Phenylephrine infusion improves blood flow to the stomach during oesophagectomy in the presence of a thoracic epidural analgesia


OBJECTIVES: Gastric tube necrosis is a major cause of mortality after oesophagectomy. The construction of the gastric tube used for oesophageal reconstruction involves a division of several arteries leading to a reduction in the blood supply at the fundus, which is used for the oesophageal anastomosis. This study was undertaken to determine the effect of thoracic epidural anaesthesia and intravenous phenylephrine on haemodynamics and blood flow in the tubularized stomach.

METHODS: Ten patients undergoing an oesophagectomy were prospectively studied. Pulmonary artery catheters were used to measure haemodynamic changes, and laser Doppler flow probes were used to measure gastric blood flow. The effects of an intraoperative thoracic epidural bolus and subsequent intravenous phenylephrine infusion were documented.

RESULTS: The administration of a thoracic epidural bolus of bupivacaine 0.25% at 0.1 ml kg resulted in a significant reduction in flux at the anastomotic end of the newly formed gastric tube from a median of 57–41 perfusion units ($P = 0.003$). A subsequent intravenous phenylephrine infusion titrated to restore mean arterial pressure significantly increased the flux at the anastomotic end from a median of 41–66 perfusion units ($P = 0.009$).

CONCLUSIONS: An intravenous phenylephrine infusion can reverse the epidural bolus-induced reduction in blood flow at the anastomotic end of the newly formed gastric tube.

Keywords: Anastomosis • Oesophageal surgery • Gastric ischaemia

INTRODUCTION

Oesophagectomy provides patients with the best chance of cure for oesophageal cancer. However, it is associated with considerable mortality and morbidity. Intrathoracic anastomotic leakage is one of the most feared complications of oesophagectomy and is responsible for a significant number of postoperative deaths and protracted hospital admissions [1]. Patients undergoing oesophageal resection usually have continuity immediately re-established with a tubularized stomach. During formation of the gastric tube, the left gastric, left gastroepiploic and short gastric arteries are divided. The blood supply to the gastric tube is then largely dependent on blood flow through the right gastroepiploic artery. The proximal end of this tube is used for the oesophageal anastomosis and derives its blood supply from an intramural plexus of vessels originating from the right gastroepiploic artery. It has been shown that perfusion to this ‘anastomotic’ end of the gastric tube is impaired [2–4]. This is potentially significant as ischaemia of the gastric tube is the major cause of anastomotic leaks and strictures after oesophagectomy [5–7].

Thoracic epidurals containing local anaesthetics are widely used to provide analgesia for patients undergoing oesophagectomy [8]. Although blood flow to the gastric tube may be increased by an epidural-induced sympathetic block, we have previously shown that the effects of epidural-induced hypotension predominate when the stomach has been tubularized for oesophageal replacement, and an intraoperative thoracic epidural bupivacaine bolus further reduces the flux at the anastomotic end of the gastric tube [4]. Although intravenous infusion adrenaline reversed this decrease in flux, there are potential disadvantages to using this agent to maintain blood pressure in the perioperative period during oesophagectomy, whereas vasoconstrictors such as phenylephrine are widely used intraoperatively in this situation. The effects of vasoconstrictors on gastric tube blood flow have not been established, and there are concerns that vasoconstriction of gastric tube blood vessels may impair gastric tube perfusion. Therefore, this study was undertaken to determine the effect of vasoconstrictor phenylephrine on blood flow in the newly formed gastric tube in the presence of functioning thoracic epidural analgesia.
MATERIALS AND METHODS

The local research ethics committee approved the study, and written informed consent was obtained from American Society of Anaesthetists I–III adult patients scheduled to undergo oesophagectomy for cancer and receive a thoracic epidural for postoperative analgesia. Patients with a contraindication to thoracic epidural analgesia, on β-blocker therapy and those with an implanted pacemaker were excluded from the study. A sample size of 10 was selected for this pilot study based on an earlier gastric tube blood flow study, which was done with 10 patients [6].

Patients were premedicated with 5 or 10 mg of oral diazepam 2 h prior to surgery. On arrival in the anaesthetic room, a 20-g radial arterial cannula, a peripheral venous cannula and a mid-thoracic epidural were inserted after local anaesthetic infiltration. A test dose was not administered to ensure that there would be no residual epidural local anaesthetic effect that might interfere with the baseline flux reading. After preoxygenation, general anaesthesia was induced with fentanyl (2 µg kg⁻¹) and propofol (2–3 mg kg⁻¹). Tracheal intubation with a left-sided double-lumen endobronchial tube (Mallinckrodt®, Broncho-Cath, Athlone, Ireland) was facilitated with suxamethonium 1.5 mg kg⁻¹. The position of the tube was confirmed with a fibreoptic bronchoscope. Patients were ventilated to normocapnea. Initially, two lung ventilation was established with the following parameters: FiO₂ of 100%, tidal volume of 6–8 ml kg⁻¹ body weight, 12–16 cycles per min and a positive expiratory end pressure (PEEP) of 0–5 cmH₂O. Anaesthesia was maintained with a mixture of oxygen, air and isoflurane. Neuromuscular blockade was maintained with intermittent boluses of atracurium. Prior to placing patients in a lateral position, a central venous catheter and a study pulmonary artery catheter were inserted via the left internal jugular vein. Nasopharyngeal temperature was monitored, and all patients received urinary catheters and nasogastric tubes. Forced air warming was used to maintain normothermia. Fluid management was standardized with warmed lactated Ringers solution administered at 10 ml kg⁻¹ h⁻¹. Blood loss was replaced with colloid if the haemoglobin concentration was greater than 8 g dl⁻¹, or with allogenic blood if the haemoglobin concentration was <8 g dl⁻¹.

All resections were carried out via a left thoraco-abdominal sixth intercostal space incision and facilitated by one lung ventilation using the following parameters: FiO₂ titrated to achieve O₂ saturation of 90–100% and a PaO₂ of 13 kPa, tidal volume of 4–6 ml kg⁻¹ body weight, at a rate of 12–16 cycles per min and a PEEP of 0–5 cmH₂O. The tumour was resected en bloc with adjacent tissue including lymph nodes from the celiac axis and its branches to the level of oesophageal transection. The latter was located to ensure the removal of at least 10 cm of uninvolved oesophagus proximal to the tumour. A tubularized stomach based on a blood supply from the right gastro-epiploic artery was formed.

Following gastric tube construction, laser Doppler flow probes (DPBC, Moor Instruments, Axminster, UK) were sutured with 5/0 prolene to the serosal surface of the proximal end of the tubularized stomach (the site of future gastro-oesophageal anastomosis) and at the distal, pyloric, end. The flow probes were attached to a laser Doppler monitor (DRT4, Moor Instruments). The flux trace on the laser Doppler monitor was confirmed, and data were archived in a laptop computer (Inspiron 8500, Dell, Ireland). The probe was adjusted, if necessary, until an optimal trace was obtained. After wrapping the tubularized stomach with a damp swab and covering the incision with a sterile drape, non-essential theatre personnel were asked to leave the theatre, and surgery was stopped for the duration of the study. Immediately prior to starting the study, an arterial blood sample was analysed to measure the haemoglobin concentration and confirm normocapnea.

Data were collected during 3- and 5-min study periods. The initial baseline study period commenced when the patients' blood pressure had been stable for 10 min. The beginning of a 5-min baseline laser Doppler flux trace was marked, pulmonary artery wedge pressure measured and three thermodilutional cardiac output measurements were performed and averaged. Standard haemodynamic variables were calculated. After 5 min, the end of baseline flux trace was marked, pulmonary artery wedge pressure re-measured, triplicate cardiac outputs averaged and haemodynamic variables calculated as before.

Patients then received a 0.1 ml kg⁻¹ bolus of epidural 0.25% levobupivacaine. The second study period commenced when the systolic blood pressure had decreased by 30% or after 20 min, whichever was earlier. During the second 5-min study period, a 5-min flux trace was marked and haemodynamic measurements were performed and averaged as before. At the end of the second study period, patients received an intravenous infusion of 400 µg ml⁻¹ of phenylephrine titrated to achieve a mean arterial blood pressure of 130% of baseline. When this blood pressure was achieved, the third 5-min study period was undertaken as described above. Immediately after completing the final study, the Doppler flow probes were removed and 0.1 ml kg⁻¹ h⁻¹ epidural infusion of a mixture containing 5 µg ml⁻¹ of fentanyl in 0.1% bupivacaine commenced and the planned surgery completed. At the end of surgery, muscle relaxation was reversed and the patients were extubated in theatre and then transferred to a recovery ward where the extent of epidural dermotome block was measured and the epidural infusion rate adjusted, if appropriate, to achieve an adequate level of analgesia.

Flux measurements acquired during each of the three 5-min study periods were averaged using Moor-Soft for Windows® DRT4 version 1.2 (for DRT4 Moni-tor v5.02). The average of the haemodynamic values obtained at the start and the end of each study period was calculated. Statistical analysis was performed using Microsoft® Excel 2007. Non-parametric tests were used to analyse the data due to the small sample size and likelihood of non-normality of distribution. Changes were evaluated in detail with Wilcoxon’s signed-rank test, to determine the significance of differences between baseline and epidural periods and between epidural and phenylephrine periods. A P-value <0.05 was taken to be significant.

RESULTS

Eighteen patients were recruited. One patient was excluded due to failure to site a thoracic epidural; 1 was excluded due to failure of the equipment to capture the flux data. Six patients were excluded due to corruption/loss of the flux data. Of the 10 patients studied, 7 were male, and their mean (SD) age was 61 (13) years.

The effects of the thoracic epidural were demonstrated by comparing the baseline and epidural study periods. There was a significant reduction in arterial blood pressure (P = 0.005), heart
at the anastomotic end was significant increase in mean arterial pressure (P = 0.005) and systemic vascular resistance (P = 0.002) following levobupivacaine administration. There was also a significant reduction in flux at the anastomotic (P = 0.003) and pyloric end (P = 0.002) of the gastric tube (Table 1 and Fig. 1).

The effects of the phenylephrine infusion were demonstrated by comparison of the epidural and phenylephrine study periods. There was a significant increase in mean arterial pressure (P = 0.002), systemic vascular resistance (P = 0.002) and central venous pressure (P = 0.005). The flux at the anastomotic and pyloric ends of the gastric tube increased, but only the increase at the anastomotic end was significant (P = 0.009; Table 1 and Fig. 1).

All patients went on to make an uneventful recovery from surgery. There were no anastomotic complications.

**DISCUSSION**

This study confirms earlier findings that a thoracic epidural injection of 0.1 ml/kg levobupivacaine decreases the blood flow at the anastomotic end of the newly formed gastric tube [2-4]. We believe this to be the first study to show that a phenylephrine infusion can reverse this. As ischaemia of the anastomotic end of the gastric tube is a major cause of anastomotic leaks [5, 6] and a relationship between low gastric tube blood flow at the site of anastomosis, as measured by laser Doppler, and subsequent anastomotic leak has been shown [3], we consider that the increase in blood flow at the anastomotic end of the gastric tube with phenylephrine infusion to potentially be clinically significant and of therapeutic value.

Laser Doppler flowmetry is based on the Doppler shift of laser light reflected from moving red cells. The laser Doppler (DRT4, Moor Instrument) calculates sub-serosal red blood cells flux. Laser light with a wavelength of 785 nm is emitted from the attached probes and reflected back from the moving red cells to the probe at a different frequency, red cell velocity can be calculated by utilizing this Doppler shift. By multiplying the number of moving cells and their velocity, flux values can be obtained. The technique has been validated against other methods of measuring tissue blood flow [9, 10] and is an established method of measuring gastric blood flow [11].

Thoracic epidurals utilizing a mixture of local anaesthetic and opioids are widely used to provide analgesia for patients undergoing oesophagectomy and may improve outcomes [8]. They have also been shown to provide some protection for the gut from decreased microvascular perfusion and other insults resulting from haemorrhagic shock [12]. The effects of epidural local anaesthetics on mesenteric blood flow are complex. In experimental animals, extensive epidural blocks have been shown to cause venuodilatation [13]. The site of the epidural is important. Hypotension after lumbar but not thoracic epidural analgesia results in reflex splanchic vasoconstriction in rabbits [14]. There is both experimental and clinical evidence that, during abdominal surgery, a thoracic epidural results in mesenteric vasodilatation and increased intestinal mucosal blood flow [15-17].

None of the above studies, however, relate to the blood flow to the anastomotic end of the newly formed gastric tube, which as a result of surgery is dependent on a submucosal plexus of vessels supplied from the right gastroepiploic artery for its perfusion [18]. We postulate that blood pressure has a significant effect on blood flow through the intramural plexus of vessels to the anastomotic end of the gastric tube and that epidural-induced hypotension further decreases perfusion at this end of

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**Table 1:** Flux (0–1000 arbitrary perfusion unit) and haemodynamic median (range) data

<table>
<thead>
<tr>
<th></th>
<th>Baseline study period</th>
<th>Epidural study period</th>
<th>P-value*</th>
<th>Phenylephrine study period</th>
<th>P-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF</td>
<td>214 (731–151)</td>
<td>203 (355–116)</td>
<td>0.002</td>
<td>220 (601–171)</td>
<td>0.48</td>
</tr>
<tr>
<td>AF</td>
<td>57 (339–39)</td>
<td>41 (112–29)</td>
<td>0.003</td>
<td>67 (345–24)</td>
<td>0.009</td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td>110 (142–86)</td>
<td>78 (86–63)</td>
<td>0.002</td>
<td>141 (173–128)</td>
<td>0.005</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>80 (95–65)</td>
<td>57 (64–47)</td>
<td>0.005</td>
<td>96 (122–80)</td>
<td>0.002</td>
</tr>
<tr>
<td>DAP (mmHg)</td>
<td>61 (71–52)</td>
<td>48 (51–38)</td>
<td>0.005</td>
<td>79 (104–69)</td>
<td>0.005</td>
</tr>
<tr>
<td>CI (l min⁻¹ m⁻²)</td>
<td>3.6 (4.8–2.0)</td>
<td>3 (3.6–1.9)</td>
<td>0.005</td>
<td>3.5 (4.1–1.7)</td>
<td>0.09</td>
</tr>
<tr>
<td>SVR (dyne⁻¹ cm⁻³)</td>
<td>815 (1665–483)</td>
<td>619 (1160–441)</td>
<td>0.002</td>
<td>1064 (2335–773)</td>
<td>0.002</td>
</tr>
<tr>
<td>HR (min⁻¹)</td>
<td>87 (100–61)</td>
<td>80 (93–58)</td>
<td>0.005</td>
<td>70 (84–46)</td>
<td>0.005</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>12 (17–8)</td>
<td>11 (15–8)</td>
<td>0.2</td>
<td>16 (20–9)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*Baseline vs epidural.
**Epidural vs phenylephrine.

PF: pyloric flux; AF: anastomotic flux; SAP: systolic arterial pressure; MAP: mean arterial pressure; DAP: diastolic arterial pressure; CI: cardiac index; SVR: systemic vascular resistance; HR: heart rate; CVP: central venous pressure.
the gastric tube. It is possible that untreated thoracic epidural-induced hypotension contributes to the development of anastomotic leaks by increasing the incidence of gastric tube necrosis at the site of the anastomosis. The incidence of postoperative hypotension in patients receiving a thoracic epidural for analgesia post-oesophagectomy is unknown, although studies suggest that hypotension occurs in 20% of patients receiving epidural analgesia after abdominal surgery [19].

An earlier prospective observational study using a laser Doppler technique showed that when compared with baseline and systemic opiates, an 18-h thoracic epidural increased Doppler technique showed that when compared with baseline and blood pressure. There is also animal experimental evidence infusion was associated with limited changes in cardiac index and blood pressure. There is also animal experimental evidence to show that thoracic epidurals may improve gastric microcirculation during gastric tube formation [21], although, again importantly, in this study administering thoracic epidural bupivacaine was associated with an increase in cardiac output and right gastroepiploic blood flow. However, at a mucosal circulatory level, blood flow is largely regulated by the cumulative cross-sectional area of the capillary bed and the arterio-venule pressure gradient, which is determined by the patient’s blood pressure. It is possible that on balance, the arterio-venous pressure gradient has a more important role in maintaining mucosal blood flow, hence the improvement in flux measurement observed in this study in response to the administration of intravenous vasoconstrictor. There is evidence to suggest that thoracic epidural use is associated with a decrease in the incidence of anastomotic leaks after oesophagectomy [22]. Thoracic epidurals are widely used to provide post-oesophagectomy analgesia as there is evidence from non-randomized trials to suggest that patients receiving thoracic epidurals after oesophagectomy have better analgesia [23], fewer respiratory complications [24], spend less time in intensive care [24] and have a lower mortality [24, 25]. We agree that there is accumulating evidence for the potential benefit of thoracic epidural analgesia in patients undergoing oesophagectomy. We do, however, consider that anaesthetists should be cautious in accepting intraoperative hypotension secondary to epidural administration or other causes in patients undergoing oesophagectomy. This study suggests that intra- and postoperative vasoconstrictors should be considered to maintain gastric tube blood flow in patients who are hypotensive during or shortly after an oesophagectomy. In conclusion, we have shown that the administration of a phenylephrine infusion reverses the epidural-induced decrease in flux at the anastomotic end of the newly formed gastric tube.

Conflict of interest: none declared.

REFERENCES