since the recommendations and endoscopists' preference for biopsy and endoscopic surveillance are different for gastric ulcers and duodenal ulcers. Various other classifications of peptic ulcer based on the location and level of acid secretion have been proposed (Johnson 1965; Vesely 1968), but none are clinically relevant based on our current understanding of the important role of *H. pylori* on the pathogenesis of peptic ulcers.

A clinically relevant method of classification of peptic ulcer is its classification into complicated versus uncomplicated peptic ulcer. Major complications of peptic ulcer include bleeding, perforation, and gastric outlet obstruction (Barksdale 2002; Hermansson 2009; Hernandez-Diaz 2013; Malmi 2014; Post 2006; Zittel 2000). Endoscopic and medical treatments are the mainstay treatment for acute peptic ulcer bleeding (Lau 2013). Surgery is usually reserved for unstable patients with recurrent bleeding after endoscopic treatment (Beggs 2014; Griffiths 2013). Emergency surgery in the form of laparoscopic or open repair of the perforated peptic ulcer is currently the mainstay treatment for perforated peptic ulcers (Bertleff 2010). The treatment of patients with gastric outlet obstruction is more controversial. Elective surgery, which includes a procedure to allow the food from the stomach to pass into the small intestine in the form of pyloroplasty or gastrojejunostomy (drainage procedure), was generally combined with another procedure to decrease the acid secretion such as truncal vagotomy, selective vagotomy (preserving the hepatic and celiac branches of the vagus), or highly selective vagotomy (division of gastric branches of the vagus preserving Latarjet's nerve to the pylorus) (Barksdale 2002). While endoscopic dilatation of the obstruction is an alternative to surgery, the high risk of iatrogenic perforation and high recurrence rate of peptic ulcer with endoscopic treatment meant that surgical treatment was preferred over endoscopic treatment (Barksdale 2002). However, it must be noted that the treatments for gastric outlet obstruction evolved and were compared before the era of the pre-proton pump inhibitor and *H. pylori* eradication.

Description of the intervention

H. pylori eradication achieves ulcer healing rates of more than 90% and is recommended for both gastric and duodenal ulcers (Malfertheiner 2012). *H. pylori* eradication as an empirical treatment (without confirmation of presence of *H. pylori*) in regions with high prevalence of *H. pylori,* and test-and-treat strategy (treatment after confirmation of presence of *H. pylori*) in regions with low prevalence of *H. pylori* has been recommended for the treatment of peptic ulcer (Malfertheiner 2012). The recommended initial treatment is a combination of proton pump inhibitor, clarithromycin, and amoxicillin or metronidazole (triple therapy) in regions with low resistance to clarithromycin (less than 20% resistance rate in the area) and triple therapy along with bismuth (quadruple therapy) in regions with high resistance to clarithromycin (greater than 20% resistance rate in the area) (Malfertheiner 2012). If this results in failure of eradication, bismuth-quadruple therapy or levofloxacin-triple therapy (replacement of clarithromycin with levofloxacin in the classical triple therapy) when triple therapy was used as the initial treatment and levofloxacin-triple therapy when bismuth-quadruple therapy was used as the initial treatment is recommended (Malfertheiner 2012). If even this treatment fails to eradicate *H. pylori*, then further treatment should be based on antibiotic susceptibility (Malfertheiner 2012).

While the requirement for long-term proton pump inhibitors is low in people with duodenal ulcers, long-term proton pump inhibitors may be required for those with gastric ulcers (Malfertheiner 2012). For refractory peptic ulcers (an ulcer that does not heal after eight to 12 weeks of treatment or one that is

associated with complications despite treatment), further evaluation of the risk factors and causes of refractory peptic ulcer including lifestyle factors such as smoking, alcohol, NSAID use, non-compliance with medical treatment, gastrinomas (gastrin-secreting tumours), and false-negative *H. pylori* tests should be carried out (Napolitano 2009). Further treatment should focus on the cause of the refractory ulcer, for example smoking or alcohol cessation advice, treatment of resistant *H. pylori*, high-dose proton pump inhibitor, or surgical excision of gastrinomas (Napolitano 2009). Various proton pump inhibitors for long-term treatment of refractory or recurrent ulcer include omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole (Katz 2010). Proton pump inhibitors are generally well tolerated, and adverse effects are relatively infrequent. The adverse effects reported most often with proton pump inhibitors are headache, gastrointestinal disturbances, and rash. Occasionally, severe allergic reactions, anaphylactic reactions, muscle weakness, reversible confusional states, mental disturbances, liver failure, kidney damage, and angina have been reported (Martindale 2011).

Surgery should be considered in patients who are intolerant or non-compliant with medications, those at high risk for complications (for example, patients dependent on NSAIDs, ulcers that fail to heal with adequate medical treatment), and recurrent peptic ulcers despite medical treatment (Napolitano 2009). Surgery for refractory or recurrent ulcers includes truncal vagotomy and drainage procedure (pyloroplasty or gastrojejunostomy), selective vagotomy and drainage, highly selective vagotomy, or partial gastrectomy (Napolitano 2009). The complications related to truncal and selective vagotomy are mortality (less than 0.5%), diarrhoea, and dumping syndrome, while the major complication associated with highly selective vagotomy is recurrent peptic ulcers (Lagoo 2014; Napolitano 2009). Vagotomy is usually performed by open surgery, although case series of laparoscopic vagotomy have been reported (Palanivelu 2006). Surgery for gastric ulcers usually involves a partial gastrectomy (Napolitano 2009). Partial gastrectomy is usually combined with vagotomy and carries a risk for mortality (about 1%), as well as diarrhoea and dumping syndrome (Csendes 2009).

How the intervention might work

Medical treatments such as proton pump inhibitors work by decreasing acid secretion (Welage 2003). Since increased acid is considered to be the cause of ulcer formation, decreasing acid may result in healing of refractory ulcers and prevention of recurrent ulcers. Vagotomy is also aimed at decreasing the stimulation of acid secretion and thus may result in healing of refractory ulcers and prevention of recurrent ulcers (Napolitano 2009), as the vagus nerve controls acid secretion. Truncal vagotomy and selective vagotomy are combined with drainage procedures (pyloroplasty or gastrojejunostomy) because of the division of vagal fibres that play a role in the drainage of food from stomach (Napolitano 2009). Partial gastrectomy is performed with the intention of decreasing the amount of acid-secreting cells (Csendes 2009).

Why it is important to do this review

Peptic ulcers cause approximately 3000 to 4500 deaths per year in the US (Peery 2012; Shaheen 2006). The estimated treatment costs are between USD 163 and USD 866 per person diagnosed with peptic ulcer, and the estimated annual costs due to lost productivity as a result of peptic ulcer are between USD 943 and USD 2424 per employed person in the US (Barkun 2010). Overall, peptic ulcers cost approximately USD 3.5 billion annually in treatment costs and lost productivity in the US (Sandler 2002). Medical management is currently the mainstay treatment for uncomplicated chronic peptic ulcers (Malfertheiner 2011). However, it should be noted that people with bleeding duodenal ulcers have a lower prevalence of *H. pylori* (Malfertheiner 2012). Despite the treatment of *H. pylori*, the recurrence rates of bleeding peptic ulcers vary between 0% and 37.5% (Lau 2011). Considering that an acute episode of bleeding results in a short-term mortality of 3% (Neumann 2013), and that an episode of peptic ulcer perforation is associated with a short-term mortality of 25% to 30% (Moller 2013), it is important to prevent complications related to recurrent or refractory peptic ulcers. Recent concerns about the risk of fractures with long-term use of proton pump inhibitors mean that it is not known whether medical or surgical management is the better treatment option for people with a refractory or recurrent peptic ulcer (Yu 2011). There have been no systematic reviews on this issue. This review will provide the best level of evidence on the comparative benefits and harms of medical versus surgical management for people with a recurrent or refractory peptic ulcer, and so allow patients and the healthcare providers involved in their care to make informed decisions or highlight the lack of evidence on this topic and provide research recommendations.

OBJECTIVES

To assess the benefits and harms of medical versus surgical treatment for people with recurrent or refractory peptic ulcer.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include randomised controlled trials. We planned to include studies reported as full text, those published as abstract only, and unpublished data. In the absence of even a single randomised controlled trial, we planned to perform a meta-analysis of observational studies clearly highlighting the selection bias in interpreting the results. We anticipated significant selection bias in observational studies of this comparison since there is a high possibility that participants with low risk are subject to surgery, and those at high risk are subject to medical treatment, and the effect estimates of a meta-analysis of such observational studies can be misleading. A single randomised controlled trial would have provided a better estimate of the effect than multiple observational studies (even if they show consistent and precise results) in this particular situation. Clearly, multiple randomised controlled trials with consistent effect estimates would have been more reliable than a single randomised controlled trial. The reason for considering observational studies was to provide an estimate of the comparative benefits for medical versus surgical management and provide information for the design of a randomised controlled trial.

Types of participants

We planned to include adults with peptic ulcer irrespective of whether they are gastric or duodenal ulcers, the prior medical treatment that they received, recurrent or refractory (however defined by authors, as long as patients had previous medical treatment for peptic ulcer that had failed), and presence or absence of previous complications. We planned to exclude patients who previously underwent surgery for peptic ulcer disease and those who were unfit for undergoing surgery. We also planned to exclude people with gastrinomas, for whom surgical removal of gastrinoma is the treatment of choice.

Types of interventions

We planned to include trials comparing medical versus surgical treatments for the treatment of peptic ulcer irrespective of the nature of the medical or surgical treatments. We anticipated proton pump inhibitor to be the medical treatment in most instances. With regards to surgery, we anticipated vagotomy (with drainage procedure as appropriate), although studies may include partial gastrectomy as the surgical treatment. We planned to exclude trials in which the comparisons solely involved comparison of different forms of medical treatment or different forms of surgical treatment. We planned to accept co-interventions, for example the use of lifestyle modification advice, provided they were used equally in both groups.

Types of outcome measures

Primary outcomes

1. Health-related quality of life (using any validated scale).
    i) Short term (four weeks to 12 months).
    ii) Medium term (one year to five years).
    iii) Long term (> five years).
2. Serious adverse events (within three months of cessation of treatment; for surgery this period refers to three months after index surgery). We planned to accept the following definitions of serious adverse events.

i) International Conference on Harmonisation - Good Clinical Practice (ICH-GCP) guideline (ICH-GCP 1996): serious adverse events defined as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/ incapacity.

ii) Other variations of ICH-GCP classifications such as the US Food and Drug Administration (FDA) classification (FDA 2006), Medicines and Healthcare products Regulatory Agency (MHRA) classification (MHRA 2013).

Secondary outcomes

1. Adverse events (within three months of cessation of treatment; for surgery this period refers to three months after index surgery). We planned to accept all adverse events reported by the study author irrespective of the severity of the adverse event.
2. Peptic ulcer bleeding.
    i) Short term (four weeks to 12 months).
    ii) Medium term (one year to five years).
    iii) Long term (> five years).
3. Peptic ulcer perforation.
    i) Short term (four weeks to 12 months).
    ii) Medium term (four years to five years).
    iii) Long term (> five years).
4. Abdominal pain.
    i) Short term (four weeks to 12 months).
    ii) Medium term (one year to five years).
    iii) Long term (> five years).
5. Long-term mortality.

The choice of the above clinical outcomes was to assess the comparative safety and clinical improvement in terms of reduced symptoms and complications resulting in an improvement in the health-related quality of life between medical and surgical treatment in people with peptic ulcers.

Reporting of the outcomes listed here was not an inclusion criteria for the review.

Search methods for identification of studies

Electronic searches

We conducted a literature search to identify all published and unpublished randomised controlled trials and non-randomised studies until September 2015. The literature search identified potential studies in all languages. We translated the non-English language papers and fully assessed them for potential inclusion in the review as necessary.

We searched the following electronic databases to identify potential studies:

- The specialised register of the Cochrane Upper GI and Pancreatic Diseases group (September 2015);
- Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 9, 2015) (Appendix 2);
- MEDLINE (1966 to September 2015) (Appendix 3);
- EMBASE (1988 to September 2015) (Appendix 4); and
- Science Citation Index (1982 to September 2015) (Appendix 5).

We also conducted a search of ClinicalTrials.gov (Appendix 6) and WHO ICTRP (World Health Organization - International Clinical Trials Registry Platform) on 18 September 2015 (Appendix 7).

Searching other resources

We checked reference lists of the only primary study and review articles for additional references. We attempted to contact authors of identified trials to ask them to identify other published and unpublished studies.

We searched for errata or retractions from eligible trials on http://www.ncbi.nlm.nih.gov/pubmed on 25 November 2015.

Data collection and analysis

Selection of studies

Two review authors (KG and EP) independently screened the titles and abstracts of all the potential studies we identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports, and two review authors (KG and EP) independently screened the full text and identified studies for inclusion and identified and recorded reasons for exclusion of the ineligible studies. We resolved any disagreements through discussion. We identified and excluded duplicates and planned to collate multiple reports of the same study so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table.

Data extraction and management

We planned to use a standard data collection form for study characteristics and outcome data that had been piloted on at least one study in the review. Two review authors (KG and EP) extracted study characteristics from included studies. We extracted the following study characteristics.

1. Methods: study design, total duration of study and run in, number of study centres and location, study setting, withdrawals, date of study.
2. Participants: number (N), mean age, age range, gender, gastric ulcer or duodenal ulcer, recurrent or refractory peptic ulcer, presence or absence of previous peptic ulcer-related complications, inclusion criteria, exclusion criteria.
3. Interventions: intervention, comparison, concomitant interventions.
4. Outcomes: primary and secondary outcomes specified and collected, time points reported.
5. Notes: funding for trial, notable conflicts of interest of trial authors.

Two review authors (KG and EP) independently extracted outcome data from the included studies. If outcomes were reported multiple times for the same time frame, for example short-term health-related quality of life was reported at three months and 12 months, we planned to choose the later time point (that is 12 months) for data extraction. For time-to-event outcomes, we planned to extract data to calculate the natural logarithm of the hazard ratio and its standard error using the methods suggested by Parmar et al (Parmar 1998).

We planned to include all randomised participants for medium-term outcomes (for example quality of life), and this was not conditional upon the short-term outcomes (for example having a low or high quality of life index at 12 months).

We planned to note in the 'Characteristics of included studies' table if outcome data were reported in an unusable way. We resolved disagreements by consensus. One review author (KG) entered the data from the data collection form into the Review Manager (RevMan) file (Review Manager 2014). We double-checked that the data were entered correctly by comparing the study reports with how the data were presented in the systematic review.

Assessment of risk of bias in included studies

Two review authors (KG and EP) independently assessed the risk of bias for each study. We planned to use the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). However, due to the lack of randomised controlled trials on the topic, we used the relevant 'Risk of bias' domains from 'A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions' (ACROBAT-NRSI) (Sterne 2014).

We assessed the risk of bias according to the following domains:

1. Bias due to confounding
2. Bias due to the selection of participants

3. Bias due to departures from intended intervention
4. Bias in the measurement of outcomes
5. Bias due to missing data
6. Bias in selection of the reported findings

We resolved any disagreements by discussion.

We graded each potential source of bias as low, moderate, serious, critical, or no information and have provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We planned to summarise the 'Risk of bias' judgements across different studies for each of the domains listed. We planned to consider bias in the measurement of outcomes separately for different key outcomes where necessary (for example for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported health-related quality of life scale). Where information on risk of bias relates to unpublished data or correspondence with a trialist, we planned to note this in the 'Risk of bias' table.

When considering treatment effects, we planned to take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to this published protocol and have reported any deviations from it in the Differences between protocol and review section of the systematic review.

Measures of treatment effect

We planned to analyse dichotomous data as risk ratio and continuous data as mean difference when the outcome was reported in the same health-related quality of life scale, or standardised mean difference when different scales were used for measuring quality of life. We planned to ensure that higher scores for continuous outcomes have the same meaning for the particular outcome, explain the direction to the reader, and report where the directions were reversed if this was necessary. We planned to calculate the rate ratio for outcomes such as adverse events and serious adverse events, where it is possible for the same person to develop more than one adverse event (or serious adverse event). If the authors had calculated the rate ratio of adverse events (or serious adverse events) in the intervention versus control based on Poisson regression, we planned to obtain the rate ratio by the Poisson regression method in preference to rate ratio calculated based on the number of adverse events (or serious adverse events) during a certain period. We planned to calculate the hazard ratio for time-to-event outcomes such as time to first adverse event (or serious adverse event).

We planned to undertake meta-analyses only where these were meaningful, that is if the treatments, participants, and the underlying clinical question were similar enough for pooling to make sense.

A common way that trialists indicate when they have skewed data is by reporting medians and interquartile ranges. When we encountered this, we planned to note that the data were skewed and to consider the implication of this.

Where multiple trial arms were reported in a single trial, we planned to include only the relevant arms. If two comparisons (for example omeprazole versus vagotomy and lansoprazole versus vagotomy) had to be entered into the same meta-analysis, we planned to halve the control group to avoid double-counting. The alternative way of including such trials with multiple arms is to pool the results of the omeprazole and lansoprazole and compare it with vagotomy. We planned to perform a sensitivity analysis to determine if the results of the two methods of dealing with multi-arm trials led to different conclusions.

Unit of analysis issues

The unit of analysis was the individual participant with refractory or recurrent peptic ulcer. As anticipated, we did not find any cluster-randomised trials for this comparison, but if we had identified cluster-randomised trials, we planned to obtain the effect estimate adjusted for the clustering effect. If this was not available, we planned to perform a sensitivity analysis excluding the trial from the meta-analysis, as the variance of the effect estimate unadjusted for cluster effect is less than the actual variance which is adjusted for cluster effect, giving inappropriately more weight to the cluster-randomised trial in the meta-analysis.

Dealing with missing data

We attempted to contact investigators or study sponsors in order to verify key study characteristics and to obtain missing numerical outcome data where possible (for example when a study is identified as abstract only). If we were unable to obtain the information from the investigators or study sponsors, we planned to impute the mean from the median (that is consider median as the mean) and standard deviation from standard error, interquartile range, or P values according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), but assess the impact of including such studies as indicated in a sensitivity analysis. If we were unable to calculate the standard deviation from standard error, interquartile range, or P values, we planned to impute standard deviation as the highest standard deviation in the remaining trials included in the outcome, fully aware that this method of imputation would decrease the weight of the studies in the meta-analysis of mean difference and shift the effect towards no effect for standardised mean difference.

Assessment of heterogeneity

We planned to use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity as per the *Cochrane Handbook for Systematic Reviews of Inter-*

ventions (greater than 50% to 60%), we planned to explore it by prespecified subgroup analysis.

Assessment of reporting biases

We attempted to contact study authors to ask them to provide missing outcome data. Where this was not possible, and the missing data were thought to introduce serious bias, we planned to explore the impact of including such studies in the overall assessment of results by a sensitivity analysis**.**

If we were able to pool more than 10 trials, we planned to create and examine a funnel plot to explore possible publication biases. We planned to use Egger's test to determine the statistical significance of the reporting bias (Egger 1997). We planned to consider a P value of less than 0.05 as statistically significant reporting bias.

Data synthesis

We planned to perform the analysis using RevMan 5.3 (Review Manager 2014). We planned to use the Mantel-Haenszel method for dichotomous data, inverse variance method for continuous data, and generic inverse variance for count and time-to-event data. We planned to use both the fixed-effect model and random-effects model for the analysis (Demets 1987; DerSimonian 1986). In case of discrepancy between the two models, we planned to report both results; otherwise we planned to report only the results from the fixed-effect model.

'Summary of findings' table

We planned to create a 'Summary of findings' table using all the outcomes. We planned to use the five Grading of Recommendations Assessment, Development and Evaluation (GRADE) considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes. We planned to use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and use GRADEpro software. We planned to justify all decisions to down- or upgrade the quality of studies using footnotes and make comments to aid the reader's understanding of the review where necessary. We planned to consider whether there was any additional outcome information that could not be incorporated into meta-analyses and to note this in the comments, stating if it supports or contradicts the information from the meta-analyses.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses.

1. Gastric ulcer versus duodenal ulcer.
2. Recurrent peptic ulcers versus refractory peptic ulcer.
3. Presence versus absence of previous complications (perforation or bleeding).
4. Different surgery (truncal vagotomy versus selective vagotomy; pyloroplasty versus gastrojejunostomy).

We planned to use all the primary outcomes in subgroup analysis. We planned to use the formal Chi^2 test for subgroup differences to test for subgroup interactions.

Sensitivity analysis

We planned to perform the following sensitivity analyses defined a priori to assess the robustness of our conclusions.

1. Excluding trials at unclear or high risk of bias (one or more of the 'Risk of bias' domains (other than blinding of surgeon) classified as unclear or high).
2. Excluding trials in which either mean or standard deviation or both were imputed.
3. Excluding cluster-randomised controlled trials in which the adjusted effect estimates were not reported.
4. Different methods of dealing with multi-arm trials (please see Measures of treatment effect).

Reaching conclusions

We planned to base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We have avoided making recommendations for practice, and our implications for research will provide a clear sense of direction for any future research in the area and any remaining uncertainties.

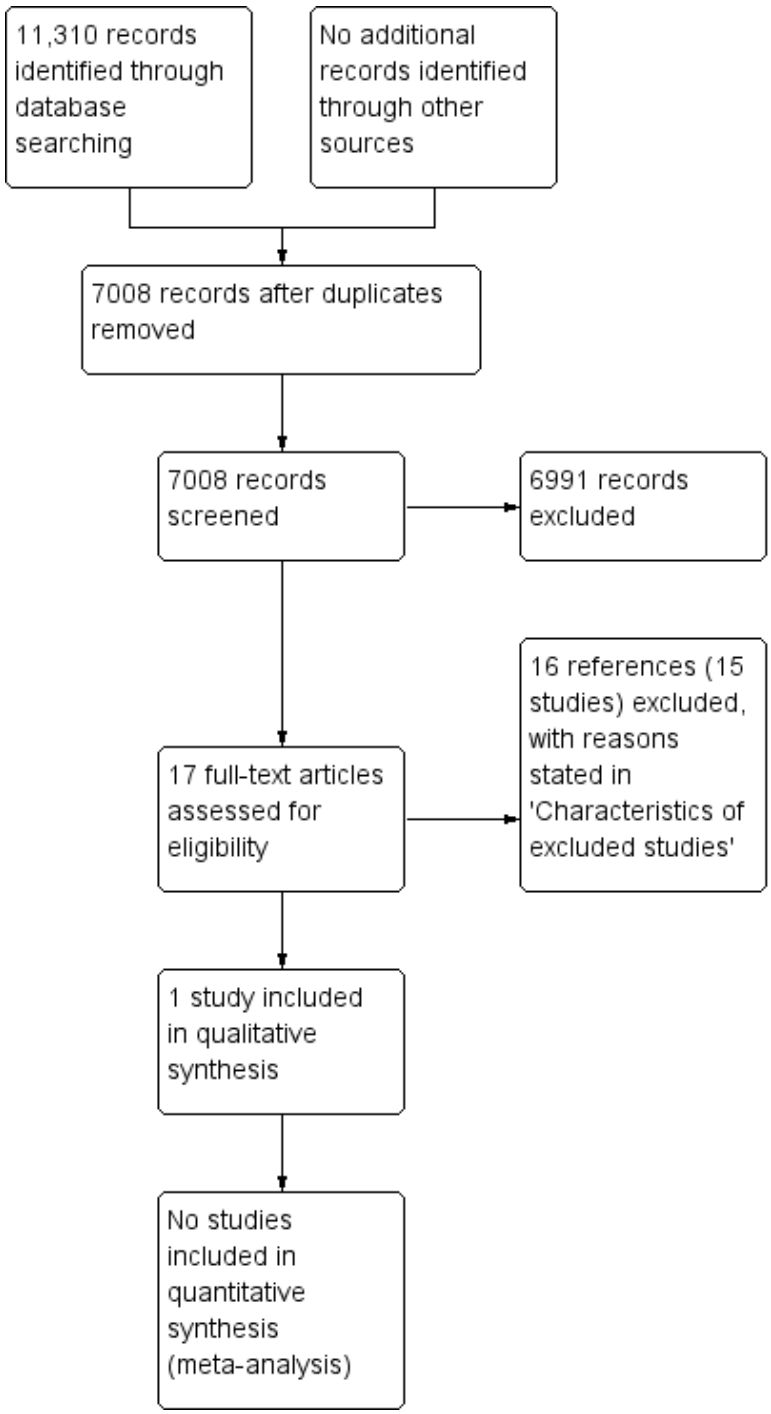
RESULTS

Description of studies

Results of the search

We identified 11,310 references through electronic searches of Cochrane (Wiley) (n = 172), MEDLINE (OvidSP) (n = 3032), EMBASE (OvidSP) (n = 6225), Science Citation Index expanded (n = 1878), ClinicalTrials.gov (n = 2), and WHO ICTRP (n = 1). There were 7008 references after removal of duplicate references. We excluded 6991 clearly irrelevant references through reading titles and abstracts. We retrieved a total of 17 full-text articles for detailed assessment. We excluded 16 references (15 studies, reports, or articles) for the reasons listed in Characteristics of excluded studies. One reference of one non-randomised study fulfilled the inclusion criteria (see Characteristics of included studies). The study flow diagram is shown in Figure 1.

Figure 1. Study flow diagram.



Included studies

We included only one non-randomised study published 30 years ago in this review (Adkins 1985). This study included 77 participants who had gastric ulcer and in whom medical therapy (histamine H2 receptor blockers, antacids, and diet) had failed after an average duration of treatment (study authors did not report whether this was mean or median) of 29 months. The authors do not state whether these were recurrent or refractory ulcers. Although it was not stated explicitly, we inferred that the participants did not have previous complications such as bleeding or perforation. Of the 77 included participants, 37 participants continued to have medical therapy, while 40 participants received surgical therapy. The surgical therapy included a number of operations such as antrectomy with or without vagotomy; subtotal gastrectomy with or without vagotomy; vagotomy; pyloroplasty and suture of the ulcer; suture or closure of ulcer without vagotomy or excision of the ulcer; proximal gastric or parietal cell vagotomy alone; suture or closure of the ulcer with proximal gastric or parietal cell vagotomy. The authors state that of the participants in the medical therapy arm, eight participants received medical therapy because they refused to undergo surgery, and 29 participants were not considered to be surgical candidates by their gastroenterologists or surgeons. In addition to the 77 participants who had failed medical treatment, this study also reported on 58 participants who had successful medical treatment and 28 participants who underwent initial surgical management . The study authors did not report complications related to medical therapy. They did report complications related to surgical treatment, but did not report these separately for participants who underwent surgical treatment for recurrent or refractory peptic ulcers. They also reported that two participants in the medical treatment group had gastric cancer (2 out of 37; 5.4%), which was identified by repeated biopsy. They did not report the proportion of participants who had gastric cancer in the surgical treatment group. They also did not report the implications of the delayed diagnosis of gastric cancer in the medical treatment group. They did not report any of the other outcomes of interest for this review, thus there was no data to calculate the effect estimates.

Excluded studies

We excluded five studies because participants had had previous peptic ulcer surgery (Chung 1998; Kinney 1988; Koo 1982; Lindenauer 1975; Neustein 1976). We excluded two studies because they did not evaluate people who had recurrent or refractory peptic ulcers (Barragry 1986; Mandache 1971). One study was excluded because people who had failed medical treatment previously were excluded (Harling 1985). We excluded one study because there was no separate data on participants who underwent surgery after recurrent or refractory ulcer (Bardhan 2003). In one study, all participants received medical treatment after perforation closure (Brehant 2008), and another study reported only on participants who received medical treatment and underwent emergency surgery because of catastrophic bleeding (Bouillot 1991); there were no comparator groups in these two studies. We excluded four reports because they were reviews or letters to editor (Amdrup 1981; Anonymous 1981; De Vernejoul 1947; Nguyen 2007).

Risk of bias in included studies

Bias due to confounding

The risk of bias due to confounding was unclear in the only study included in this review, as baseline characteristics were not reported (Adkins 1985). We therefore classified this domain as 'No information'.

Bias due to the selection of participants

The only study included in this review reported that the reason for participants receiving medical treatment was because of participant's or physician's preference (Adkins 1985). As this might have introduced bias, we have classified this domain as 'critical' risk of bias.

Bias due to departures from intended intervention

The only study included in this review did not report whether the patient care other than medical or surgical treatment was identical in the two groups (Adkins 1985). We therefore classified this domain as 'No information'.

Bias in the measurement of outcomes

The only study included in this review did not report whether the outcome assessors were blinded (Adkins 1985). We therefore classified this domain as 'No information'.

Bias due to missing data

All participants with gastric ulcers who failed medical treatment were included in the only study included in this review (Adkins 1985), therefore this domain was classified as 'low' risk of bias.

Bias in selection of the reported findings

The only study included in this review did not adequately report on any of the outcomes that can be expected to be reported in a study of this nature, such as mortality and complications. (Adkins 1985). We therefore classified this domain as 'critical' risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Medical treatments compared with surgery for refractory or recurrent peptic ulcer

The only study included in this review did not report any of the outcomes of interest for this review (Adkins 1985). The study authors reported that two participants in the medical treatment group (2 out of 37; 5.4%) had gastric cancer, which was identified by repeated biopsy. They did not report the proportion of participants who had gastric cancer in the surgical treatment group. They also did not report the implications of the delayed diagnosis of gastric cancer in the medical treatment group.

Since the study did not report data that could be analysed, we could not perform any of the planned analyses.

DISCUSSION

Summary of main results

We included only one non-randomised study published 30 years ago in this review (Adkins 1985). This study included 77 participants who had gastric ulcer and in whom medical therapy (histamine H2 receptor blockers, antacids, and diet) had failed after an average treatment duration of 29 months. The study authors reported that two participants in the medical treatment group (2 out of 37; 5.4%) had gastric cancer, which was identified by repeated biopsy. They did not report the proportion of participants who had gastric cancer in the surgical treatment group. They also did not report the implications of the delayed diagnosis of gastric cancer in the medical treatment group. They did not report any other outcomes of interest.

Overall completeness and applicability of evidence

The only study included in this review was published 30 years ago. The medical treatment used in this study was histamine H2 receptor blockers and antacid. As the current recommended treatment for peptic ulcers is proton pump inhibitors, the results of the study are not applicable to the current situation. In the absence of any evidence from randomised or non-randomised studies, we have discussed the major issues that must be considered when deciding whether a person undergoes medical or surgical treatment for recurrent or refractory peptic ulcer.

The first issue is gastric cancer in refractory gastric ulcers. Gastric cancer can present as gastric ulcer, sometimes without the typical characteristics of a malignant gastric ulcer such as associated mass lesion, elevated irregular ulcer borders, and abnormal adjacent mucosal folds. The sensitivity of endoscopy for detecting malignancy is approximately 72% to 95% (Bustamante 2002; Gielisse 2015; Manas 2009), so many endoscopists may perform a routine biopsy of all gastric ulcers (ASGE Standards of Practice Committee 2010). Follow-up endoscopy examination of patients with a previous negative endoscopic biopsy revealed that approximately 0.9% to 4.5% of patients have gastric cancer despite an initial negative endoscopic biopsy (Eckardt 1992; Hopper 2006; Hosokawa 2001). A recent study showed that none of the participants with a previous negative endoscopic biopsy had gastric cancer (Gielisse 2015), that is a single endoscopy with biopsy had a 100% sensitivity in detecting gastric cancer in gastric ulcer. However, these excellent results have not been replicated in other studies as mentioned above. Treatment of gastric cancer may be delayed because of the misdiagnosis of malignant gastric ulcer as peptic ulcer (Podolsky 1988). In addition, approximately 1.6% (1470 out of 92,250) of patients with pre-malignant lesions with atrophic gastritis, intestinal metaplasia, and dysplasia developed gastric cancer (de Vries 2008). Most of these cancers developed in people with severe dysplasia (de Vries 2008). Routine surgery for refractory or recurrent gastric ulcers will result in earlier treatment of gastric cancers and avoid the risk of pre-malignant lesions turning malignant. However, this exposes the patients to the complications of partial gastrectomy, which carries a risk for mortality (about 1%), as well as diarrhoea and dumping syndrome (Csendes 2009).

Other major factors that must be considered in addition to the risk of malignancy in gastric ulcers are the risk of bleeding and perforation in people who are treated medically and surgically for recurrent or refractory peptic ulcer, as mentioned in the Background, as well as health-related quality of life and loss of productivity after medical and surgical treatment.

With the increasing role of bariatric surgery in obese people (NICE 2014), the issue about medical versus surgical treatment of refractory or recurrent peptic ulcers may become an important issue in this population, as 0.6% to 25% of people who undergo Roux-en-Y gastric bypass surgery (a common bariatric surgery) develop peptic ulcers (Coblijn 2014; Edholm 2015). These are called 'marginal ulcers', 'ischaemic ulcers', or 'anastomotic ulcers' (Coblijn 2014). While about two-thirds of marginal ulcers can be treated medically, the remaining ones need endoscopic or surgical treatment, mostly in the form of revisional surgery (Coblijn 2014). Vagotomy has been proposed as an alternative for revisional surgery for people with refractory marginal ulcers (Hunter 2012). Given the number of deaths and the socioeconomic importance of peptic ulcer (which might increase with the growing popularity of bariatric surgery), it is important to determine the relative benefits and harms of medical versus surgical treatment for people with refractory or recurrent peptic ulcers.

Quality of the evidence

The only study that was included in this review had unclear risk of bias in most domains and critical risk of bias in bias due to

confounding and selective outcome reporting. This study did not report any outcome of interest, therefore the quality of evidence could not be formally determined using GRADE methodology.

Potential biases in the review process

We planned to include randomised controlled trials only if at least one randomised controlled trial was available for this review. However, in the absence of any randomised controlled trials, we have reported the best available evidence on the topic. We removed the randomised controlled trial filter to ensure that observational studies were not removed by the electronic filters. Two review authors independently selected studies without using any language restrictions and extracted data, decreasing the likelihood of potential errors in study selection and data extraction. However, this is a systematic review of non-randomised studies. There is no requirement for mandatory registration, and many studies may not have been submitted to the journals by study authors, particularly if the morbidity related to peptic ulcers was high. We therefore cannot rule out publication bias.

Agreements and disagreements with other studies or reviews

This is the first systematic review on the topic. We are unable to recommend a definitive treatment algorithm as suggested by Napolitano et al because of the paucity of information (Napolitano 2009).

AUTHORS' CONCLUSIONS

Implications for practice

There is no study that provides the relative benefits and harms of medical versus surgical treatment for recurrent or refractory peptic ulcers.

Implications for research

Studies that evaluate the natural history of recurrent and refractory peptic ulcers are urgently required to determine whether randomised controlled trials comparing medical versus surgical management in patients with recurrent or refractory peptic ulcers or both are necessary. Such studies will also provide information for the design of such randomised controlled trials. The initial medical management should include proton pump inhibitors as a minimum and may consider *H. pylori* eradication therapy, particularly in areas of high prevalence of *H. pylori*, before concluding that a peptic ulcer is recurrent or refractory. Participants should also be screened and treated for gastrinomas prior to classifying them as recurrent or refractory ulcers. The medical treatment of recurrent and refractory peptic ulcers should include proton pump inhibitors. A minimum follow-up of two to three years will allow the calculation of the incidence of complications and gastric cancer (in gastric ulcers only) in recurrent and refractory peptic ulcers. In addition to complications related to treatment and disease, health-related quality of life and loss of productivity should also be measured.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Adkins 1985

Methods	Retrospective cohort study
Participants	Country: USA Number included: 77 Number of eligible people excluded: 0 (0%) Revised sample size: 77 Average age: not stated Gender: not stated Gastric ulcer: 77 (100%) Duodenal ulcer: not stated Recurrent peptic ulcer: not stated Refractory peptic ulcer: not stated Presence of previous peptic ulcer-related complications: none (not stated explicitly in the study but can be inferred) **Inclusion criteria** People with gastric ulcer who failed medical therapy after histamine H2 receptor blockers, antacids, and diet (average duration (mean or median - not stated) of medical treatment: 29 months)
Interventions	Group 1: medical treatment (n = 37) Further details: histamine H2 receptor blockers, antacids, and diet Group 2: surgical treatment (n = 40) Further details: several operation types
Outcomes	None of the outcomes of interest were reported adequately
Notes	2 participants in the medical treatment group had gastric cancer, which was identified by repeated biopsy

Risk of bias

Bias	Authors' judgement	Support for judgement
Bias due to confounding	Unclear risk	**No information** Comment: Authors do not provide baseline characteristics between those who continued medical treatment and who underwent surgery
Bias due to selection of participants to intervention and control	High risk	**Critical risk of bias** Quote: "Eight of these 37 have refused surgical treatment, and 29 for some reason apparently have not been considered to be surgical candidates by their gastroenterologists and/or by their surgeons" Comment: This could have introduced selection bias

Adkins 1985 (*Continued*)

Bias due to differences in co-interventions which were different between the groups	Unclear risk	**No information** Comment: This information was not available
Bias in the measurement of outcomes	Unclear risk	**No information** Comment: This information was not available
Bias due to missing data	Low risk	**Low risk of bias** Comment: All participants with gastric ulcers during the period were included in the report
Bias in selection of the reported findings	High risk	**Critical risk of bias** Comment: None of the outcomes that can be expected to be reported in a study of this nature such as mortality and complications were reported adequately

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Amdrup 1981	Review
Anonymous 1981	Review
Bardhan 2003	No separate data on participants who underwent surgery after refractory ulcer
Barragry 1986	Did not evaluate recurrent or refractory ulcers
Bouillot 1991	Participants received medical treatment, and all underwent emergency surgery due to catastrophic bleeding
Brehant 2008	All participants received medical treatment after perforation closure
Chung 1998	Participants had had previous surgery for peptic ulcer disease
De Vernejoul 1947	Letter to editor
Harling 1985	People who had failed earlier treatment with cimetidine were excluded
Kinney 1988	Participants had had previous surgery for peptic ulcer disease
Koo 1982	Participants had had previous surgery for peptic ulcer disease
Lindenauer 1975	Participants had had previous surgery for peptic ulcer disease
Mandache 1971	Did not evaluate recurrent or refractory ulcers

(*Continued*)

Neustein 1976	Participants had had previous surgery for peptic ulcer disease
Nguyen 2007	Review

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Glossary of terms

Adjacent: nearby.
Anaphylactic shock: life-threatening allergic reaction characterised by breathing difficulties or very low blood pressure or both.
Antral ulcers: ulcers in the antrum, the lower part of the stomach.
Antrectomy: removal of antrum, the lower part of the stomach.
Benign: non-cancerous (in this context).
Bismuth: anti-ulcer drug.
Clarithromycin, amoxicillin, metronidazole: antibiotics
Diarrhoea: frequent and loose stools
Dumping syndrome: feeling of fullness after a small meal, abdominal pain, light-headedness, and urgent requirement to pass stools.
Duodenum: first part of small intestine.
Dyspepsia: indigestion resulting in fullness, bloating, early satiety, and nausea.
Eradication: destruction.
Erosions: break only in the mucosa without a break in the deeper layers (in this context).
Endoscopy: the insertion of a tube with a camera and light through the mouth (in this context) to allow visual examination of the oesophagus (food pipe), stomach, and the upper part of the small intestine.
Gastrectomy: removal of complete stomach or part of stomach.
Gastric outlet obstruction: obstruction to the flow of food from the stomach into the small bowel.
Gastric: stomach.
Gastric mucosa: mucosa (inner lining) of the stomach.
Gastrin: hormone that increases secretion of acid in the stomach. This hormone is secreted by the gastric mucosa (inner lining of the stomach).
Gastrointestinal: digestive.
Gastrojejunostomy: creating a connection between stomach and the jejunum, the second part of the small intestine.
Helicobacter pylori (H. pylori): a bacterium found usually in the stomach that is believed to be the cause of a number of diseases, including stomach ulcers and stomach cancer.
Highly selective vagotomy: division of the branches of the vagus nerve that control the acid secretion without dividing the nerve branches that control the valve-like mechanism that allows food to pass from the stomach into the small bowel.
Histamine H2 receptor blockers: medicines that block the action of a chemical called histamine resulting in a decreased production of stomach acid. Histamine stimulates the stomach cells to secrete stomach acid.
Iatrogenic: accidental or unintentional complication caused by a medical examination or treatment.
Iron deficiency anaemia: an abnormal decrease in red blood cells caused by low iron levels in the blood.
Jaundice: yellowish discolouration of skin and white of the eye and dark urine resulting from accumulation of bile pigments (waste products normally excreted in bile).
Lymphadenopathy: enlarged lymph glands or lymph nodes.
Malignant: cancer (in this context).
Mass: lump (in this context).
Metaplasia: replacement of cell type with another cell type that is native to another site within the body or transformation of one tissue into another.
Mucosa: inner lining of food pipe, stomach, and bowel.
Pathogenesis: mechanism of how a disease or a complication is caused.
Person-years: equivalent to 1000 persons at risk of developing peptic ulcer followed for one year or 500 persons at risk of developing peptic ulcer followed for two years, and so on.

Proton pump inhibitor: proton pump is the pump that is responsible for secreting acid by the stomach cells. Proton pump inhibitors are drugs that decrease the secretion of acid by blocking these pumps.
Pyloroplasty: widen the opening in the lower part of the stomach.
Pylorus: the lower end of the stomach, which is controlled by a valve-like mechanism that allows food to pass from the stomach into the small bowel.
Satiety: the feeling of having eaten enough or too much.
Selective vagotomy: division of branches of the vagus that supply the stomach without dividing those supplying the liver.
Truncal vagotomy: division of the abdominal vagus nerve trunks, which control acid secretion and the movement of the intestines.

Appendix 2. CENTRAL search strategy

#1 MeSH descriptor: [Stomach] explode all trees
#2 stomach or gastr*
#3 MeSH descriptor: [Duodenum] explode all trees
#4 duoden*
#5 peptic*
#6 MeSH descriptor: [Esophagus] explode all trees
#7 esophag* or oesophag*
#8 MeSH descriptor: [Peptic Ulcer] explode all trees
#9 (peptic adj5 ulcer*) or (stomach adj5 ulcer*) or (duoden* adj5 ulcer*) or (gastroduoden* adj5 ulcer*)
#10 #1 or #2 or #3 or #4 or #5 or #5 or #6 or #7 or #8 or #9
#11 (recurrent or refractory or non-healing or fail*)
#12 MeSH descriptor: [Gastrectomy] explode all trees
#13 gastrectomy
#14 MeSH descriptor: [Vagotomy] explode all trees
#15 vagotomy
#16 (pyloroplasty or gastrojejunostomy or antrectomy or antrum resection or antral resection)
#17 #12 or #13 or #14 or #15 or #16
#18 #10 and #11 and #17

Appendix 3. MEDLINE search strategy

1. exp stomach/
2. stomach.mp.
3. gastr*.mp.
4. exp duodenum/
5. duoden*.mp.
6. peptic*.mp.
7. exp esophagus/
8. esophag*.mp.
9. oesophag*.mp.
10. exp peptic ulcer/
11. (peptic adj5 ulcer*).mp.
12. (stomach adj5 ulcer*).mp.
13. (duoden* adj5 ulcer*).mp.
14. (gastroduoden* adj5 ulcer*).mp.
15. or/1-14
16. (recurrent or refractory or non-healing or fail*).tw.
17. exp gastrectomy/
18. gastrectomy.tw.
19. exp Vagotomy/
20. vagotomy.tw.
21. pyloroplasty.tw.

22. gastrojejunostomy.tw.
23. (antrectomy or antrum resection or antral resection).mp.
24. or/17-23
25. 15 and 16 and 24
26. exp animals/ not humans.sh.
27. 25 not 26

Appendix 4. EMBASE search strategy

1. exp stomach/
2. stomach.mp.
3. gastr*.mp.
4. exp duodenum/
5. duoden*.mp.
6. peptic*.mp.
7. exp esophagus/
8. esophag*.mp.
9. oesophag*.mp.
10. exp peptic ulcer/
11. (peptic adj5 ulcer*).mp.
12. (stomach adj5 ulcer*).mp.
13. (duoden* adj5 ulcer*).mp.
14. (gastroduoden* adj5 ulcer*).mp.
15. or/1-14
16. (recurrent or refractory or non-healing or fail*).tw.
17. exp gastrectomy/
18. gastrectomy.tw.
19. exp vagotomy/
20. vagotomy.tw.
21. exp pyloroplasty/
22. pyloroplasty.tw.
23. exp gastrojejunostomy/
24. gastrojejunostomy.tw.
25. exp stomach antrum resection/
26. (antrectomy or antrum resection or antral resection).mp.
27. or/17-26
28. 15 and 16 and 27

Appendix 5. Science Citation Index search strategy

1 TS= (stomach or gastr* or duoden* or peptic* or esophag* or oesophag* or (peptic and ulcer*) or (stomach and ulcer*) or (duoden* and ulcer*) or (gastroduoden* and ulcer*)
2 TS= (recurrent or refractory or non-healing or fail*)
3 TS= (gastrectomy or vagotomy or pyloroplasty or gastrojejunostomy or antrectomy or antrum resection or antral resection)
4 #1 AND #2 AND #3

Appendix 6. ClinicalTrials.gov search strategy

"Interventional" [STUDY-TYPES] AND ("Phase 2" OR "Phase 3" OR "Phase 4") [PHASE] | "peptic ulcer" OR "duodenal ulcer" OR "gastric ulcer" | gastrectomy OR vagotomy OR pyloroplasty OR gastrojejunostomy OR antrectomy OR "antrum resection" OR "antral resection"

Appendix 7. WHO ICTRP search strategy

Title: gastrectomy or vagotomy or pyloroplasty or gastrojejunostomy or antrectomy or antrum resection or antral resection
Condition: peptic ulcer or gastric ulcer or duodenal ulcer

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Conceiving of the review: KG

Designing the review: KG

Co-ordinating the review: KG

Designing search strategies: KG

Data extraction: KG, EP

Data analysis: KG

Writing the review: KG

Securing funding for the review: KG

Performing previous work that served as the foundation of the current study: KG

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KSG: none known.

EP: none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Since we identified no randomised controlled trials, we included non-randomised studies in order to provide the best currently available evidence. As a result, we made the following modifications to the protocol.

1. We did not use the filter for randomised controlled trials for the electronic searches of the databases.

2. We used 'A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions' (ACROBAT-NRSI) tool for assessment of risk of bias rather than the standard Cochrane 'Risk of bias' tool for randomised controlled trials.