TITLE

Meta-analysis of randomised clinical trials comparing open and laparoscopic anti-reflux surgery

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ABSTRACT:

Objective: The aim was to conduct a meta-analysis of the randomised evidence to determine the relative merits of laparoscopic anti-reflux surgery (LARS) and open anti-reflux surgery (OARS) for proven gastro-oesophageal reflux disease.

Methodology: A search of the Medline, Embase, Science Citation Index, Current Contents and PubMed databases identified all randomised clinical trials that compared LARS and OARS and were published in the English language between 1990 and 2007. The meta-analysis was prepared in accordance with the Quality of Reporting of Meta-analyses (QUOROM) statement. The six outcome variables analysed were operating time, hospital stay, return to normal activity, perioperative complications, treatment failure and requirement for further surgery. Random effects meta-analyses were performed using odds ratios and weighted mean differences.

Results: Twelve trials were considered suitable for the meta-analysis. A total of 503 patients underwent OARS and 533 had LARS. For three of the six outcomes the summary point estimates favoured LARS over OARS. There was a significant reduction of 2.68 days in the duration of hospital stay for the LARS group compared with the OARS group (WMD -2.68, 95% confidence interval (CI) -3.54 to -1.81; $P < 0.0001$), a significant reduction of 7.75 days in return to normal activity for the LARS group compared with the OARS group (WMD -7.75, 95% CI -14.37 to -1.14; $P = 0.0216$) and lastly there was a statistically significant reduction of 65% in the relative odds of complication rates for the LARS group compared with the OARS group (OR 0.35, 95% CI 0.16 to 0.75; $P = 0.0072$). Duration of operating time was significantly longer (39.02 minutes) in the LARS group (WMD 39.02, 95% CI 17.99 to 60.05; $P = 0.0003$). Treatment failure rates were comparable between the two groups (OR 1.39, 95% CI 0.71 to 2.72; $P = 0.3423$). Despite this the requirement for further surgery was significantly higher in the LARS group (OR 1.79, 95% CI 1.00 to 3.22; $P = 0.05$).

Conclusions: Based on this meta-analysis, the authors conclude that LARS is an effective and safe alternative to OARS for the treatment of proven gastro-oesophageal reflux disease. LARS enables a faster convalescence and return to productive activity, with a reduced risk of complications and a similar treatment outcome to that of an open approach. However, there is a significantly higher rate of re-operation (79%) in the LARS group.

INTRODUCTION:

Rudolph Nissen introduced the antireflux effect of wrapping the gastric fundus around the distal oesophagus in 1956[1]. This procedure, the "open Nissen fundoplication", and its modifications have since been employed to treat moderate to severe gastro-oesophageal reflux disease (GORD) where medical therapy has failed[2]. Laparoscopic Nissen fundoplication (LNF) was described in 1991 by Dallemagne following the success of laparoscopic cholecystectomy[3]. The laparoscopic approach was utilised on the premise that there would be less postoperative discomfort and pain, faster recovery time, reduced rate of wound infection and incisional hernia formation and improved cosmesis. However, shortcomings of this minimally invasive approach include the risk of major complications which relate specifically to the use of laparoscopy. These include bowel perforation or major vascular injury on port insertion, physiological derangements secondary to a pneumoperitoneum, a more complex and difficult technique with a protracted learning curve, greater cost due to introduction of new technologies and longer operating time, and the potential for higher recurrence rate. Initial studies described a number of complications, including oesophageal and gastric perforations, paraoesophageal herniations and wrap migration into the chest, and hiatal fibrosis, at least during the early phase of the learning curve[4-7]. Additionally, some studies questioned the claimed benefits of laparoscopic anti-reflux surgery (LARS), due to an increased rate of postoperative dysphagia, sometimes necessitating re-operation[8-10]. In contrast, open anti-reflux surgery (OARS) has been consistently proven to provide long-term control of reflux symptoms[11-13]. However, recent randomised studies have suggested that the differences between LARS and OARS are of a lesser magnitude than those documented by earlier, non-randomised studies[2]. A greater depth of experience with LARS, coupled with improved surgical techniques, equipment and training is believed to underlie this outcome alignment and therefore the authors believe that the potential benefits of LARS compared with OARS can now be reasonably assessed in the form of a meta-analysis. The timing for such a review is further supported by a recent study reporting a greater percentage of patients experiencing regression of Barrett's change in those undergoing anti-reflux surgery compared

with medical therapy alone[14]. Nineteen randomised controlled trials[2,15-32] comparing these procedures have been published over the last 17 years (Table 1), This meta-analysis considers pooled data from all of the available randomised clinical trials that compared laparoscopic and open methods of anti-reflux surgery, and was prepared in accordance with the Quality of Reporting of Meta-analyses (QUOROM) statement[33].

MATERIAL AND METHODS:

Randomised controlled trials of any size that compared OARS with LARS in both adult and paediatric populations, and which were published in full peer-reviewed journals in the English language between 1990 and 2007 were eligible for inclusion. Unpublished studies and abstracts presented at national and international meetings were excluded. Similarly, duplicate publications and non-randomised comparative trials were also excluded.

Trials were identified by conducting a comprehensive search of Medline, Embase, Science Citation Index, Current Contents and PubMed databases, using medical subject headings 'fundoplication', 'anti-reflux', 'comparative study', 'prospective studies', 'randomised controlled trials', 'random allocation' and 'clinical trial'. Manual search of the bibliographies of relevant papers was also carried out to identify trials for possible inclusion.

Nineteen randomised controlled trials met the inclusion criteria[2,15-32]. Of these, several involved the presentation of data derived from the same cohort of patients at different follow-up times. This was particularly relevant to longer-term outcome measures such as treatment failure and re-operation rates. For the purpose of accurate statistical analysis, in the aforementioned instances we considered all the data derived from a particular cohort of patients as being a single trial event. This reduced the apparent number of included trials to twelve (Figure 1).

Data extraction and critical appraisal were carried out by four authors (MJP, AM, MAM, BM). Standardised data extraction forms[33] were used by ~~all~~ these authors to independently and blindly summarise ~~all~~ the randomised controlled trials meeting the inclusion criteria. The authors were not blinded to the source of the document or authorship for the purpose of data extraction. The data was~~ere~~ compared and discrepancies were resolved by consensus.

Objective analyses focusing on six outcome variables were undertaken. These included operating time, hospital stay, return to normal activity, perioperative complications, treatment failure and requirement for further surgery. Studies that did not mention a specific outcome (or variable) were excluded from the analysis for that endpoint (Figure 2-7). Rates of conversion to an open procedure from the laparoscopic approach were also noted. Outcome measures including postoperative pain, analgesia requirements and hospital costs were not considered in the meta-analysis owing to variations in reporting methodology, lack of data and the inability to devise uniform objective analysis of these outcomes. The quality of the randomised clinical trials was assessed using Jadad's scoring system (Table 2)[34].

Additionally, subgroup analysis according to study quality was undertaken, with high quality studies (Jadad score ≥ 3 or more) considered separately to those of lower quality (Jadad score < 3).

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STATISTICAL ANALYSIS:

Meta-analyses were performed using odds ratios (ORs) for binary outcome and weighted mean differences (WMDs) for continuous outcome measures (Table 3 and Figures 2-7). The slightly amended estimator of OR was used to avoid the computation of reciprocal of zeros among observed values in the calculation of the original OR[35]. Random effects models, developed using the inverse variance weighted method approach, were used to combine the data[36]. Heterogeneity among studies was assessed using the Q statistic proposed by Cochran[36-38] and I^2 index introduced by Higgins and Thompson[39,40]. If the observed value of Q is larger than the critical value at a given significant level (α), in this case 0.05, we conclude that there is statistically significant between-studies variation. The drawback of Q statistic is that its

statistical power depends on the number of studies. The I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance and unlike Q it does not inherently depend upon the number of studies considered[40]. In order to pool continuous data, mean and standard deviation are required. However, some of the published clinical trials did not report the mean and standard deviation, but rather reported the size of the trial, the median and range. Using these available statistics, estimates of the mean and standard deviation were obtained using formulas proposed by Hozo et al[41]. Funnel plots were synthesized (Figure 8) in order to determine the presence of publication bias in the meta-analysis. Both total sample size and precision (1/standard error) were plotted against the treatment effects (OR of outcome variable) for re-operation rate, failure rate and complication rate[36,42,43]. All the resulting funnel plots are asymmetrical, suggesting the existence of publication bias[42,43]. The number of studies included in the funnel plots, indicated by the number of plotted points, are not large enough for the detection of study bias[42,44]. All estimates were obtained using a computer program written in R[45]. All plots were obtained using the meta-package[46].

RESULTS

There was almost a perfect agreement (κ=0.99) between the four authors regarding the inclusion and exclusion of various randomised controlled trials. Based on this agreement, a total of twelve randomised prospective clinical trials that included 1036 anti-reflux operations (LARS 533, OARS 503) were considered suitable for meta-analysis[2,15-32]. Patient demographics and selection methods were detailed in all of the available studies. Both subjective and objective determinants of gastro-oesophageal reflux disease were utilised pre- and post-operatively in all of the available studies, including the variable use of upper gastrointestinal endoscopic investigation, barium swallow, 24 hour oesophageal manometry and pH studies.

Open and laparoscopic anti-reflux surgery was performed using a loose 360 degree Nissen fundoplication technique in eleven of the twelve trials. Hakanson et al[32] utilised a partial posterior fundoplication with a 250 to 270 degree wrap in both the OARS and LARS groups. Variability existed with respect to division of the short gastric vessels, performance of hiatoplasty, and the use of a bougie or gastric tube for calibration.

Study quality was generally poor, with a mean Jadad score of 2.58 (range 2 – 5) (Table 2). This was the result of the method of randomisation not being defined in a number of studies, the ability to blind participants not being consistently possible, and a description of withdrawals and drop-outs not always being provided. This has been observed in other reviews and meta-analyses of surgical trials[47-49].

There was a significant reduction of 2.68 days (Figure 2) in the duration of hospital stay for the LARS group compared with the OARS group (WMD -2.68, 95% confidence interval (CI) -3.54 to -1.81; $P < 0.0001$) and a significant reduction of 7.75 days (Figure 3) in return to normal activity for the LARS group compared with the OARS group (WMD -7.75, 95% CI -14.37 to -1.14; $P = 0.0216$). However, operating time was 39.02 minutes longer (Figure 4) for the LARS group compared with the OARS group (WMD 39.02, 95% CI 17.99 to 60.05; $P = 0.0003$). There was a statistically significant reduction of 65% in the relative odds of complication rates (Figure 5) for the LARS group compared with the OARS group (OR 0.35, 95% CI 0.16 to 0.75; $P = 0.0072$). The outcome variable of failure rate (Figure 6) was found not to be statistically significant between the LARS and OARS groups (OR 1.39, 95% CI 0.71 to 2.72; $P = 0.3423$). Despite this, there was a statistically significant increased re-operation rate of 79% (Figure 7) for the LARS group compared to the OARS group (OR 1.79, 95% CI 1.00 to 3.22; $P = 0.05$).

DISCUSSION:

Debate has always followed the implementation of a laparoscopic alternative to a satisfactory open surgical procedure[50]. Laparoscopic anti-reflux surgery is no exception. Its supporters argue that it couples effective surgical management of proven gastro-oesophageal reflux disease with the proposed benefits of minimal access surgery, these being reduced post-operative pain, reduced hospital stay and reduced time to recommencement of normal activity. Its opponents argue that it is less effective than the open approach, and that the risk of operative complications and treatment failure far outweigh the apparent short term benefits offered by the laparoscopic approach. A number of randomised controlled trials have been undertaken to investigate the issues referred to above[2,15-32]. Confounding factors including patient selection criteria, sample size, operative techniques, outcome descriptors and duration of follow up have fuelled the ongoing debate despite reasonable attempts being made by the authors to provide trials of high quality. The authors of this paper have undertaken a meta-analytical review based on the available randomised controlled trial data in an attempt to provide clarification.

Nine of the twelve available trials reported duration of hospital stay in a form suitable for inclusion within the meta-analysis (Figure 2). Pooling of the available data revealed a statistically significant reduction of 2.68 days in length of hospital stay in the LARS group compared with the OARS group. In the subgroup analysis, the pooled data showed a ~~Based on Jadad score of <3 vs ≥3, the polled data continue to show sign~~sign**ificant reduction in the length of postoperative hospital stay in both groups. T**herefore the study quality appears to have had minimal impact on this result.~~his may represent a true biological effect of LARS over OARS and the quali ty of study may have a minimal impact on this variable.~~ Reduction in length of hospital stay using LARS has obvious cost benefits and allows for greater efficiency within a surgical unit.

Seven of the twelve available trials reported time to return to normal activity. Six of these were suitable for inclusion within the meta-analysis (Figure 3). Pooling of the available data

revealed a statistically significant reduction in time to return to normal activity of 7.75 days in the LARS group compared with the OARS group (Figure 3). Subgroup analysis, based on the vlues of Jadad score, failed to reveal any difference attributable to study quality. These findings are commonly reported in trials assessing laparoscopic surgery, and are believed to be secondary to a reduction in trauma to the abdominal wall with the laparoscopic approach, that results in a reduced inflammatory response[26,51-53]. Lower levels of post-operative pain, as determined by reduced analgesia requirements, have been shown to result in earlier mobilisation, with a subsequent reduction in respiratory complications, compared with the open approach[52-53]. An earlier return to normal activity has beneficial effects not only for the patient, but also for their family, workplace and the wider community. Interestingly, review of the available data sets for the OARS group also suggest a generalised trend towards a reduced length of hospital stay and a faster return to normal activity compared with that observed in historical data sets for OARS. This could be attributed to improvements in nursing and allied health care and a better appreciation of early mobilization and adequate nutrition.

Ten of the twelve available trials reported operating times. Nine of these were suitable for inclusion in the meta-analysis (Figure 4). All but one[26] of the trials revealed a longer operating time in the LARS group compared with the OARS group. Pooling of these trials revealed a 39.02 minute longer operating time in the LARS group compared with the OARS group, which was statistically significant (Figure 4). Subgroup analysis, based the values of Jadad score, failed to reveal any difference attributable to study quality. ~~**Based on Jadad score of <3 vs ≥3, the polled data continue to show significant longer operating time for LARS in both groups.**~~ A protracted operating time exposes the patient to a longer duration of anaesthesia, and a greater risk of thermic, thromboembolic, cardiac and respiratory complications. In addition, it negatively impacts on the efficiency of the operating staff and the operating complex as a whole, and imparts a higher overall cost to the procedure. The difference in operating time is likely to lessen in the future as the use of LARS becomes more commonplace in the operating suite, and surgical training and techniques improve. This has

been observed in other laparoscopic procedures as they have become more frequently utilised and the surgical technique has become standarized[5,50].

Complication rates were analysed for the two treatment groups by eleven of the twelve trials. This is one area that has caused much debate, with initial trials comparing LARS and OARS suggesting a higher complication rate with LARS[4-7]. These initial trials expressed concerns regarding the inherent risks of the laparoscopic approach, including access complications and the physiological derangements resulting from a pneumoperitoneum. These concerns were coupled with reports of significant operative complications, including oesophageal and gastric perforations, wrap migration, paraoesophageal herniations and hiatal fibrosis[4-7]. Subsequently Viljakka et al[54] performed a 32-year audit of 827 anti-reflux operations and found that complication rates were 14% for LARS and 24% for OARS. From a numerical standpoint the rates as reported by Viljakka et al[54] suggest there has been a trend towards fewer complications in those undergoing laparoscopic anti-reflux surgery. Our meta-analysis of the pooled data supports this trend, revealing a statistically significant difference in complication rates between LARS and OARS, with fewer complications occurring in the LARS group (Figure 5). However, subgroup analysis revealed that studies of higher quality (Jadad score ≥ 3 or more) failed to show any statistically significant difference in complication rates. ~~**Based on Jadad score of <3 vs ≥3, the polled data continue to show significantly fewer complications in lower quality studies compared to higher quality studies. It is entirely possible that poor quality studies may have inherent increased risk of bias when reporting complications rates.**~~

Other studies have considered individual complications. Luostarinen et al[55] reported OARS being associated with a 1.0 to 8.5% risk of splenic injury, a 0% to 1.9% risk of oesophageal perforation, 0.8 to 9.6% risk of pulmonary complications and a mortality rate of 0% to 1.3%[50]. Perdikis et al[56] reported LARS being associated with a 1.0% perforation rate, a 1.1% bleeding rate, a 0.1% splenectomy rate, and a 0.2% mortality rate[55]. There was a range of

complications reported by the trials included in this meta-analysis, with varying impacts on patient morbidity (Table 4). Those causing minimal patient morbidity, including atelectasis, urinary retention, postoperative ileus, deep vein thrombosis and wound complications, were observed more commonly than those causing significant patient morbidity. A trend was observed in the OARS group for more complex wound complications, including infection and dehiscence, to occur[26]. Incisional hernia formation was statistically significantly more common in the OARS group than the LARS group at eleven year follow-up in the trial conducted by Salminen et al[16]. Complications causing more significant patient morbidity including splenic injury, oesophageal perforation, liver laceration, pneumothorax, subphrenic abscess formation and a wrap haematoma were reported amongst both the LARS and OARS groups (Table 4). One mortality was reported in the LARS group by Hakanson et al[32] however this occurred two months after surgery, with the patient succumbing to complications of diabetes unrelated to the timing of surgery[32]. Salminen et al[16] reported twelve mortalities in the OARS groups and four mortalities in the LARS group during the eleven year follow up period. All were the result of unrelated causes[16].

In light of the findings of this meta-analysis, specifically the subgroup analysis~~Despite such findings~~, one must consider the impact of variability in the reporting of complications. Certainly in today's climate of early hospital discharge many minor post-operative complications are being managed either in the outpatient or general practice setting, and thus the treating surgical team are not necessarily aware of their development. This may lead to an under reporting of minor complications especially in a laparoscopic group. Appropriate mechanisms to ensure inclusion of all perioperative complications are vital for the correct determination of adverse event and complication occurrence. Apart from generalised comments emphasising the reporting of complications, no formal mechanism was discussed in any of the available trials. Considering the findings of the subgroup analysis, it is likely that higher quality studies utilised superior methodology that resulted in more comprehensive reporting of complications. Although a statistically significant finding was observed overall,

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~~Unfortunately, inter-observer variability needs to be considered, and although a statistically significant finding was observed~~the results of the subgroup analysis suggest ~~,~~ a robust conclusion cannot be adequately drawn.

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Conversion from a laparoscopic to an open procedure was reported in eleven of the twelve trials. The mean conversion rate was 6.3% (Table 5). Listed reasons for conversion range from poor visibility due to a large left hepatic lobe, to operative complications that were unable to be managed laparoscopically. This conversion rate is low compared with that deemed acceptable in other laparoscopic procedures. Whether it is likely to change with time is hard to determine. Conversion due to poor visibility secondary to an enlarged left hepatic lobe may become more prevalent as the rate of obesity in the general population increases. Conversely, laparoscopic surgery is becoming increasingly utilised throughout the surgical community, with the range of operative capabilities being expanded with time. This coupled with improvements in surgical equipment, training and techniques, means that the surgeon's ability to manage significant operative complications is likely to improve with time. The net impact these developments will have on conversion rate is unknown. A longer follow-up period is required to determine this matter further, particularly in order to elucidate the effect of the learning curve for LARS.

Ten of the twelve available trials undertook subjective and objective analyses of treatment outcome, with a range of modalities being employed pre and post-operatively to assess the effect of LARS and OARS on gastro-oesophageal reflux. The trial performed by McHoney et al[28] did not perform an analysis of treatment outcome. The trials performed by Laine et al[15] and Salminen et al[16] followed the same cohort of patients and were analysed as one group. The discrepancies in methodology between the available trials meant that in order to assess treatment outcome, measures of treatment failure (defined as recurrence of gastro-oesophageal reflux symptoms or dysphagia at the longest follow up post-operatively) and re-operation (defined as re-operation for gastro-oesophageal reflux disease) rates had to be

utilised. Although imperfect, as capture rates and duration of follow up impact upon such reporting, and outcome descriptors vary between trials, this data was available for both treatment groups and was analysed accordingly. Amongst the pooled data, there was no statistically significant difference in treatment failure rate between the LARS and OARS groups (Figure 6). Subgroup analysis, based on the values of Jadad score, failed to reveal any difference attributable to study quality. There was, however, a statistically significant increase in the rate of re-operation for the LARS group compared with the OARS group (Figure 7). Subgroup analysis revealed that the higher quality studies concur with this overall finding. ~~**Based on Jadad score of <3 vs ≥3, the polled data continue to show significantly higher reoperation rate in higher quality studies compared to lower quality studies. It is entirely possible that higher quality studies may have a better capturing rate for reporting reoperation in their patients.**~~

As stated above, treatment outcome is hard to define. A number of trials have focused on the requirement for proton pump inhibitor use post-surgery as a measure of treatment failure. This has been refuted by Jenkinson et al[57], whose findings are also supported by Draissma et al[30]. They concluded that a high proportion of patients whose symptoms improved with proton pump inhibitor use still had pathologic levels of acid reflux, and that most patients who complained of gastro-oesophageal reflux symptoms after anti-reflux surgery had no evidence of persistently excessive acid reflux on 24 hour pH studies[30,57]. Draissma et al[30] questioned whether such symptoms were present pre-operatively or could be attributed to alterations in gastrointestinal physiology as a result of fundoplication. An earlier study by Lord et al[58] also concludes that disease recurrence is difficult to quantitate. Ultimately, persistence of gastro-oesophageal reflux symptoms as an indicator of treatment failure is debatable, but considering the primary goal of anti-reflux surgery is to eliminate gastro-oesophageal reflux symptoms, its use as a marker of failure is obvious. Appropriate pre-operative assessment of the presence and severity of gastro-oesophageal reflux is required,

and the persistence of symptoms post-operatively requires a planned investigative response. Rates of recurrent gastro-oesophageal reflux are reported as being between 0% and 5% after LARS and 0% and 20% after OARS[2,9,15-32,51,59,60]. Dysphagia is similarly used as an indicator of treatment failure. A number of trials comment on post-operative dysphagia and suggest that this is a more common occurrence in the immediate post-operative stage in the LARS group[2,15,17-19,40]. However, this is found to settle with time, with similar rates of dysphagia being reported between OARS and LARS groups at 5 years[30]. In this meta-analysis, treatment failures, including the presence of dysphagia, were obtained by considering the data reported at the longest follow up review. This ranged from three months to eleven years and five months. Trials to date report long term dysphagia rates of up to 15% in the OARS group and 20% in the LARS group[7,61,62]. Because of the number of variables present which impact on the occurrence of dysphagia and its reporting, the overall rate of dysphagia in the LARS group will only be truly appreciated with a longer duration of follow up and with robust assessment methodology.

Re-operation rates are reported as being between 2% and 10% after LARS and OARS respecitvely[10,63,64]. The most common mechanism of treatment failure requiring re-operation is wrap herniation[65]. This meta-analysis found a statistically significant difference in re-operation rates for treatment failure between the LARS and OARS groups, with a 79% higher re-operation rate in the LARS group. Re-operation, for any surgical condition, poses additional concerns both for the surgeon and the patient. Surgical adhesions and post-surgical inflammatory tissue changes in the involved surgical field impart a greater level of difficulty for the surgeon and place the patient at a higher risk of perioperative complications. Complication occurrence in re-do anti-reflux surgery is reported as being as high as 37%, a value much higher than the 14% observed in primary procedures[54,65]. Despite this, evidence exists to support its effectiveness for the management of recurrent heartburn, dysphagia and regurgitation[65,66]. Additionally, the laparoscopic approach is deemed appropriate in selected patients[65]. As stated earlier, the current definition of treatment failure is flawed. When considering re-operation for recurrence of gastro-oesophageal reflux disease, it is important to

objectively determine the presence of disease recurrence, and to consider the higher risk of complications reported for re-do LARS.

CONCLUSIONS:

The findings as listed above are in keeping with current opinion and practice. Indeed, LARS is being increasingly utilised throughout both the public and private health sector despite a comprehensive meta-analysis not having been previously performed. ~~Its utility in relieving gastro-oesophageal reflux symptoms in the patient in which medical therapy has failed is clinically evident and supported by previous randomised and retrospective trials. The recent report of Barrett's oesophagus regression in patients undergoing anti-reflux surgery lends further support~~[14]. The present meta-analysis is an attempt to answer some of the important and contentious issues surrounding LARS, drawing upon a total of 1036 patients, the largest body of information so far available for the comparison of LARS and OARS in the English literature. Laparoscopic antireflux surgery combines the short term benefits associated with a reduced hospital stay and earlier return to normal activity with long term outcomes similar to those seen in the open antireflux approach. However even with experience, the operating time for LARS remains longer compared to its open counterpart. Complication rates were observed to be lower in the laparoscopic group compared with the open group. Treatment failure rates did not differ between the two groups. Despite this re-operation rates for treatment failure were higher in the laparoscopic group. Based on the current meta-analysis one can conclude that LARS ~~is a suitable and safe option for the treatment of proven gastro-oesophageal reflux disease. LARS~~ enables a faster convalescence and return to productive activity, with a reduced risk of complications and a similar treatment outcome to that of the open approach.

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None

AUTHORS' CONTRIBUTIONS:

1. MAM was responsible for the concept and design of this meta-analysis. Furthermore he takes full responsibility for the integrity of the work as a whole, from inception to published article.

2. MAM, MJP, AM and BM were responsible for acquisition and interpretation of the data.

3. SK and RMY were ~~involved~~ responsible ~~in~~ for adopting appropriate statistical methods as well as analysing and interpretation of the data in depth from the statistical point of view.

4. All authors were involved in drafting the manuscript and revising it critically for important intellectual content and have given final approval of the version to be published. Furthermore all authors have participated sufficiently in the work to take public responsibility for its content.

CONFLICTS OF INTERESTS:

None

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Table 1: Details of all prospective randomised trials that compared laparoscopic and open anti-reflux surgery published in the English literature

Authors	Type of Patients	Year/Country	Number of patients		Follow up (months)
			LARS	OARS	
Laine et al[15] / Salminen et al[16]	Adults	1996 / 2007 /Finland	55	55	12 / 137
Heikkkinen et al[17-19]	Adults	1999 / 2000 / 2000 / Finland	22	20	24
Perttila et al[20]	Adults	1999 / Finland	10	10	Not available
Nilsson et al[21,23,24]/Wenner et al al[22]	Adults	2000 / 2001 / 2002 / 2004 / Sweden	30	30	60
Bais et al[25]	Adults	2000 / 2006 / The Netherlands	57	46	3
Chrysos et al[26]	Adults	2001 / Greece	56	50	12
Luostarinen et al[27]	Adults	2001 / Finland	13	15	12
Ackroyd et al[2]	Adults	2004 / UK	52	47	12
McHoney et al[28]	Children	2004 / UK	20	20	Not available
Franzen et al[29]	Adults	2005 / Sweden	45	48	33-79
Draaisma et al[30]	Adults	2006 / The Netherlands	79	69	60
Hakanson et al[32]	Adults	2006 / Sweden	99	93	36

Table 2: Jadad's Score

Authors	Year/Country	Jadad Score	Randomization	Blinding	Withdrawal
Laine et al[15] / Salminen et al[16]	1996 / 2007 / Finland	2	1	0	1
Heikkkinen et al[17-19]	1998 / 2000 / 2000 / Finland	3	2	0	1
Perttila et al[20]	1999 / Finland	1	1	0	0
Bais et al[25]	2000 / 2006 / The Netherlands	2	1	0	1
Nilsson et al[21,23,24] / Wenner et al[22]	2000 / 2001 / 2002 / 2004 / Sweden	5	2	2	1
Chrysos et al[26]	2001 / Greece	2	1	0	1
Luostarinen et al[27]	2001 / Finland	3	2	0	1
Ackroyd et al[2]	2004 / UK	3	2	0	1
McHoney et al[28]	2004 / UK	3	2	0	1
Franzen T et al[29]	2005 / Sweden	2	1	0	1
Draaisma et al[30]	2006 / The Netherlands	2	1	0	1
Hakanson et al[32]	2006 / Sweden	3	2	0	1

Table 3: Summary of pooled data comparing LARS and OARS

Outcomes Variables	Jadad score	Number of patients	Number of studies	Pooled OR or WMD (95% CI)	Test for overall effect		Test for heterogeneity		
					Z	p-value	Q	p-value	I-squared index
Duration Of Hospital Stay	Less than 3	329	4	-2.91(-3.55,-2.28) †	-8.99	<0.0001	5.51	0.1378	45.56%
	At least 3	416	5	-2.34(-4.16,-0.53) †	-2.53	0.0113	30.35	<0.0001	86.82%
		745	**9**	**-2.68(-3.54,-1.81) †**	**-6.06**	**<0.0001**	**40.89**	**<0.0001**	**80.43%**
Return To Normal Activity	Less than 3	93	1	-7.60(-12.67,-2.53)†	-2.94	0.0033	NA	NA	NA
	At least 3	416	5	-6.83(-16.04,2.38) †	-1.45	0.1461	17.31	0.0017	76.89%
		509	**6**	**-7.75(-14.37,-1.14) †**	**-2.30**	**0.0216**	**18.80**	**0.0021**	**73.40%**
Operating Times	Less than 3	329	4	35.65(-0.63,71.94) †	1.93	0.0541	74.81	<0.0001	95.99%
	At least 3	416	5	42.01(20.38,63.64) †	3.81	<0.0001	37.28	<0.0001	89.27%
		745	**9**	**39.02(17.99,60.05) †**	**3.64**	**0.0003**	**146.78**	**<0.0001**	**94.54%**
Complication Rate	Less than 3	580	6	0.18(0.07,0.48) *	-3.44	0.0006	10.84	0.0547	53.87%
	At least 3	416	5	0.61(0.23,1.58) *	-1.02	0.3075	7.69	0.1038	47.98%
		996	**11**	**0.35(0.16,0.75)***	**-2.69**	**0.0072**	**27.02**	**0.0026**	**62.99%**
Failure rate	Less than 3	536	5	1.31(0.41,4.14) *	0.46	0.6481	15.55	0.0037	74.28%
	At least 3	416	5	1.52(0.74,31.4) *	1.14	0.2545	4.95	0.2925	19.19%

		952	**10**	**1.39(0.71,2.72)***	**0.95**	**0.3423**	**21.11**	**0.0122**	**57.37%**
Re-operation rate	Less than 3	536	5	1.45(0.63,3.35) *	0.88	0.3791	4.70	0.3198	14.89%
	At least 3	416	5	2.89(1.02,8.22) *	1.99	0.0464	1.24	0.8712	0%
		952	**10**	**1.79(1.00,3.22)***	**1.96**	**0.0500**	**7.10**	**0.6262**	**0%**

95% CI = 95% confidence intervals. * = OR odds ratio; † = WMD weighted mean difference.

Table 4: Overview of complication rates reported in various RCTs

Authors[Ref]	Patients (n)		Complications (n)		Details of Complications (n)	
	LARS	OARS	LARS	OARS	LARS (n)	OARS (n)
Laine et al[15]/Salminen et al[16]	55	55	3	7	Oesophageal perforation 2 Large intraoperative bleed 1	Splenic injury 2 (splenectomy 2) Pneumonia 1 Subphrenic abscess 1 Wound infection 3
Heikkinen et al[17-19]	22	20	3	5	Wrap haematoma 1 Trocar wound bleed 1 Vomiting 1	Liver laceration 1 Pneumonia 1 Vomiting 2 Wound haematoma 1
Pertilla et al[20]	10	10	0	0	Bleeding 1	
Bais et al[25]	57	46	5	10	Splenic injury 2 (splenectomy 1) Pneumothorax 2 Subphrenic abscess 1 Cicatricial hernia 1	Splenic injury 2 (splenectomy 2) Pneumothorax 1 Subphrenic abscess 1 Cicatricial hernia 2 Wound infection 4
Nilsson et al[21,23,24]/Wenner et al[22]	25	30	4	0	Oesophageal injury (bleed) 1	

					Liver injury 1 Pneumothorax 2	
Chrysos et al[26]	56	50	12	42	Atelectasis/pneumonia 9 Deep vein thrombosis 1 Wound infection 2	Splenic injury 3 (splenectomy 0) Atelectasis 20 Pneumonia 13 Pleural effusion 6 Deep vein thrombosis 3 Wound infection 13 Wound dehiscence 4
Luostarinen et al[27]	13	15	1	0	Fundic perforation (late) 1	
Ackroyd et al[2]	52	47	7	12	Atelectasis 2 Urinary retention 4 Post op ileus > 2 days 1	Atelectasis 5 Urinary retention 6 Post op ileus > 2 days 1
Franzen et al[29]	45	48	0	2		Splenic injury 1 (splenectomy 1) Wound infection 1
Draaisma et al[30]	79	69	1	0	Cicatricial hernia 1	
Hakanson et al[32]	99	93	2	12	Pneumonia 1 Pneumothorax 1	Pneumonia 2 Pneumothorax 2 Deep mediastinal/peritoneal infection 1

						Gastric ulcer 1 Intestinal obstruction 1 Wound dehiscence 1 Urinary tract infection 1 Postoperative confusion 1

Table 5: Overview of conversion rate of various RCTs

Author	Patient (n)		Conversion rate LARS to OARS		Reasons for conversion (n)
	LARS	OARS	n	%	
Laine et al[15]	55	55	5	9	Technical difficulties 2 Bleeding 1 Oesophageal perforation 2
Heikkinen et al[17-19]	22	20	1	4.4	Inadequate visualisation 1
Pertilla et al[20]	10	10	0	0	Bleeding 1 (converted to open but excluded from analysis)
Bais et al[25]	57	46	5	8.8	Splenic injury 2 (splenectomy 1) Adhesions 1 Couldn't divide short gastric vessels 1 Hypercapnia 1
Nilsson et al[21,23,24]/Wenner et al[22]	25	30	5	2	Inadequate visualisation (large left lobe of liver) 1 Pneumothorax 2 Oesophageal bleed 1 Liver bleed secondary to trocar 1
Luostarinen et al[27]	13	15	1	7.7	Technical difficulties (obesity) 1
Ackroyd et al[2]	52	47	5	9.6	Obesity/fatty liver 2

					Adhesions 1 Bleeding 1 Equipment failure 1
Draaisma et al[30]	79	69	6	7.6	Figures only
Hakanson et al[32]	99	93	5	5	Technical difficulties (large left hepatic lobe/excess intraperitoneal fat)

Figure: 1: QUOROM Diagram Template

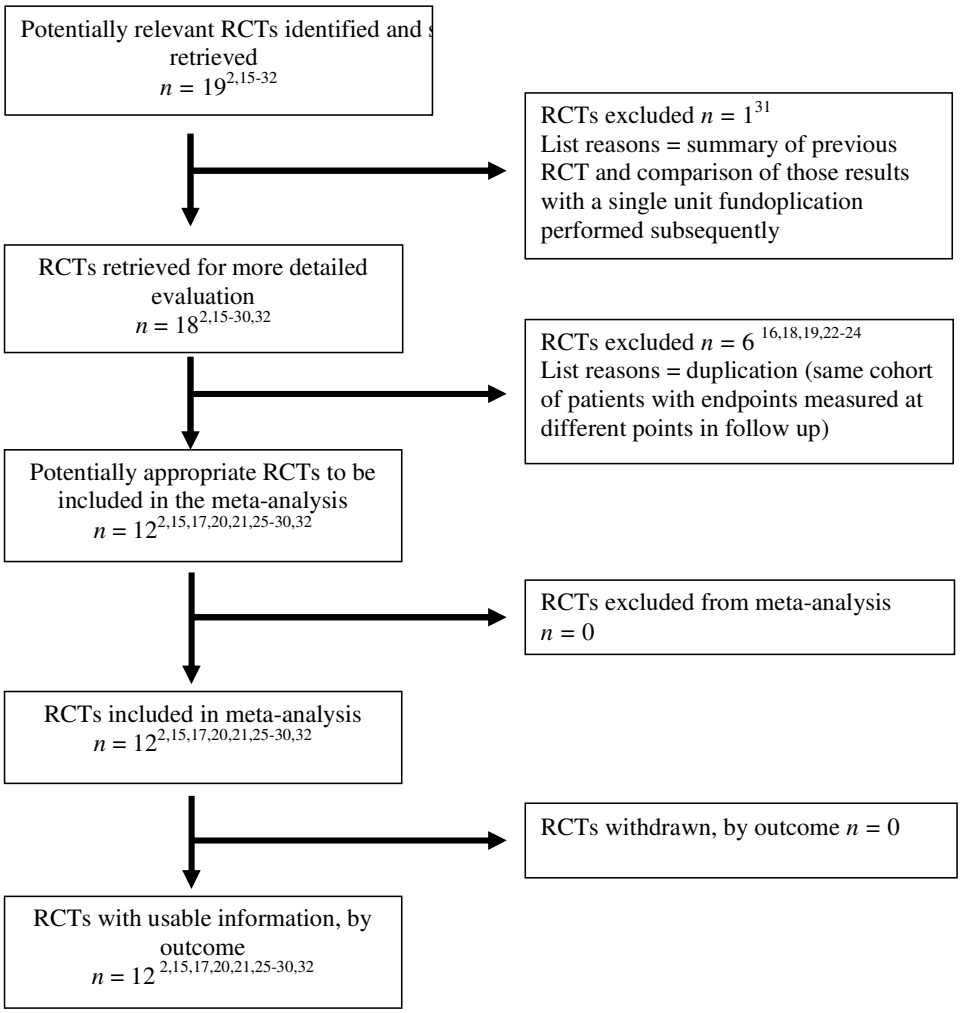
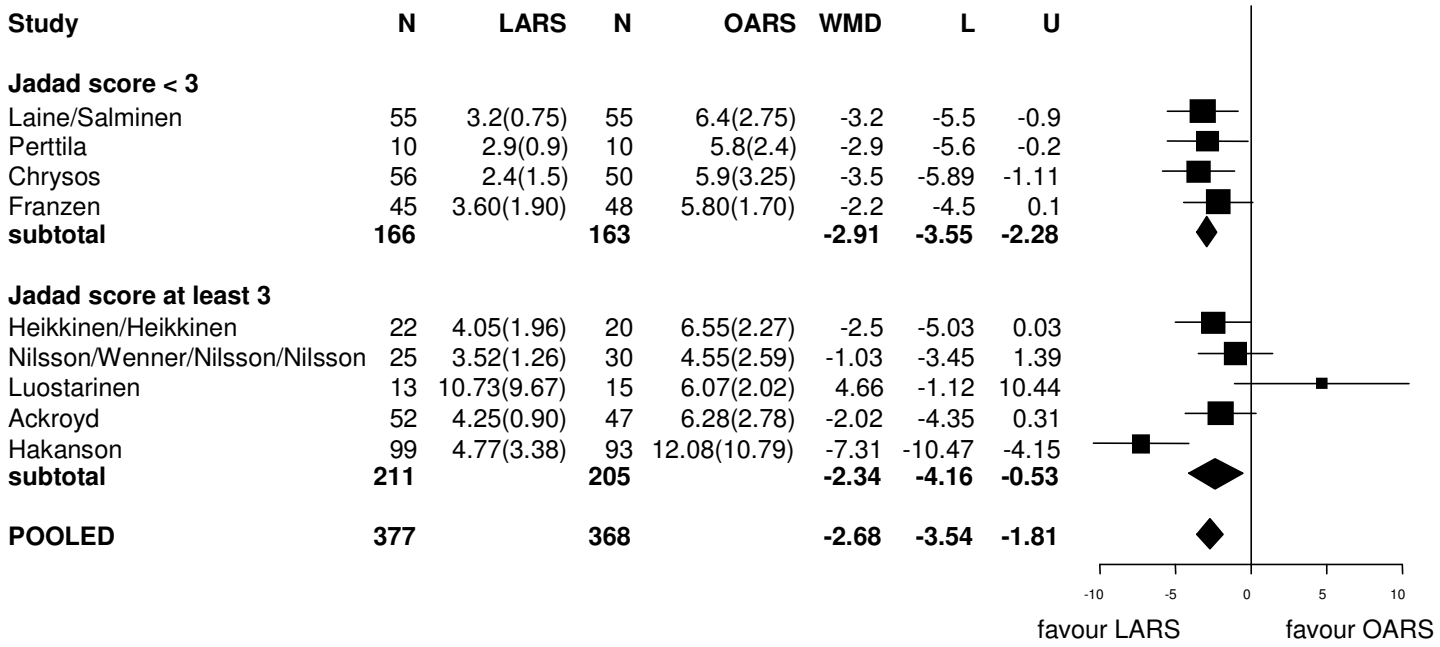
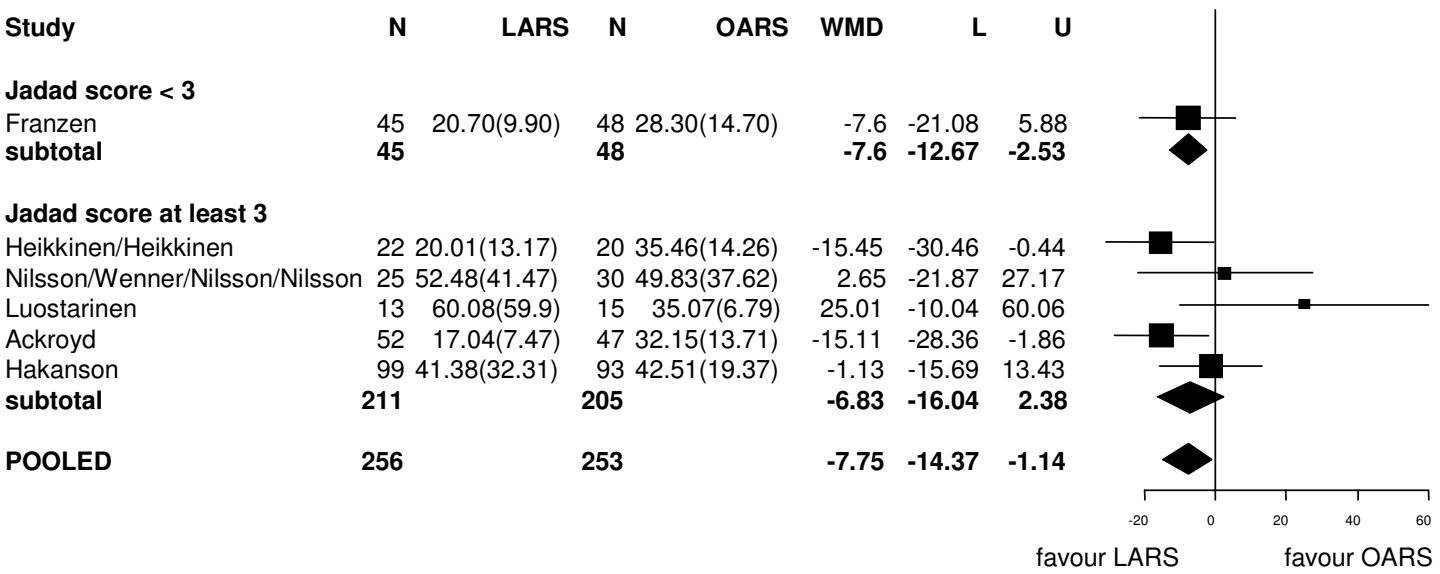


Figure 2: Duration of hospital stay (days)



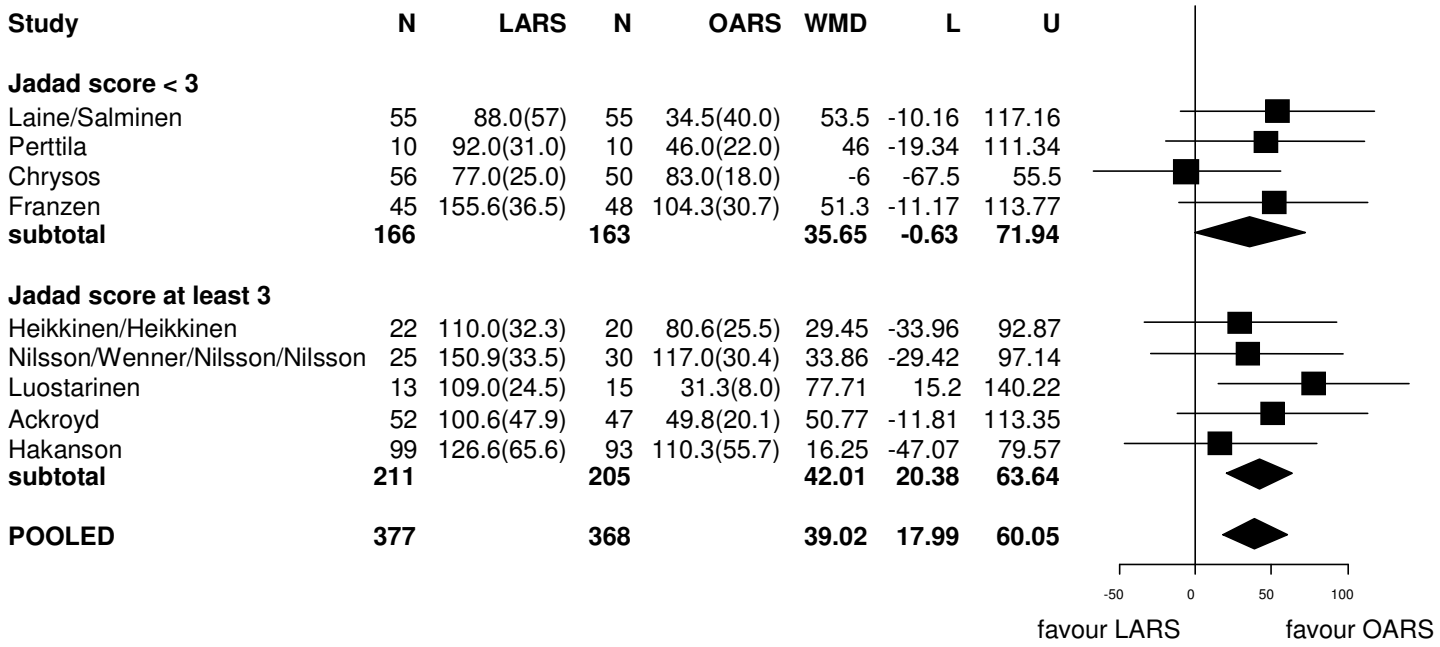
Values in left panel are mean (standard deviation), weighted mean difference and 95% confidence interval. In the graph, squares indicate point estimates of treatment effect (mean difference, i.e. mean for LARS group of patients – mean for OARS group of patients) with the size of the squares representing the weight attributed to each study. The horizontal lines represent 95% confidence interval for mean differences. The pooled estimate of duration of hospital stay (days) is the weighted mean difference, obtained by combining all mean differences using the inverse variance weighted method and is represented by the diamond. The size of the diamond depicts the ninety-five percent confidence interval. Values to the left of the vertical line at zero favour LARS.

Figure 3: Return to normal activity (days)



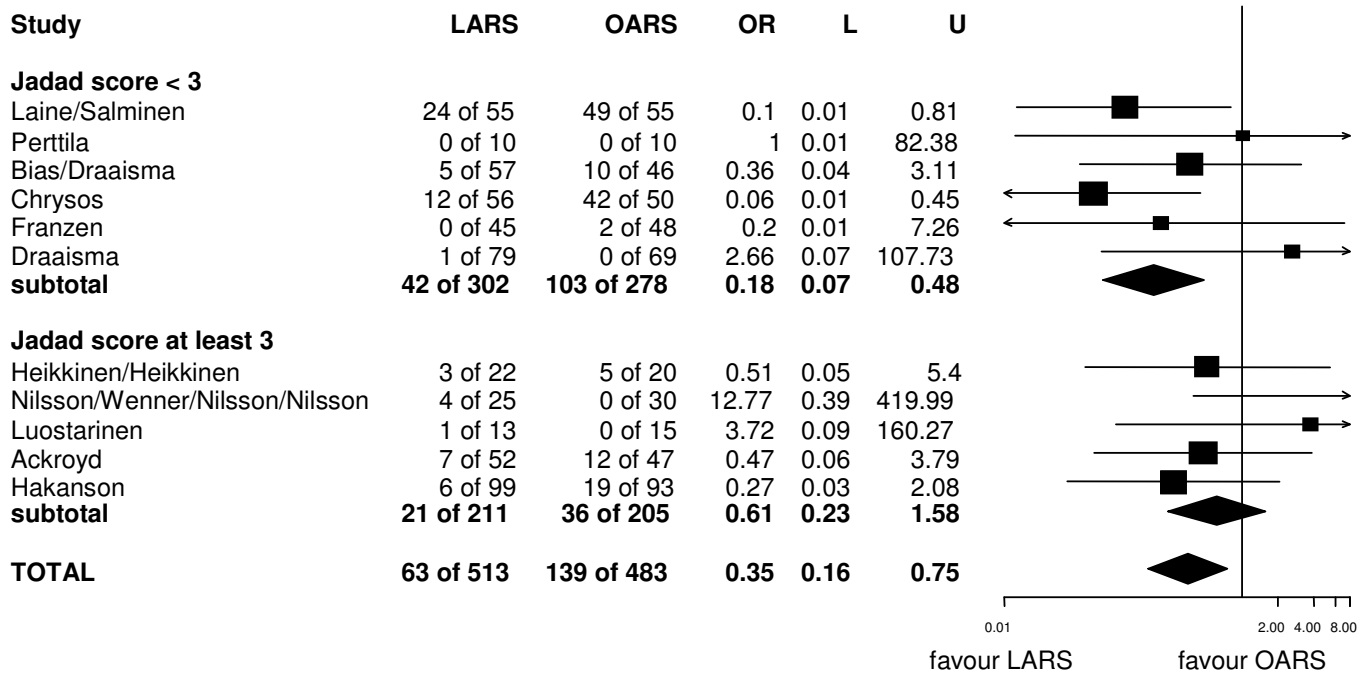
Values in left panel are mean (standard deviation), weighted mean difference and 95% confidence interval. In the graph, squares indicate point estimates of treatment effect (mean difference, i.e. mean for LARS group of patients – mean for OARS group of patients) with the size of the squares representing the weight attributed to each study. The horizontal lines represent 95% confidence interval for mean differences. The pooled estimate of return to normal activity (days) is the weighted mean difference, obtained by combining all mean differences using the inverse variance weighted method and is represented by the diamond. The size of the diamond depicts the ninety-five percent confidence interval. Values to the left of the vertical line at zero favour LARS.

Figure 4: Operating times (minutes)



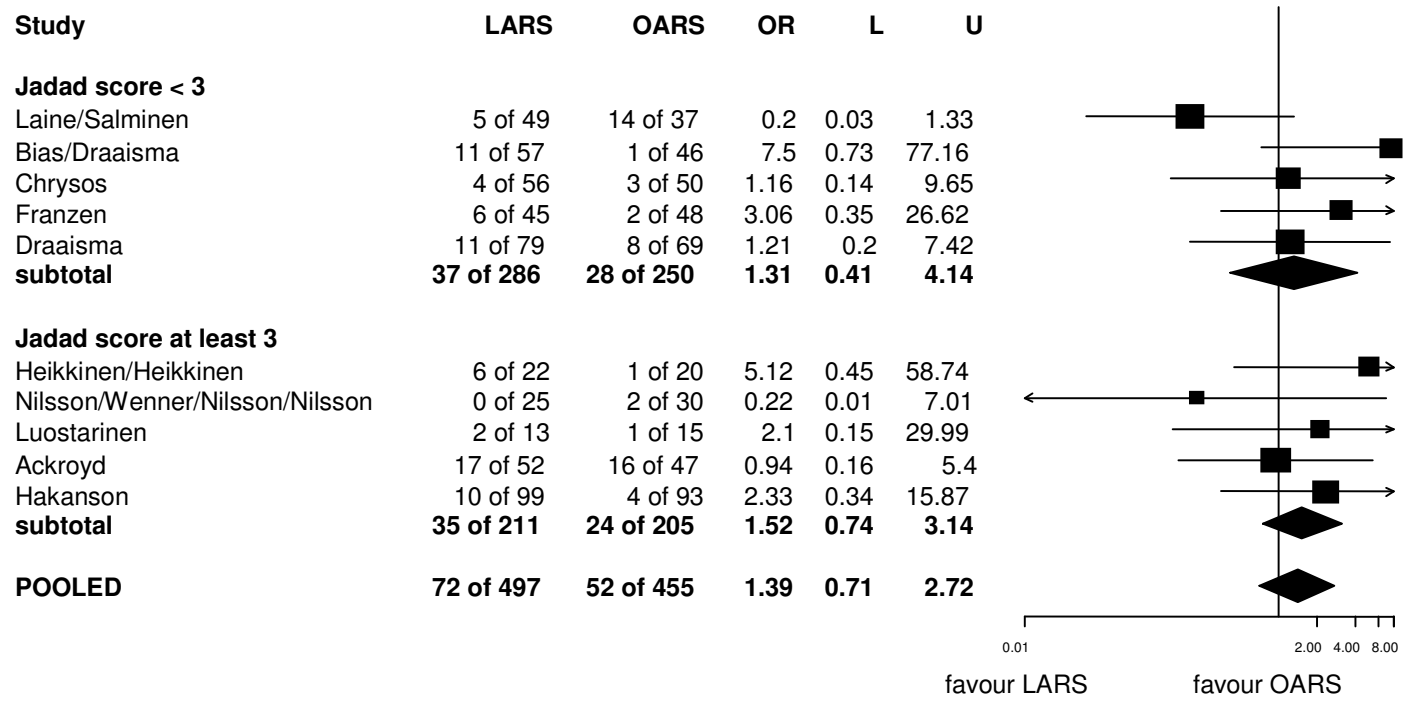
Values in left panel are mean (standard deviation), weighted mean difference and 95% confidence interval. In the graph, squares indicate point estimates of treatment effect (mean difference, i.e. mean for LARS group of patients – mean for OARS group of patients) with the size of the squares representing the weight attributed to each study. The horizontal lines represent 95% confidence interval for mean differences. The pooled estimate of operating time (minutes) is the weighted mean difference, obtained by combining all mean differences using the inverse variance weighted method and is represented by the diamond. The size of the diamond depicts the ninety-five percent confidence interval. Values to the left of the vertical line at zero favour LARS.

Figure 5: Odds ratio for complication rate



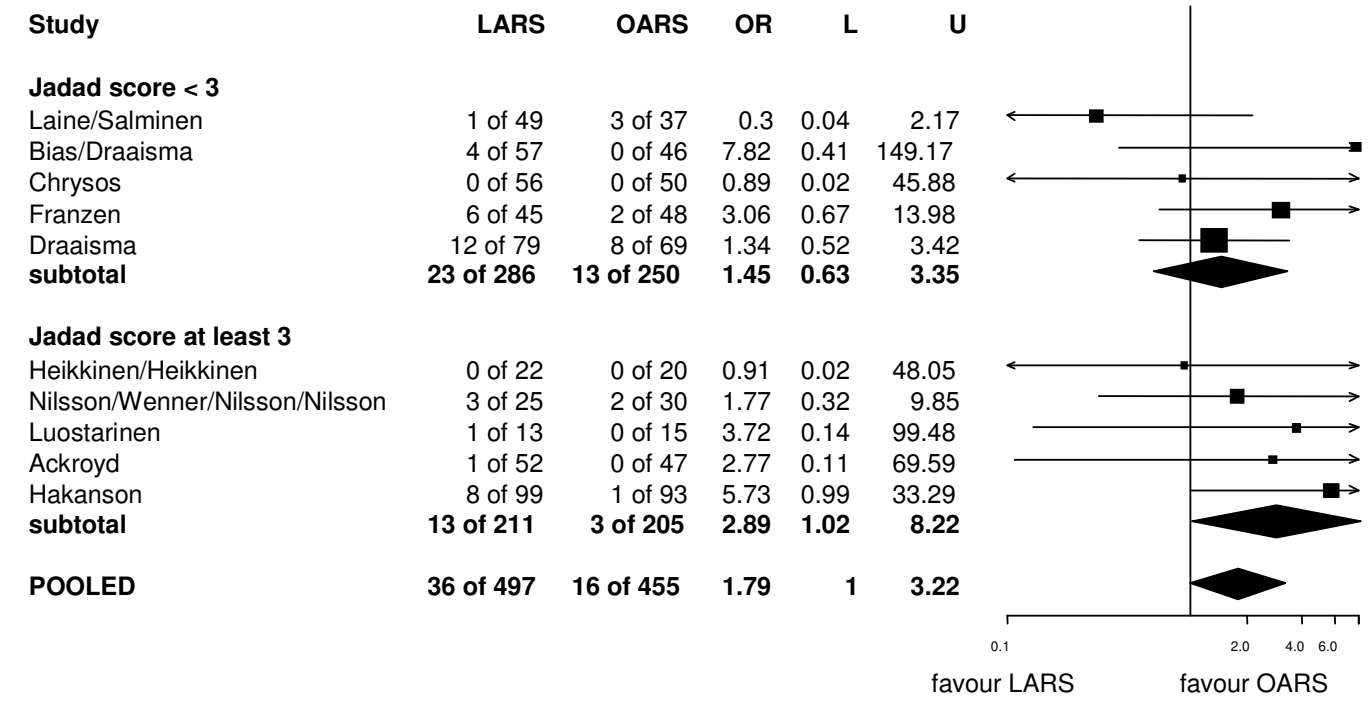
In the graph, squares indicate point estimates of treatment effect (odds ratio for LARS over OARS groups) with the size of the squares representing the weight attributed to each study. The horizontal lines represent 95% confidence interval for odds ratio. The pooled estimate for complication rate is the pooled odds ratio obtained by combining all odds ratios of the eleven studies using the inverse variance weighted method, and is represented by the diamond. The size of the diamond depicts the ninety-five percent confidence interval. Values to the left of the vertical line at one favour LARS.

Figure 6: Odds ratio for failure rate



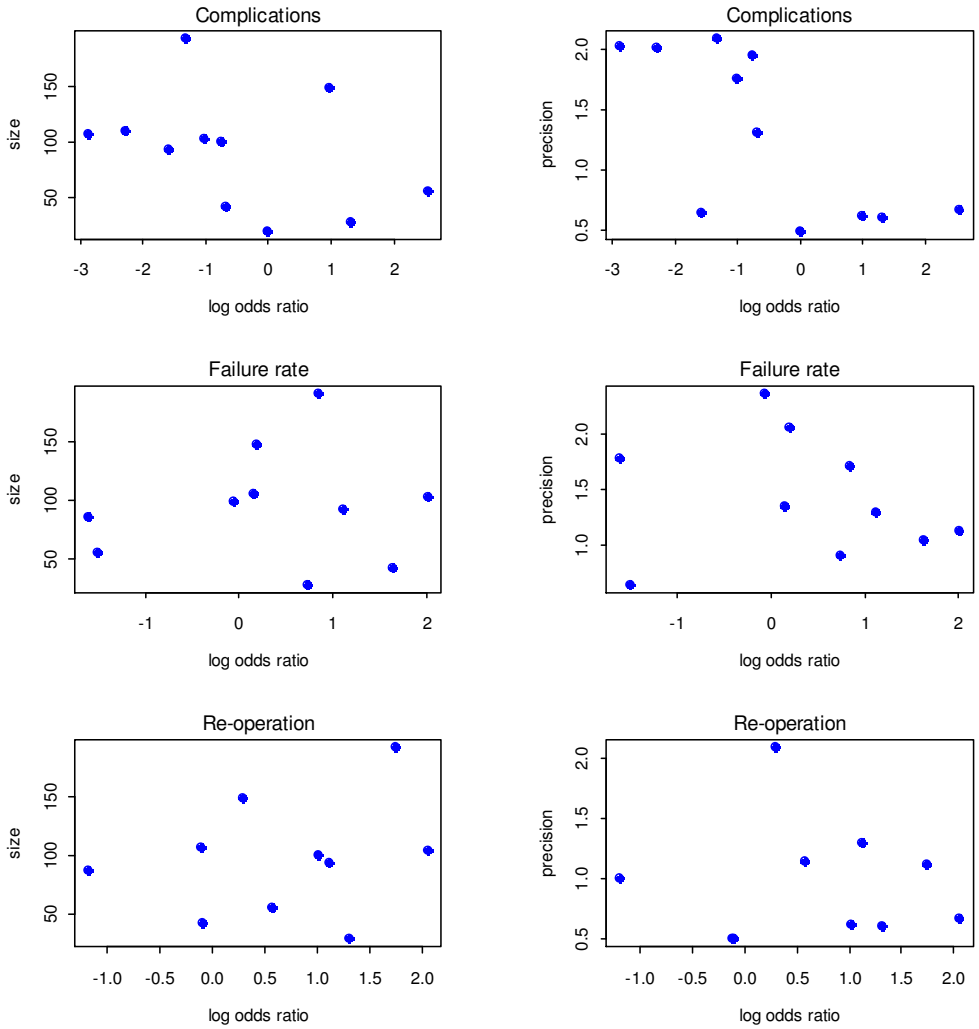
In the graph, squares indicate point estimates of treatment effect (odds ratio for LARS over OARS groups) with the size of the squares representing the weight attributed to each study. The horizontal lines represent 95% confidence interval for odds ratio. The pooled estimate for failure rate is the pooled odds ratio obtained by combining all odds ratios of the ten studies using the inverse variance weighted method, and is represented by the diamond. The size of the diamond depicts the ninety-five percent confidence interval. Values to the left of the vertical line at one favour LARS.

Figure 7: Odds ratio for re-operation rate



In the graph, squares indicate point estimates of treatment effect (odds ratio for LARS over OARS groups) with the size of the squares representing the weight attributed to each study. The horizontal lines represent 95% confidence interval for odds ratio. The pooled estimate for re-operation rate is the pooled odds ratio obtained by combining all odds ratios of the ten studies using the inverse variance weighted method, and is represented by the diamond. The size of the diamond depicts the ninety-five percent confidence interval. Values to the left of the vertical line at one favour LARS.

Fig 8: The funnel plots suggesting existence of publication bias. Precision = 1/standard error.



STUDY HIGHTLIGHTS

What is current knowledge

- Laparoscopic Nissen fundoplication (LNF) is a relatively new surgical procedure for treating gastroesophageal reflux disease
- Open fundoplication on the other hand is a tried and tested method of treating gastroesophageal reflux disease
- Ninteen RCTs comparing LARS vs OARS have been published to date in the English literature to determine the relative merits of these two procedures
- In general, the overall benefits of these procedures are similar. Some studies report that more than 90% of patients are free of heartburn after the operation and satisfied with their choice, even after five years.
- LARS however seems to be associated with early hospital discharge and quicker return to normal activity compared to OARS
- To date LARS is associated with longer operating time compared to OARS

What is new here

- No meta-analysis to date exists comparing the mertis of LARS vs OARS
- The present meta-analysis is the largest body of information so far available for the comparison of LARS and OARS in the English language literature.
- Based on the current meta-analysis one can conclude that LARS is a suitable and safe option for the treatment of proven gastro-oesophageal reflux disease as it enables a faster convalescence and return to productive activity, with a reduced risk of complications and a similar treatment outcome to that of open approach. However, there is a significant increased risk of re-operation rate in the LARS group.