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[Intervention Protocol]

Medical versus surgical treatment for refractory or recurrent peptic ulcer

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

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

BACKGROUND

Description of the condition

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 (i.e. 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 patients with a duodenal ulcer, upper abdominal pain typically occurs on a empty stomach or during the night and usually is relieved by eating or 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 some 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 US (Manuel 2007), while the incidence of complications of peptic ulcer has remained constant from 1980 in 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 with '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 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, routine biopsy in gastric ulcers that are typical of NSAID-associated lesions, i.e. 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 the ulcer is benign (Breslin 1999). Routine biopsy is not recommended in duodenal ulcers since duodenal ulcers are extremely unlike 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 is 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 currently 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). Currently, emergency surgery in the form of laparoscopic or open repair of the perforated peptic ulcer is 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), which 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 for 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 with a combination of proton pump inhibitor, clarithromycin, and amoxicillin or metronidazole (triple therapy) in regions with low resistance to clarithromycin (< 20% resistance rate in the area) and the triple therapy along with bismuth (quadruple therapy) in regions with high resistance to clarithromycin (> 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 after 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 treatment of the cause of the refractory ulcer, for example, smoking cessation advice or alcohol cessation advice, treatment of resistant *H. pylori*, or 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 include 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 (< 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 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 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) (Napolitano 2009) because of the division of vagal fibres that play a role in the drainage of food from stomach. 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 US (Peery 2012; Shaheen 2006). The estimated treatment costs is between US $163 and US $866 per person diagnosed with peptic ulcer and the estimated annual costs due to lost productivity due to peptic ulcer is between US $943 and US $2424 per employed person in US (Barkun 2010). Overall, peptic ulcers cost approximately US $3.5 billion annually in treatment costs and lost productivity in US (Sandler 2002). Currently, medical management is the mainstay treatment for the treatment of 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 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. There have been recent concerns about the risk of fractures with long-term use of proton pump inhibitors (Yu 2011). So, it is not known whether medical or surgical management is better for people with a refractory or recurrent peptic ulcer. 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 the comparative benefits and harms of medical versus surgical management for people with recurrent or refractory peptic ulcers and provide research recommendations.

See Appendix 1 for a glossary of terms used in the Background.

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 will include randomised controlled trials (RCTs). We will 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 will perform a meta-analysis of observational studies clearly highlighting the selection bias in interpreting the results. We anticipate 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 will provide a better estimate of the effect than multiple observational studies (even if they are showing consistent and precise results) in this particular situation. Clearly, multiple randomised controlled trials with consistent effect estimates are more reliable than a single randomised controlled trial. The reason for including observational studies is 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 will include adults with peptic ulcer irrespective of whether they are gastric or duodenal ulcers, recurrent or refractory (however defined by authors), and presence or absence of previous complications. We will exclude patients who have previously undergone surgery for peptic ulcer disease and those who are unfit for undergoing surgery.

Types of interventions

We will include trials comparing medical versus surgical treatments for the treatment of peptic ulcer irrespective of the nature of the medical or surgical treatments. In most instances, we anticipate proton pump inhibitor to be the medical treatment. With regards to surgery, we anticipate vagotomy (with drainage procedure as appropriate), although studies may include partial gastrectomy as the surgical treatment. We will exclude trials in which the comparisons solely involve comparison of different forms of medical treatment or different forms of surgical treatment. We will accept co-interventions, for example, the use of lifestyle modification advice, provided that 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 will accept the following definitions of serious adverse events.
    i) ICH-GCP International Conference on Harmonisation - Good Clinical Practice 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 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 will 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 year 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 is 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 patients with peptic ulcers.

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

Search methods for identification of studies

Electronic searches

We will conduct a literature search to identify all published and unpublished randomised controlled trials. The literature search will identify potential studies in all languages. We will translate the non-English language papers and fully assess them for potential inclusion in the review as necessary.

We will search the following electronic databases for identifying potential studies:

- Cochrane Central Register of Controlled Trials (CENTRAL) (Appendix 2);
- MEDLINE (1966 to present) (Appendix 3);
- EMBASE (1988 to present) (Appendix 4); and
- Science Citation Index (1982 to present) (Appendix 5).

We will also conduct a search of ClinicalTrials.gov (Appendix 6) and WHO ICTRP (World Health Organization - International Clinical Trials Registry Platform) (Appendix 7).

Searching other resources

We will check reference lists of all primary studies and review articles for additional references. We will contact authors of identified trials and ask them to identify other published and unpublished studies.

We will search for errata or retractions from eligible trials on http://www.ncbi.nlm.nih.gov/pubmed and report the date this was done within the review.

Data collection and analysis

Selection of studies

Two review authors (trained research assistants or students or colleagues of K Gurusamy) will independently screen titles and abstracts for inclusion all the potential studies we identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports and two review authors (research assistants or students or colleagues of Dr K Gurusamy) will independently screen the full text and identify studies for inclusion and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult third person (K Gurusamy). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table.

Data extraction and management

We will use a standard data collection form for study characteristics and outcome data which has been piloted on at least one study in the review. Two review authors (research assistants or students or colleagues of K Gurusamy) will extract study characteristics from included studies. We will extract the following study characteristics.

1. Methods: study design, total duration 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, and 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 (research assistants or students or colleagues of K Gurusamy) will independently extract outcome data form included studies. If outcomes were reported multiple times for the same time point, for example, short-term health-related quality of life was reported at three months and 12 months, the later time point (i.e. 12 months) will be chosen for data extraction. For time-to-event outcomes, we will 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).

All randomised participants will be included for medium outcomes (for example, quality of life) and this will not be conditional upon the short-term outcomes (for example, having a low or high quality of life index at 12 months).

We will note in the 'Characteristics of included studies' table if outcome data were reported in an unusable way. We will resolve disagreements by consensus or by involving a third person (K Gurusamy). One review author (K Gurusamy) will enter the data from the data collection form into the Review Manager file. We will double check that the data are entered correctly by comparing the study reports with how the data are presented in the systematic review.

Assessment of risk of bias in included studies

Two review authors (research assistants or students or colleagues of K Gurusamy) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreement will be resolved by discussion or by involving a third assessor (K Gurusamy). We will assess the risk of bias according to the following domains.

1. Random sequence generation.

2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We will grade each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgment in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary e.g. 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 will note this in the 'Risk of bias' table.

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

Assesment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as risk ratio and continuous data as mean difference when the outcome is reported in the same health-related quality of life scale or standardised mean difference when different scales are used for measuring the quality of life. We will 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 will 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 have calculated the rate ratio of adverse events (or serious adverse events) in the intervention versus control based on Poisson regression, we will 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 will calculate the hazard ratio for time-to-event outcomes such as time-to-first adverse event (or serious adverse event).

We will undertake meta-analyses only where these are meaningful i.e. if the treatments, participants and the underlying clinical question are 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 encounter this, we will note that the data are skewed and consider the implication of this.

Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons (e.g. omeprazole versus vagotomy and lansoprazole versus vagotomy) must be entered into the same meta-analysis, we will 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 will perform a sensitivity analysis to determine if the results of the two methods of dealing with multi-arm trials lead to different conclusions.

Unit of analysis issues

The unit of analysis will be individual patients with refractory or recurrent peptic ulcer. We do not anticipate any cluster-randomised trials for this comparison but if cluster-randomised trials are identified, we will obtain the effect estimate adjusted for the clustering effect. If this is not available, we will 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 will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). If we are unable to obtain the information from the investigators or study sponsors, we will impute the mean from the median (i.e. consider median as the mean) and standard deviation from standard error, inter-quartile 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 are unable to calculate the standard deviation from standard error, inter-quartile range, or P values, we will impute standard deviation as the highest standard deviation in the remaining trials included in the outcome, fully aware that this method of imputation will 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 will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity as per *Cochrane Handbook for Systematic Reviews of Interventions* (> 50% to 60%), we will explore it by pre-specified subgroup analysis.

Assessment of reporting biases

We will attempt to contact study authors to ask them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, the impact of including such studies in the overall assessment of results will be explored by a sensitivity analysis**.**

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible publication biases. We will use Egger's test to determine the statistical significance of the reporting bias (Egger 1997). A P value of < 0.05 will be considered statistically significant reporting bias.

Data synthesis

We will perform the analysis using RevMan 5.3 *(*Review Manager 2014). We will 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 will use both the fixed-effect model Demets 1987) and random-effects model (DerSimonian 1986) for the analysis. In case of discrepancy between the two models, we will report both results; otherwise we will report only the results from the fixed-effect model.

'Summary of findings' table

We will create a 'Summary of findings' table using all the outcomes. We will use the five 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 pre-specified outcomes. We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and using GRADEpro software. We will justify all decisions to down- or up-grade the quality of studies using footnotes and make comments to aid reader's understanding of the review where necessary. We will consider whether there is any additional outcome information that was not able to be incorporated into meta-analyses and note this in the comments and state if it supports or contradicts the information from the meta-analyses.

Subgroup analysis and investigation of heterogeneity

We plan 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.

All the primary outcomes will be used in subgroup analysis.

We will use the formal Chi^2 test for subgroup differences to test for subgroup interactions.

Sensitivity analysis

We will 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 of 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 are not reported.
4. Different methods of dealing with multi-arm trials (please see Measures of treatment effect).

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice and our implications for research will give the reader a clear sense of where the focus of any future research in the area should be and any remaining uncertainties.

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* *Indicates the major publication for the study*

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 intestines.
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.
Highly selective vagotomy: division of the branches of the vagus nerve that controls the acid secretion without dividing the nerves that control the valve like mechanism that allows food to pass from the stomach into the small bowel.
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 discolourisation 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 enlarged lymph nodes.
Malignant: cancer (in this context).
Mass: lump (in this context).
Metaplasia: replacement of cell type with another cell type which 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 that is controlled by a valve like mechanism which 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 controls 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. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp animals/ not humans.sh.
11. 9 not 10
12. exp stomach/
13. stomach.mp.
14. gastr*.mp.
15. exp duodenum/
16. duoden*.mp.
17. peptic*.mp.
18. exp esophagus/
19. esophag*.mp.
20. oesophag*.mp.
21. exp peptic ulcer/
22. (peptic adj5 ulcer*).mp.
23. (stomach adj5 ulcer*).mp.
24. (duoden* adj5 ulcer*).mp.
25. (gastroduoden* adj5 ulcer*).mp.
26. or/12-25
27. (recurrent or refractory or non-healing or fail*).tw.
28. exp gastrectomy/
29. gastrectomy.tw.
30. exp Vagotomy/
31. vagotomy.tw.
32. pyloroplasty.tw.
33. gastrojejunostomy.tw.
34. (antrectomy or antrum resection or antral resection).mp.
35. or/28-34
36. 26 and 27 and 35
37. 11 and 36

Appendix 4. EMBASE search strategy

1. Clinical trial/
2. Randomized controlled trial/
3. Randomization/
4. Single-Blind Method/
5. Double-Blind Method/
6. Cross-Over Studies/
7. Random Allocation/
8. Placebo/
9. Randomi?ed controlled trial*.tw.
10. Rct.tw.
11. Random allocation.tw.

12. Randomly allocated.tw.
13. Allocated randomly.tw.
14. (allocated adj2 random).tw.
15. Single blind*.tw.
16. Double blind*.tw.
17. ((treble or triple) adj blind*).tw.
18. Placebo*.tw.
19. Prospective study/
20. or/1-19
21. Case study/
22. Case report.tw.
23. Abstract report/ or letter/
24. or/21-23
25. 20 not 24
26. exp stomach/
27. stomach.mp.
28. gastr*.mp.
29. exp duodenum/
30. duoden*.mp.
31. peptic*.mp.
32. exp esophagus/
33. esophag*.mp.
34. oesophag*.mp.
35. exp peptic ulcer/
36. (peptic adj5 ulcer*).mp.
37. (stomach adj5 ulcer*).mp.
38. (duoden* adj5 ulcer*).mp.
39. (gastroduoden* adj5 ulcer*).mp.
40. or/26-39
41. (recurrent or refractory or non-healing or fail*).tw.
42. exp gastrectomy/
43. gastrectomy.tw.
44. exp vagotomy/
45. vagotomy.tw.
46. exp pyloroplasty/
47. pyloroplasty.tw.
48. exp gastrojejunostomy/
49. gastrojejunostomy.tw.
50. exp stomach antrum resection/
51. (antrectomy or antrum resection or antral resection).mp.
52. or/42-51
53. 40 and 41 and 52
54. 25 and 53

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 TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*)

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

CONTRIBUTIONS OF AUTHORS

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