Laparoscopic ischaemic conditioning of the stomach may reduce gastric-conduit morbidity following total minimally invasive oesophagectomy

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Abstract

Objective: Oesophagectomy, whether open or minimal access, is associated with a significant incidence of gastric-conduit-related complications. Previous animal and human studies suggest that ischaemic conditioning of the stomach prior to oesophagectomy improves perfusion of the gastric conduit. We have adopted laparoscopic ligation of the left gastric artery 2 weeks prior to minimally invasive oesophagectomy, having identified a relative high incidence of gastric-tube complications through a cumulative summation (CUSUM) analysis.

Methods: This study included 77 consecutive patients who underwent a Total MIO (thoracoscopic oesophageal mobilisation, laparoscopic gastric tube formation, cervical anastomosis). The ligation group comprised 22 consecutive patients, excluding those with middle-third squamous tumours or early-stage adenocarcinoma, who underwent ligation 2 weeks prior to MIO at staging laparoscopy. The control group comprised 55 patients who did not undergo ischaemic conditioning in this way. We have defined conduit-related complications as: leak managed conservatively (L); tip necrosis requiring resection and re-anastomosis (TN) and conduit necrosis needing resection and oesophagostomy (CN). The values are reported as medians. The effect of ligation of the left gastric artery was followed with a CUSUM analysis.

Results: Ligation was performed 15.5 days pre-operatively (median). There were no complications and the length of hospital stay was 1 day. Although gastric mobilisation at MIO was technically more difficult after ligation, there was no significant difference in operating time (ligation, 407 min; control, 425 min) or blood loss (ligation and control, 500 ml). There was less gastric-conduit morbidity in the ligation group (two of 22, 10%; one L, one CN) compared with the control group (11 of 55, 20%; four L, five TN, two CN), but these differences did not reach statistical significance (p = 0.211 and p = 0.176 Fisher’s exact test).

The CUSUM analysis showed that during ligation of the left gastric artery, conservatively treated gastric-conduit-related morbidity (leak, resection and re-anastomosis or conduit necrosis) remained within safe limits (10%). Conduit-related morbidity increased after stopping ligation.

Conclusion: In this non-randomised clinical setting, our results suggest that ischaemic conditioning of the stomach prior to MIO is safe. There is a trend to reduced morbidity related to gastric-conduit ischaemia, which was demonstrated by a CUSUM analysis. A randomised trial is needed before ligation of the left gastric artery can be routinely recommended.

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Keywords: Laparoscopy; Delay phenomenon; Ischaemia; Minimally invasive; Oesophagectomy; CUSUM

1. Introduction

While operative mortality after oesophagectomy has decreased in recent years [1,2], postoperative morbidity is still a significant problem. Minimal-access techniques for oesophageal resection [3–8] may reduce the impact of oesophagectomy on quality of life, but have not yet been shown to reduce postoperative morbidity [9].

Perfusion of the transposed gastric conduit is a major determinant of outcome after open oesophagectomy; [10] this is also the case after minimal-access oesophagectomy. We have recently published a series of 70 consecutive total minimally invasive oesophagectomies in which we report nine of 70 gastric-conduit complications (13%), ranging from conservatively managed leaks to conduit necrosis [8]. Luketich and co-workers report an 11.7% leak rate [3].

The causes for gastric-conduit failure are multifactorial, but include poor perfusion of the fundus after mobilisation, the upper part of the transposed stomach being particularly at risk from rarefaction of intramural vessels. Until recently, ischaemia of the gastric conduit has been accepted as inevitable in some patients. However, the discovery of the...
'delay phenomenon' in plastic surgery, whereby a graft is rendered ischaemic prior to translocation to increase its vascularity [11], has been recognised to be of potential benefit to the gastric conduit [12].

There is a significant body of literature showing the potential benefit of ischaemic conditioning of the stomach in animal studies. Urschel and colleagues demonstrated reduced perfusion of the rat stomach after ligation of the left gastric artery, which was followed by a gradual recovery of perfusion (the delay phenomenon), reaching 81% of baseline by 2 weeks and a near-normal perfusion by 3 weeks [12]. Further studies in the rat demonstrated a beneficial effect of ischaemic conditioning on oesophageogastric anastomotic wound healing [13]. Reavis and colleagues demonstrated the delay phenomenon in opossums [14]; those animals which had undergone ligation of the right, left and short gastric arteries demonstrated vasodilatation, angiogenesis and an increased blood flow to the fundus when compared to animals undergoing immediate operation or sham procedures.

Reduced perfusion at the proximal end of the human gastric tube by measurement of mucosal $\rho_{CO_2}$ has been shown to be the lowest at 18 h postoperatively, but to recover to baseline levels in uncomplicated patients by 4 days [15]. Recently, interstitial $\rho_{O_2}$ has been shown to fall substantially in the fundus of the human stomach after ligation of the left gastric artery, confirming its major contribution to the blood supply of the fundus [16].

Three studies in humans have investigated the potential therapeutic benefit to ischaemic conditioning of the stomach. Akiyama and colleagues showed a reduced leak rate (2% vs 8% in control group) and improved perfusion of the conduit (67% vs 33% in control group) after embolisation of the left gastric, right gastric and splenic arteries ($n = 54$, non-randomised) [17]. Nguyen and colleagues reported no leaks in nine patients in whom the left gastric artery had been ligated at staging laparoscopy 2 weeks prior to minimally invasive oesophagectomy [18]. Holscher and co-workers have demonstrated that laparoscopic ligation of the left gastric artery and mobilisation of the conduit 5 days before open intrathoracic reconstruction may reduce conduit-related morbidity [19].

We report our experience of laparoscopic ligation of the left gastric artery 2 weeks prior to minimally invasive oesophagectomy and relate them to gastric-conduit-related morbidity using the CUSUM analysis.

2. Patients and methods

Between April 2004 and June 2007, 77 patients underwent total minimally invasive oesophagectomy. Neo-adjuvant chemotherapy was given to patients greater than stage T2 in accordance with the MRC OEO2 protocol [20]. During the period of this study, 77 patients were listed for and completed a three-stage minimally invasive oesophagectomy, who form the basis of this report. During this time period, one patient was converted to thoracotomy due to adhesions. Nine other patients underwent an electively planned hybrid procedure. No completely open procedures were performed.

As a result of high conduit-related morbidity in the first 41 patients, patient #42 onwards was offered ligation of the left gastric artery at the time of staging laparoscopy. Informed consent was obtained. Ligation and staging laparoscopy was performed 14 days prior to oesophagectomy in line with the published practice of Nguyen and colleagues [18]. Patients were given anti-thrombo-embolic stockings to wear and low-molecular-weight heparin was prescribed. Patients with early adenocarcinoma or middle-third squamous tumours were excluded, as they did not routinely undergo a staging laparoscopy.

Staging laparoscopy was undertaken with a pneumoperitoneum of 12 mmHg, using a 10-mm camera port to the left of the midline. Nathanson liver retractor (Cook® Medical Inc., Bloomington, IN, USA) was inserted and three operating ports used (left upper quadrant, 5-mm; left lateral, 10-mm; right lateral, 5-mm).

After a thorough staging assessment, the lesser omentum was opened and the lesser curve retracted to the patient’s left, lifting the stomach to place the left gastric pedicle on stretch. The artery and vein were identified and divided after securing with non-absorbable ligatures, Ligaclip® (10-M/L, Ethicon EndoSurgery® Inc., Cincinnati, OH, USA) or 30-mm vascular stapler (2.5 mm ENDOGIA™; Autosuture, Norwalk, CT, USA) (Fig. 1). Dissection was kept to a minimum required to display the vessel safely; if lymph nodes were dissected they were removed and sent for histological examination. One litre of warmed ADEPT™ Adhesion Reduction Solution (4% Icodextrin Solution, Innovata PLC, Farnham, Surrey, UK) was run into the peritoneal cavity to reduce adhesion formation.

Two weeks later, patients underwent total minimally invasive oesophagectomy [8,21]. The gastric conduit was formed without exteriorisation, taking precautions previously described to fashion the optimum gastric tube [8].

Conduit-related complications were identified in all patients by clinical signs, failure of C-reactive protein to fall or chest-drainage appearance. Contrast swallow was routinely performed on postoperative day 5, and any suspicion of leak investigated by endoscopy. In the absence of non-viable gastric mucosa at endoscopy, leaks were treated conservatively either by stent or nasogastric suction. If necrosis was seen in the

Fig. 1. Photograph of left gastric artery pedicle after division at staging laparoscopy.
gastric tube, the patient underwent urgent re-operation with resection of the gastric conduit back to healthy tissue and re-anastomosis or resection, cervical oesophagostomy and feeding jejunostomy.

We have classified gastric-conduit failures as follows (Fig. 2):

- **Type I** — anastomotic leak not associated with significant mucosal necrosis at endoscopy, managed conservatively;
- **Type II** — conduit-tip necrosis requiring resection and re-anastomosis;
- **Type III** — necrosis of a substantial length of the conduit requiring resection with insufficient viable conduit to restore continuity.

Twenty-two consecutive eligible patients underwent laparoscopic ligation of the left gastric artery as part of the staging laparoscopy following neo-adjuvant chemotherapy where indicated (ligation group). Fifty-five patients did not undergo laparoscopic ischaemic conditioning (control group).

### 3. Statistical analysis

Continuous variables are expressed as medians. A p-value of less than 0.05 was considered as statistically significant.

Statistical analyses were performed using the Statistical Package for Social Science 14.0 software package for Windows (SPSS, Chicago, IL, USA).

The CUSUM technique (ES Page, Cambridge University), which involves the sequential calculation of a cumulative sum (i.e., a sequential analysis technique) [22], was used to demonstrate deviations from an acceptable failure rate. An acceptable limit for gastric-conduit-related complications was set at 10% for the purposes of the analysis.

### 4. Results

Minimally invasive oesophagectomy was completed in 77 consecutive patients (67 males and 10 females) with a median age of 69 years (range: 42—83 years). Laparoscopic ischaemic conditioning was performed at 15.5 days (median) prior to oesophagectomy (range: 9—112 days, interquartile range: 13—25 days). Median operative time for staging laparoscopy and ligation was 70 min (range: 52—101 min). There were no procedure-related complications and all patients had an uneventful discharge (median stay: 1 day).

Minimally invasive oesophagectomy in both the ligation and control groups were comparable in terms of operative parameters (Table 1). Abdominal dissection was technically more difficult in the ligation group in view of adhesions and induration of tissues around the lesser curve of the stomach, although this did not appear to increase operation time or blood loss. Median in-patient stay was 12 days in both the groups (ranges: MIO, 8—103; MIO + ligation, 7—86); prolonged length of stay was associated with complications.

General complication rates were similar in both the groups (Table 2). There was less morbidity related to gastric-conduit failure in the ligation group (two out of 22, 10%) compared to the control group (11 of 55, 20%), though this difference did not reach statistical significance (p = 0.176 by Fisher’s exact test). Odds ratio was 0.4 (95% confidence interval: 0.08—1.96). There were no instances of type II R.G. Berrisford et al. / European Journal of Cardio-thoracic Surgery 36 (2009) 888—893

### Table 1
Comparison of MIO and MIO + ligation group.

<table>
<thead>
<tr>
<th></th>
<th>MIO</th>
<th>MIO + LIC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>55</td>
<td>22</td>
<td>ns</td>
</tr>
<tr>
<td>Total operating time (min)</td>
<td>425 (315—780)</td>
<td>407 (304—485)</td>
<td>ns</td>
</tr>
<tr>
<td>Laparoscopic time (min)</td>
<td>180 (90—255)</td>
<td>150 (90—255)</td>
<td>ns</td>
</tr>
<tr>
<td>Total lymph node count</td>
<td>23 (7—48)</td>
<td>20 (8—69)</td>
<td>ns</td>
</tr>
<tr>
<td>Abdominal lymph node count</td>
<td>11 (0—31)</td>
<td>9.5 (1—41)</td>
<td>ns</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>500 (150—3600)</td>
<td>500 (350—1300)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Range in parentheses.

### Table 2
General complications.

<table>
<thead>
<tr>
<th></th>
<th>MIO</th>
<th>MIO + LIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Temporary vocal cord paresis</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Chylothorax</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Mediastinal effusion</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
gastric-conduit failure in the ligation group compared to five cases in the control group, but one type I and one type III conduit failure (Table 3).

Complications related to gastric-conduit failure in the first 42 patients (i.e., prior to instituting ligation) are plotted as a CUSUM chart (Fig. 3). Each successful operation without conduit failure is represented by the line moving an increment of 0.1 in a negative direction, away from the red line (marking a maximum acceptable gastric-conduit-related complication rate), starting from a zero baseline. In the event of conduit failure (e.g., patient #17), the line moved in a positive direction, towards the red line, by 0.9. By patient #41, the cut-off for acceptable gastric-conduit failure rate was breached. At this point, we introduced laparoscopic ligation of the left gastric artery as a pilot study.

Fig. 4 shows that, despite two complications from conduit failure (types I and III), gastric-tube-related morbidity remained within acceptable limits, beneath the red line. In the absence of a statistically significant difference in conduit failure between the ligation and control groups (p = 0.176, Fisher’s exact test), and a subjective increase in difficulty of dissection at oesophagectomy, the pilot study was terminated at patient #72 (Fig. 4). Gastric-conduit-related morbidity from patient #73 onwards (no pre-operative ligation) caused the CUSUM line to again breach the red line into unacceptable rates.

Despite the high incidence of gastric-tube-related morbidity in these 77 patients, unplanned admission to the intensive care unit was only necessary in seven patients (median stay: 8 days; range: 2–38 days). There was one death in this series (in-hospital mortality and 30-day mortality one in 77, 1%), secondary to a catastrophic mediastinal haemorrhage at day 14. The patient developed profound hypovolaemic shock during weaning from ventilatory support for postoperative respiratory failure. Post-mortem examination confirmed right haemothorax, but the cause and exact site of the haemorrhage were not established.

5. Discussion

This series of 77 consecutive minimally invasive oesophagectomies documents a relatively high rate of gastric-tube-related morbidity (13 of 77, 17%), despite a low 30-day and in-hospital mortality (one of 77, 1%). Early recognition and prompt treatment ensured that no patient in this series died from their gastric-conduit-related complication, although three underwent defunctioning cervical oesohageostomy.

There are few other substantial series of totally minimally invasive oesohageostomy published, so comparisons are few. Luketich and colleagues describe an overall leak rate of 11.7%, 3.2% gastric-tip necrosis (seven of 222) and 0.5% conduit ischaemia rate (one of 222) [3] and Nguyen and co-authors describe a leak rate of 8.6%, although they do not describe infarction.

There is no doubt that fashioning the gastric conduit as an intra-corporeal procedure does not allow the surgeon to stretch the stomach and flatten it in an antero-posterior dimension as thoroughly as in open surgery. This will lead to a shorter tube, with less excess to resect from the tip prior to anastomosis. Other authors have described minimally invasive oesohageostomy with a small laparotomy to deliver the stomach and fashion the conduit outside the body [5,7]. However, Smithers and colleagues describe one gastric necrosis (type III) in 23 (4%) patients with this approach; Palanivelu describes a patient who died of multisystem failure but does not describe about the patients’ conduit.

Average rates of gastric-conduit ischaemia after open oesohageostomy have been estimated to be 3.2% overall, although different definitions of gastric-conduit ischaemia have been used [10]. It is likely that historical series have under-estimated gastric ischaemia; patients who have died

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Table 3
Gastric-conduit failure.

<table>
<thead>
<tr>
<th></th>
<th>MIO</th>
<th>MIO + LIC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Type I — simple anastomotic leak</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Type II — conduit tip necrosis</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Type III — complete conduit ischaemia</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Total GCF morbidity</td>
<td>11/55</td>
<td>20%</td>
</tr>
</tbody>
</table>

Observed differences are not of statistical significance.

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Fig. 3. CUSUM plot for patients 1–41 showing gastric-conduit-related complications (black points — type I, circle; type II, triangle; type III, square). Red dotted line marks limit of pre-set acceptable complication rate (10%). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

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Fig. 4. CUSUM plot for patients 42–76 showing gastric-conduit-related complications (black points — type I, circle; type II, triangle; type III, square). Red dotted line marks limit of pre-set acceptable complication rate (10%). Green line indicates the period of laparoscopic left gastric artery ligation and blue line indicates cessation of ligation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

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from postoperative pneumonia or multisystem failure may have had underlying conduit ischaemia, which was undiagnosed in the absence of postoperative endoscopy. In a recent non-randomised comparison of open vs minimally invasive oesophagectomy, Smithers and colleagues reported leaks in 10 of 114 (8.7%) and gastric necrosis in two of 114 (1.7%) patients after open surgery compared with one of 23 (4%) leaks and one of 23 (4%) gastric necrosis after minimally invasive surgery [7]. These differences were not significant.

Ischaemia of the gastric conduit is likely to be multifactorial. Too narrow a gastric tube is associated with a higher leak rate (27.6% with a 3–4-cm tube, compared to 6.1% with a 6-cm tube) [3]. Failure to divide the right crus with tension in the conduit, as well as too narrow a hiatus, can lead to constriction of the conduit and its vascular supply as it passes through the diaphragm. Insufficient mobilisation of the distal stomach and pylorus will compromise conduit length and allow less conduit tip to be resected before anastomosis. Failure to preserve the gastro-epiploic arcade to the upper fundus will compromise blood flow to the tip of the conduit. Traction forces applied to the conduit in transporting it through the mediastinum to the neck (in particular, in patients with high body mass index and bulky omentum) can result in conduit damage and subsequent ischaemia. The route chosen for the conduit may also influence perfusion of the tip [16]. Failure to keep the stomach orientated correctly during application of the staplers can result in spiralling of the tube and an asymmetry of the gastric tube in relation to the vascular arcade.

Our experience with ligation of the left gastric artery at staging laparoscopy suggests that it is feasible. It does result in increased difficulty of dissection and abdominal lymphadenectomy at subsequent resection in some patients. The CUSUM plot suggested that conduit-ischaemia-related complications remained within acceptable limits when patients underwent ligation. Further complications observed after stopping ligation gave further support to pre-operative ligation.

Holscher and colleagues have shown that ligating the left gastric artery and mobilising the stomach at 5 days pre-operatively is feasible. They point out that the strongest adhesions and tissue induration occur after 7 days and chose their interval accordingly. Our difficulty in re-operating on some patients at 14 days confirms this point. However, is 4 days a sufficient time for the delay phenomenon to improve conduit vascularity or does it simply allow potential ischaemic areas to declare themselves? Holscher and colleagues based their choice of a 4-day delay on their previous demonstration of return of maximum perfusion at day 4 using mucosal $P_{O_2}$ analysis. This is in keeping with studies on skin and myocutaneous flaps in different tissues from different species of animal, which showed the most dramatic increase in blood flow occurring at days 3–5 [11]. In the rat stomach, however, Laser Doppler flowmetry has been used to show that perfusion reached basal values on the 14th day after ligation of the left gastric artery [23]. This is consistent with work by Lamas and colleagues, who have recently investigated apoptosis, necrosis and neo-vascularisation at various intervals after ligation of the left gastric artery in rats. They demonstrated initial tissue injury, highest at 3 and 6 days post ischaemia. From day 10, apoptosis and necrosis started to decrease and by day 15 complete histological recovery and maximum neo-vascularisation occurred [24].

At 5 days after ligation of left gastric and short gastric arteries, Holscher and colleagues report two of 83 patients with circumscribed necrosis of the upper fundus at 5 days. Despite ligation, they report a five of 83 (6%) leak rate but had no type II or III conduit ischaemia after open intra-thoracic anastomosis.

Our use of CUSUM analysis has allowed us to maintain a clear perspective on gastric-tube-related complications during our series of minimally invasive oesophagectomies. We confirm its usefulness in monitoring adverse events [25] with a relatively new operation and recommend its application.

Ischaemic conditioning of the stomach may present us with a tool for reducing gastric-conduit-related morbidity after open or minimal access-oesophagectomy [26]. A prospective randomised controlled trial is needed to verify the potential advantage of laparoscopic ligation of the left gastric artery before this technique can be recommended.

Acknowledgements

The authors express their thanks to Dr D Sanders and Dr M Rucklidge, consultant anaesthetists, and Mr P Froeschle, consultant thoracic surgeon, Royal Devon & Exeter NHS Foundation Trust for their care of patients comprising this series.

References

Appendix A. Conference discussion

Dr T. Lerut (Leuven, Belgium): I have two comments rather than questions. First of all, I am profoundly convinced that the problems of leakage and tube necrosis are related to technical manipulations and surgical, say, errors. In fact in your second series you have one conduit necrosis despite the clamping of the gastric arteries. So I wonder whether if you had not ligated somewhere during the mobilisation the gastro-epiploic artery, because to have a complete necrosis of the conduit, there must be a major vascular trauma on the gastro-epiploic artery. Did you check this?

And secondly, I think either you do believe inremoval of lymphadenectomy or you don’t, but, as you know, I do. So I am very much concerned about the adhesions, because at the second week that is where you get the most inflammatory reaction. I had a similar experience with preconditioning, albeit anecdotal, not for stomach but for a colon interposition, and I was astonished how much fibrosis that you get, and that might jeopardize your possibilities of lymphadenectomy and also cause some dissemination of tumour cells due to more extensive manipulation.

Dr Veeramootoo: I will try to answer those two questions separately. Your first question about the fact that we still had a type 3 failure in one patient, reflects the fact that the vascularity of the stomach is very variable in different people. Some people have an incomplete gastro-epiploic arcade, and it is difficult to acknowledge this at the time of surgery. If you do some kind of imaging pre-operatively, maybe we could identify those people, but I think the knowledge is lacking in that respect.

In regards to lymph node dissection at the time of MIO, we are performing a similar formal nodal dissection at the time of the MIO and we spend less time doing the resection in the abdominal bed. Despite the fact that we have had adhesions in some of these patients after ligation, we have not actually noticed any significant drop in our nodal harvest. We certainly take your point, but I don’t think we have encountered this problem to a big extent.

Dr J. O’Dell (Jacksonville, FL): Have you thought about mobilising the whole stomach and leaving it within the abdominal cavity 2 weeks beforehand?

Dr Veeramootoo: This is an interesting question, but I think it has been done by Holscher from Germany, and we are pretty happy with our practice at the moment. There is no substantial evidence that doing that will actually benefit the operation, and we are not comfortable with the idea of leaving this whole conduit in the abdomen and giving the patient a feeding tube. We are not really keen on doing that at this present time. If there is further evidence that this should be done, we might need to change our practice, but not at the moment.