

Pulmonary morbidity following esophagectomy is decreased after introduction of a multimodal anesthetic regimen

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Abstract : Respiratory morbidity is the most frequent complication after esophagectomy, which can occur in 50% of the patients treated for esophageal cancer. We tested the hypothesis whether an anesthetic regimen, emphasizing intraoperative fluid restriction and early extubation could, positively influence postoperative morbidity, without affecting the gastric tube reconstruction. We introduced an anesthetic regimen, based on early extubation and a controlled intraoperative fluid management (net fluid balance < 4 L) in combination with the use of norepinephrine to maintain mean arterial blood pressure > 65 mmHg. Postoperative morbidity and mortality were compared with a similar group of patients operated one year before.

From June 2005 till September 2006, 83 patients were treated according to the new regimen (NR) and compared to a similar number of patients from the same period in 2003-2005 (standard regimen : SR). Applying the NR resulted in significantly less fluid administration (balance of 3.5 ± 0.2 L NR vs. 5.1 ± 0.2 L SR, $p < 0.05$) resulting in fewer patients developing pneumonia (26% in the NR group vs. 42% in the SR group, $p < 0.05$). Similar per operative blood loss and urine output and occurrence of leakage or ischemia of the gastric tube anastomosis occurred in both groups.

Respiratory morbidity is significantly reduced with the introduction of a new anesthetic regimen directed at intraoperative fluid restriction and early extubation, without increasing anastomotic leakage of the gastric tube reconstruction.

Key words : Abdominal surgery ; fluid therapy ; oesophagus ; postoperative care/recovery.

INTRODUCTION

Esophageal resection with gastric tube reconstruction is a major intervention with considerable postoperative morbidity. Despite improvements in surgical techniques and perioperative care, the postoperative course is often complicated, with respiratory morbidity as the most frequent (30-50%) non-surgical complication (1, 2).

Brodner and co-workers have shown that a multimodal approach consisting of thoracic epidur-

al analgesia, early tracheal extubation and forced mobilization postoperatively resulted in improved outcome after surgery (3). In our institution, the anesthetic regimen for esophagectomy consisted of general anesthesia in combination with thoracic epidural analgesia, followed by prolonged sedation and mechanical ventilation in the ICU. In order not to compromise gastric tube perfusion, hypotensive episodes were treated with administration of fluid, avoiding vasoactive medication. As a result, the net fluid balance largely increased in the first 24 hours, up to 10 L in some cases. It is not unlikely that this affects postoperative recovery. Recently, a reduction in per operative fluid administration has been shown to benefit patient recovery following abdominal surgery (4-6).

In an attempt to reduce our own morbidity rates, we decided to adjust our anesthetic regimen directed at early extubation and intraoperative fluid restriction in combination with the use of a vasopressor to maintain mean blood pressure above 65 mm Hg. To evaluate the effect of this regimen on

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postoperative morbidity, patients were compared with a similar number of patients operated one year earlier.

METHODS

Institutional Ethical Review Board (Erasmus University Hospital, Rotterdam) and written informed consent for the use of their data for scientific purposes were obtained.

1. Anaesthesia

In both the standard (SR) and new regimen (NR), general anesthesia was induced with propofol, fentanyl or sufentanil, and a non-depolarizing muscle relaxant, and maintained by inhalation anesthesia using sevoflurane and air. All patients were mechanically ventilated with a mixture of oxygen in room air (FiO₂ of 0.40) and a positive end expiratory pressure at 5 cm H₂O. In all patients hemodynamic monitoring consisted of radial arterial blood pressure and right atrial pressure measurements.

Before induction of general anesthesia, an epidural catheter was inserted at the mid-thoracic interspace (T6-T8) tested with 3 ml bupivacaine 0.5%. Before starting surgery, the epidural block was topped up with 10 ml bupivacaine 0.25%, directly followed by a continuous administration of a mixture of bupivacaine 0.125% with fentanyl 2.5 µg/ml at a rate of 10 ml/h throughout the operation and continued on the ICU. If no effective epidural block could be established per operatively, analgesia was provided with fentanyl intravenously, followed in the ICU by continuous administration of fentanyl 50-100 µg/hr i.v. in case of postoperative mechanical ventilation (in the SR group), or patient-controlled analgesia with morphine i.v. (bolus of 1 mg, lockout of 6-10') when extubated (in the NR group). In both groups, the presence of postoperative pain was continuously evaluated by an acute pain service using numeric rating scales. If necessary, infusion rates were adjusted or alternative forms of analgesia were used, until pain scores (Visual Analogue Scale) were less than four on a scale from zero (no pain) to ten (maximum pain).

In the SR group, propofol sedation and mechanical ventilation were continued overnight in the ICU. Depending on respiratory function, extubation occurred on postoperative day one. In the NR group, patients were extubated at the latest two hours after arrival at the ICU. To be extubated, the patient must be awake, cooperative, hemodynamic

stable, and having a temperature above 35,5°C and an oxygen saturation higher than 93% on 40% inspired oxygen.

2. Fluid and vasopressor therapy

In the SR group, fluid therapy was not strictly regulated. Each patient received 500-1000 ml colloid (Voluven®, hydroxyethylstarch 130 kD, Fresenius, 's Hertogenbosch the Netherlands) at the start of the procedure to compensate for the epidural induced vasodilatation. Maintenance infusion throughout the procedure was set at 10-15 ml/kg bodyweight/hr of crystalloid solution (saline or lactated Ringer's solution), aiming at mean arterial blood pressures (MAP) above 65 mm Hg and right atrial pressures (RAP) between 10 and 15 mm Hg. Persisting hypotension (MAP below 65 mm Hg) was first treated with administration of additional amounts of colloid, and if no adequate reaction (RAP > 15 mm Hg and MAP < 65 mm Hg) was obtained vasopressors were administered.

In the NR group, we aimed to reduce of the net per operative fluid balance below 4 liters. Crystalloids were administered in a maintenance infusion of 250 ml/hr and additional amounts were given until a diuresis of minimal 0,5 ml/kg/h is achieved. Mean arterial pressure was maintained at or above 65 mm Hg with administration of norepinephrine if necessary. No compensation for epidural related vasodilatation was administered and colloids were used 1 :1 to compensate for blood loss. Blood loss was calculated as the surgical aspirations and the weight of the used gauzes with a correction for fluid used for flushing the surgical area. ASA guidelines for erythrocyte transfusion were used (6). Standard fluid administration in the ICU consisted of 2 litres of fluid per 24 hours, 1500 ml crystalloid solutions and enteral feeding, which was started after arrival on the ICU at a 21 ml / h through a naso-jejunal feeding tube (positioned during surgery).

3. Data collection

Data were collected retrospectively (November 2003 – April 2005) and prospectively (June 2005 until September 2006). As such, 84 patients were included in the SR and 83 in the NR group. Patient characteristics, operation characteristics, total per operative blood loss, urine production and the types and volumes of infusion fluids that were administered during the procedure and the total per operative fluid balance were obtained

for each patient. In addition, the daily fluid balance on the ICU was recorded until the fourth post-operative day.

Postoperative surgical and cardiopulmonary 30 day-morbidity were scored in all patients. Surgical morbidity included leakage and/or ischemia of the gastric tube (determined by endoscopy or esophageal contrast videography), hemorrhage, chylothorax, recurrent nerve paresis, wound infection and pleural empyema. Cardiopulmonary morbidity included pneumonia (based on chest X-ray and positive sputum culture), arrhythmias, myocardial infarction, decompensatio cordis, lung emboli and cerebral infarction. Additionally, the frequency of re-intubation and re-admission to ICU, and in-hospital and 30 day mortality were scored. Finally, duration of intensive care and total hospital stay were recorded.

4. Statistical analysis

All continuous variables are described as mean \pm SEM or as median and range if not normally distributed; binominal variables are described in percentages. For analysis of between group differences an unpaired *t*-test, analysis of variance or a χ^2 test was performed. $P < 0.05$ was considered significant. All analyses were performed using SPSS 11.5 for Windows (SPSS inc, Chicago, USA).

RESULTS

Patient and procedural characteristics (Table 1) and tumour classification characteristics (data not shown) were similar in both groups. Significantly less crystalloid and colloid fluids were administered in the new regimen (NR) group, leading to a significantly less positive fluid balance at the end of the operation procedure, i.e. 3683 \pm 241 ml (NR) vs. 5100 \pm 277 ml (SR) (Table 2). Per operative urine production was 1.77 \pm 0.15 in the SR-group vs. 1.17 \pm 0.10 ml/kg/hr in the NR-group. There were no differences in both groups according to the per operative hemodynamics. Vasopressors were used in 79% (SR) versus 75% (NR) considered not significant. In the ICU, daily fluid balance was only lower in the NR group on the day of surgery (Fig. 1).

All patients in the NR group were extubated, according the protocol, in the operation room or in the 2 hours after entering the ICU.

Postoperative data are shown in Table 3. The incidence of postoperative pneumonia was signifi-

Table 1

Patient and surgical characteristics

	SR (n = 84)	NR (n = 83)
Male / Female (%)	73 / 27	69 / 31
Age (year)	63 \pm 2	62 \pm 1
Bodyweight (kg)	81 \pm 3	79 \pm 2
ASA I/II/III	29 / 50 / 21	23 / 58 / 19
Type surgery :		
THO/TTO (%)	83 / 17	78 / 22
Successful TEA (%)	96	92
Time surgery (min)	235 \pm 7	229 \pm 7
Time total procedure (min)	328 \pm 11	329 \pm 9

SR = standard regimen; NR = new regimen; ASA : American Society of Anesthesiologists classification; type of surgery : transhiatal (THO) and transthoracic (TTO) oesophagectomy; TEA : thoracic epidural analgesia. Data are expressed as percentage of total or as mean \pm SEM.

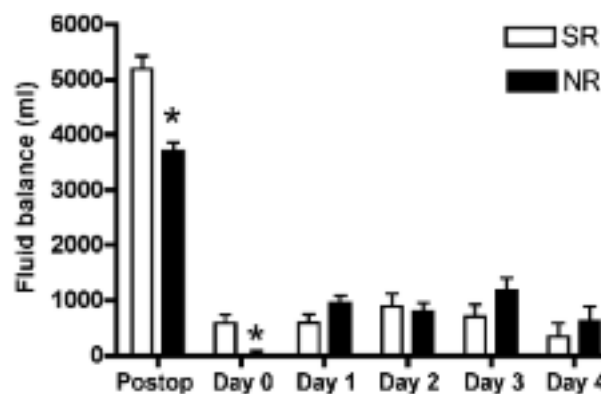
Table 2

Peroperative fluid therapy

	SR (n = 84)	NR (n = 83)
Fluids in		
Crystalloids (ml)	5630 \pm 189	3670 \pm 266 *
Colloids (ml)	1917 \pm 94	1460 \pm 77 *
Packet cells (ml)	589 \pm 43	600 \pm 133
Fluids out		
Blood loss (ml)	1432 \pm 92	1129 \pm 115
Urine production (ml/kg/hr)	1.77 \pm 0.15	1.17 \pm 0.10
Total fluid balance (ml)	+ 5100 \pm 277	+ 3683 \pm 241 *

SR = standard regimen; NR = new regimen. Data are expressed as mean \pm SEM.

* $P < 0.05$ vs. standard regimen.



SR = standard regimen, NR = new regimen. Postop reflects the fluid balance directly following surgery whereas Day 0 reflects the fluid balance on the ICU from the remaining part of the day. Data expressed as mean \pm SEM; * $P < 0.05$ vs SR.

Fig. 1. — Fluid Balance following esophagectomy.

cantly reduced in the NR group compared to SR group ($p < 0.01$) while the reintubation rate was not significantly different between groups. Total cardiopulmonary morbidity was significantly reduced

Table 3
Morbidity and mortality following esophagectomy

	SR (n = 84)	NR (n = 83)	P-value
<i>Surgical morbidity</i>			
Leakage anastomosis	13	14	1.000
Recurrent nerve paresis	10	5	0.274
Wound infection	8	5	0.767
Chylothorax	3	1	0.360
Pleural empyema	7	3	0.322
Bleeding/haematoma	3	1	0.360
<i>Total</i>	33	24	0.285
<i>Cardio-pulmonary morbidity</i>			
Arrhythmias	9	10	1.000
Pneumonia	42	16	< 0.01
CVA	1	4	0.369
Decompensatio cordis	5	2	0.436
Pulmonary Embolism	2	2	1.000
Myocardial infarction	1	0	0.489
<i>Total</i>	44	26	0.012
ICU re-admission	7	7	1.000
Re-intubation	23	14	0.177
<i>Mortality</i>			
Overall 30 days morbidity	68	50	0.023
30 days mortality	4	3	0.398
In hospital mortality	9	5	0.398
<i>Duration</i>			
ICU stay	4 (2-65)	4 (1-57)	0.062
Hospital stay	17 (9-94)	14 (8-72)	0.095

SR = standard regimen ; NR = new regimen. Data expressed as percentage of group total or (for Duration) median (range).

in the NR group, which is attributed in particular to the decreased occurrence of pneumonia (Table 3).

Overall 30-day morbidity was significantly less in the NR group (50%) compared to the SR group (68%) (Table 3). Although in-hospital mortality was lower (5%) in the NR group than in the SR group (9%), this was not significantly different. ICU and hospital stay were comparable in both groups (Table 3).

DISCUSSION

With the introduction of an adjusted anesthetic regimen, directed at early extubation and conservative fluid management, based on the patients' urine output, postoperative pulmonary morbidity in patients undergoing esophagectomy could be significantly reduced. Our fluid management resulted in a lower positive fluid balance less than four litres.

The role of intraoperative fluid therapy in major abdominal surgery patients is subject of an ongoing debate. Recent clinical trials investigating the effect of a restrictive fluid management found a

significant reduction in postoperative complications (4-6). In contrast, studies using the goal directed fluid therapy (based on optimization of stroke volume) found a reduction in postoperative morbidity and hospital stay but to reach this goal more fluid had to be administered (7, 8). Looking specifically at esophagectomy patients, several studies actually favour fluid restriction (9, 10). Neal and colleagues used an intraoperative fluid replacement therapy, guided by urine output of minimal 0.5 ml/kg/h in 56 patients undergoing esophagectomy. If urine output fell below these parameters, extra fluid was administered. In addition, vasopressors and extra volume were used to maintain blood pressure. Limited fluid administration was not associated with high morbidity rates but it was shown to reduce the need for postoperative bronchoscopy and tracheotomy (11).

These observations can be explained by the systemic inflammatory response induced by esophagectomy, leading to a fluid shift, accumulation of fluids in the extra vascular space and hence pulmonary edema (12). Administration of steroids, suppressing the inflammatory response and the concomitant fluid shift, was shown to reduce postoperative respiratory morbidity and organ dysfunction in these patients (13, 14). However, their benefit is not undisputed and steroids are not used for this purpose in our institution (15).

In our study we did not only apply restrictive fluid management but we also extubated the patients earlier. Several studies have already shown that a short interval between surgery and extubation is associated with lower morbidity rates (16-18). It can be hypothesized that early extubation actually contributed to less postoperative pulmonary morbidity because it led to a significantly smaller positive fluid balance due to less sedation-related hypotensive episodes. This is supported by the observation that after the operation day, daily fluid balances were similar in both groups.

The incidence of pulmonary complications varies in literature. Recently Orringer reported 2% pneumonia/atelectasis in two thousand transhiatal esophagectomies, describing the clinically significant pneumonia prolonging the hospital stay beyond 10 days (19). In an English multi-centre study, pulmonary complications occurred in 40.5% of the patients following esophagectomy (20). These variations can be due to the use of definitions. Defining pneumonia is difficult in patients after surgery because increased temperature, numbers of leukocytes and levels of C-reactive protein are usually increased. In addition, the postoperative

chest X-ray leads to confusing results with atelectasis, pleural effusion, pulmonary contusion and venous congestion interfering with infectious infiltrates. We defined pneumonia as an infiltrate on the chest X-ray in combination with a positive sputum culture. Using this definition our incidence in pneumonia decreased significantly from 42% to 16%.

Our incidence of leakage of the cervical esophagogastronomy is relative high (13% (SR) and 14% (NR)) but it is within the normal range (5-26%) (21). Results of anastomotic leakage reported in literature are confusing because in trans-thoracic esophagectomy it is not always clear if a cervical- or intrathoracic anastomosis is studied. Also the discrimination between clinical significant and radiological findings is confusing. In this study, all the anastomotic leakages, determined by endoscopy or esophageal contrast videography, are reported.

In conclusion an anesthetic regimen directed at a restricted preoperative fluid management, using a well-defined haemodynamic endpoint of fluid resuscitation and early extubation, could reduce the pulmonary morbidity rates following esophagectomy. Because of the complexity of perioperative management of esophagectomy with gastric tube reconstruction the introduction of standardized clinical care pathways should be encouraged by hospital administration and healthcare authorities.

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