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## Thoracic epidural analgesia or intravenous morphine analgesia after thoracoabdominal esophagectomy: a prospective follow-up of 201 patients.

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**Thoracic epidural analgesia or intravenous morphine  
analgesia following thoraco-abdominal esophagectomy:  
A prospective follow-up of 201 patients.**

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## Abstract

**Objective:** Thoraco-abdominal esophagectomy is a major surgical procedure that carries significant postoperative morbidity and mortality. Since the choice of analgesic technique may influence outcome, the impact of thoracic epidural or intravenous analgesia was investigated following esophagectomy.

**Design:** Prospective observational study during January 1996 until January 2002.

**Setting:** University hospital.

**Participants:** All patients undergoing thoraco-abdominal esophagectomy during the period.

**Interventions:** Patients were prospectively monitored during a six-year period. Duration of surgery, intraoperative blood loss, fluid administration, postoperative intubation time, ICU stay, pain relief and related side effects, postoperative complications, hospital stay, in-hospital and long-term mortality were compared in relation to analgesic technique.

**Measurements and Main Result:** Thoracic epidural analgesia with bupivacaine/morphine was utilized in 166 patients, and intravenous morphine analgesia was used in 35 patients.

Postoperative intubation time and ICU stay were similar in both groups. Patients with epidural analgesia experienced less pain. Sedation, respiratory depression, hallucinations and confusion were more common in the intravenous morphine group. Postoperative weight did not differ between the groups, despite fluid replacement was higher in the epidural group during the first 24 h. The in-hospital mortality rate was 0.5 %.

**Conclusions:** No differences in morbidity/mortality rates depending on analgesic treatment were observed in patients undergoing thoraco-abdominal esophagectomy. Thoracic epidural analgesia provided better pain relief with fewer opioid related side effects than intravenous morphine analgesia. However, postoperative epidural analgesia was associated with more technical difficulties.

## **Key Words**

Adverse effects: Sedation; Pruritus; Leg weakness; Respiratory depression;

Analgesia: Postoperative;

Drugs: Epidural bupivacaine/morphine; Intravenous morphine;

Epidural catheter placement; Thoracic;

Morbidity/Mortality: Surgical; Postoperative;

Surgery: Esophagectomy; Thoraco-abdominal;

Duration: Postoperative analgesia; Hospital stay; ICU stay;

Endotracheal intubation;

## Introduction

It has been recommended that esophagectomy should be conducted in large numbers at major hospitals to achieve the most favorable outcome (1;2). Esophagectomy is a major surgical procedure associated with a relatively high perioperative morbidity and mortality, and the patients have a high incidence of coexisting disease (3;4). Factors contributing to the survival rates for these patients are the surgical technique and perioperative care.

The perioperative use of thoracic epidural analgesia for esophagectomy is beneficial since it provides more efficient pain relief during mobilization compared to intravenous analgesia (5). In addition, postoperative epidural pain relief shortens the duration of endotracheal intubation, intensive care stay, and causes less perioperative complications (3;6-11).

Previous reports regarding morbidity/mortality following esophagectomy often evaluate retrospective patient populations operated over an extended time period and including a limited number of patients (6;12-14). In the present prospective clinical study, we monitored 201 consecutive thoraco-abdominal esophagectomies performed during a six-year period, 1996-2002, at Lund University Hospital. We aimed at investigating differences in outcome based on the analgesic technique. Pain relief with associated side effects, fluid management, postoperative intubation, extended intensive care stay, total hospital stay, perioperative complications and mortality were the major determinants in this study.

We hypothesized that combined general anesthesia and thoracic epidural analgesia followed by postoperative patient controlled epidural pain relief would result in more efficient analgesia, lower complication rates, earlier discharge from the hospital and lower mortality

than if the patients received general anesthesia with subsequent patient controlled intravenous morphine analgesia.



## Methods

The Ethics Committee at Lund University Hospital gave its approval to the study. Prospective data sheets related to the analgesic treatment, medical records, and a surgical database were reviewed for perioperative events. According to the committee, written patient consent was not needed for this review, but patients had the possibility to decline participation in the study following a newspaper advertisement outlining the investigation.

This observational study included all patients undergoing thoraco-abdominal esophagectomy from January 1996 until January 2002 at the Department of Surgery, Lund University Hospital. The patients were prospectively planned for general anesthesia combined with thoracic epidural anesthesia followed by postoperative continuation of the epidural blockade, or general anesthesia with postoperative intravenous analgesia, respectively. Selected data from 175 patients included in this investigation has been included as a part of a large clinical study including 2,696 patients (15).

The esophagectomy was made through separate abdominal and posterolateral right chest incisions. The abdomen was explored through an upper midline incision. In patients with limited disease the most proximal part of the stomach including perigastric lymph nodes along the coeliac trunk and along the left gastric artery were removed *en bloc* with the esophagus. A less extensive lymph node dissection was performed in patients with advanced disease. The spleen was usually salvaged. The thoracic part of the esophagus was resected through the right posterolateral thoracotomy and included a dissection of paraesophageal lymph nodes. The exposed lung was gently retracted by one of the assisting surgeons. If any oxygenation difficulties occur, the lung was briefly allowed to expand. The esophageal substitute consisted either of a gastric tube, or a jejunal or colon interponate. Four staff surgeons were responsible

for the surgical procedures. Tumor classification was performed according to the TNM classification suggested by the International Union against Cancer (UICC).

Thoracic epidural analgesia was used unless generally accepted contraindications to epidural blockade were present, technical difficulties with epidural catheter placement occurred, or the epidural technique was deferred by the patient. On the morning of surgery, with the patient in a sitting position, an anesthesiologist inserted the epidural catheter with a midline approach through a vertebral interspace between Th6-L1. The epidural space was identified by the loss of resistance technique. Before induction of general anesthesia, an epidural bolus dose of 3 - 4 ml mepivacaine 20 mg/ml (Carbocain® 2%, AstraZeneca, Sweden) was injected, and intrathecal catheter placement was ruled out. A transparent dressing affixing the catheter to the skin enabled daily inspections of the insertion site. The rest of the catheter was taped along the left side of the patient's back. Twenty anesthesiologists were involved with the anesthetic management over the six-year period and assisted by senior residents or CRNA's.

Induction of general anesthesia was performed with thiopental and fentanyl. Endotracheal intubation with a standard single-lumen oro-tracheal tube was facilitated using succinylcholine or rocuronium. Maintenance of general anesthesia with mechanical ventilation was performed with oxygen/nitrous oxide and a volatile anesthetic agent, incremental doses of fentanyl, and a non-depolarizing muscle relaxant. The epidural blockade was established during general anesthesia with a bolus dose of 2 - 4 mg preservative free morphine, and 4-6 ml mepivacaine 20 mg/ml followed by 5-8 ml/h. In patients without epidural anesthesia, the intraoperative analgesic treatment was titrated with 50-200 µg doses of fentanyl, or alternatively an IV fentanyl infusion of 50-200 µg/h. Dopamine was infused at 1-5µg/kg/h to maintain systemic blood pressure during the epidural blockade (16).

Depending on the duration of surgery, and the attending anesthesiologist's judgment of the patient status, the patient was extubated in the operating room, or transferred intubated and sedated to the intensive care unit (ICU). In general, the patient was extubated in the operating room if the surgical procedure lasted less than eight hours, was younger than 70 years, normothermic with no history of reduced ventilatory capacity or cardiac disease. All patients were equipped with a nasogastric tube, urinary catheter, and two chest tubes placed in the right pleural cavity.

Postoperative analgesia was started at the end of surgery. For epidural analgesia a solution of bupivacaine 2.5 mg/ml and morphine 0.05 mg/ml was utilized at 1-5 ml/h plus patient controlled analgesia (PCEA) in doses of 1-5 ml with a lockout interval of 30 minutes (EPI group). Intravenous morphine was started at the end of surgery (IV group) in patients without an epidural catheter. The continuous infusion was set at 1-2 mg/h, and the patient controlled analgesia PCA mode at 0.5 - 2 mg with a lockout interval of 10 minutes. In all patients the primary intent was to continue the analgesic treatment until at least the 6<sup>th</sup> postoperative day. According to departmental standards the chest tubes were pulled on the 6-7<sup>th</sup> postoperative day following a chest x-ray with contrast swallow, or later if there were suspicions of an intrathoracic leak.

In the surgical ward with the patient extubated and awake, the nurses recorded heart rate, respiratory rate and level of sedation every third hour during the analgesic treatment. Pain was evaluated by the patients with an 11-point verbal numeric rating scale (NRS-11) at rest and during mobilization (17;18). A NRS level less than 4 at rest was considered as an adequate

level of analgesia (19). An anesthesiologist visited the patient daily for treatment evaluation, dose adjustments, and registration of treatment and side effects.

Data were obtained from medical records, a surgical database, and a database for the prospectively registered pain treatment. Demographics such as age, weight, gender, surgical diagnose, ASA classification, and co-existing disease were obtained. A history of congestive heart failure and COPD were defined by previous diagnosis and current medication. The day of surgery was defined as Day 0, the first postoperative day as Day 1, etc. However, the weight on Day 0 was determined the day before surgery. Perioperative data such as surgical procedure, duration of surgery, blood loss, fluid administration the first 24 h, the use of inotropic drugs, postoperative intubation time, ICU stay, hospital stay and in-hospital mortality were recorded. Prolonged ICU stay was defined as greater than 48 h. To evaluate a relationship between fluid administration, and cardio-respiratory complications, we divided the patients into three arbitrary groups according to fluid administration during the first 24 h from start of anesthesia: low (0-6000 ml), medium (6001-11,000 ml) and high (>11,000 ml), respectively. The frequency of atrial fibrillation and pulmonary complications (respiratory insufficiency, pneumonia, aspiration, pneumothorax, and pleural effusion) were reported separately for each group. Colloids, i.e. hydroxyethyl starch, dextran, and plasma, administered during the first 24 h from start of anesthesia, were summarized as one entity for each group.

Perioperative complications as reoperation, sepsis, cardio-pulmonary events including atrial fibrillation, respiratory failure, and side effects related to the pain regimen (nausea/vomiting, pruritus, sedation, respiratory depression, orthostatism, insufficient treatment, nightmares, hallucinations and confusion) were registered. Nausea/vomiting reported by the nurse or

patient, and pruritus necessitating treatment were registered. Sedation was defined as difficulty awakening the patient verbally. Respiratory depression was defined as a respiratory rate less than 8 breaths/min. Orthostatism was defined as a reaction with dizziness during mobilization. Lower limb motor blockade was defined as inability to ambulate due to muscular weakness or discomfort from reduced limb control. Interrupted analgesic treatment was defined as treatment terminated earlier than planned due to inadequate pain relief, epidural catheter displacement or adverse effects. Insufficient analgesia necessitating change of analgesic technique was recorded. In-hospital mortality was defined as any cause of in-hospital death within 30 days of the primary surgical procedure.

## **Statistics**

Data were analyzed using SPSS for Windows (version 11.5, Chicago, Illinois). Nominal data were compared by Fisher's exact test or by the Chi-square test. Friedman's test was performed for comparisons between groups when more than two sets of data were assessed within the same treatment group. For pairwise comparisons of continuous variables the Mann-Whitney U- test was used for non-related samples. Mortality was expressed as cumulative survival according to the Kaplan-Meier method. Data was expressed as median (range) unless otherwise indicated. A p-value less than 0.05 was considered statistically significant.

## Results

During a six-year period, from January 15, 1996 until January 14, 2002, 201 consecutive patients undergoing esophagectomy were investigated at the Department of Surgery, Lund University Hospital. Twelve patients were diagnosed with non-malignant disease (EPI 9 vs. IV 3, ns.), and 189 with esophageal cancer (EPI 157 vs. IV 32, ns.). For demographic data see Table 1. The EPI group included 166 patients and the IV group 35 patients. Patients received general anesthesia combined with postoperative intravenous analgesia due to sciatic pain (n=13), clotting disorder (n=7), patient deferral (n=4), carcinoid disease (n=1), technical difficulties (n=8), and undocumented reason (n=2). The primary analgesic treatment was maintained for approximately 6 days in both groups (Table 2). In the EPI group, 83 % of all epidural catheters were inserted between Th 6-10. Seven patients (4 %) with postoperative epidural analgesia demonstrated signs of lower limb motor block. In these patients the epidural catheter was inserted between Th 7-8 (n=1), Th 8-9 (n=2), Th 10-11 (n=1), Th 11-12 (n=2) and L1-2 (n=1).

Despite the same therapeutic goal for adequate pain relief at rest, the overall NRS scoring was significantly lower in the EPI group compared with the IV group, both at rest and during mobilization, on postoperative Day 1 ( $p<0,02$  and  $p<0,001$  respectively; Fig 1). Analgesic drug utilization is presented in Table 2. The analgesic infusion rate decreased over time in both groups ( $p<0.001$ ; Fig 2).

Opioid related side effects, such as sedation, respiratory depression, hallucinations and confusion were more common in the IV group than in the EPI group (Table 2). The epidural treatment was terminated earlier than planned in 62 patients due to insufficient analgesia

(n=23), catheter displacement (n=27), orthostatism (n=5), motor blockade (n=5), and hallucinations (n=2). Seventeen of these patients were switched to intravenous morphine PCA, the other patients received sc morphine as needed. In the IV group the treatment was stopped earlier than intended in 9 patients due to confusion (n=3), hallucinations (n=4), sedation (n=3), insufficient analgesia (n=3), and respiratory depression (n=2). Six patients in the IV group had more than one reason for early termination. One IV patient was switched to epidural therapy after 26 days.

An inflammatory reaction around the insertion site of one epidural catheter was detected during removal of the catheter. A bacterial culture of the catheter tip demonstrated growth of *Stenotrophomonas maltophilia*. However, the patient had no signs of systemic infection.

Thirty-four patients were extubated immediately after surgery (29/166 in the EPI group, and 5/35 in the IV group; ns). The median postoperative intubation time was 9 h (EPI 9.4 (1-65) h vs. IV 9.3 (1-67) h) for patients transferred intubated to the ICU. Respiratory complications such as respiratory insufficiency, pneumonia, and pleural effusion were reported in 28 patients with no difference between the EPI and IV groups (22/166 vs. 6/35 patients, respectively; ns). There was no correlation between the amount of intravenous fluids (low, medium or high volume treatment) during the first 24 hours and postoperative respiratory failure.

Intraoperative blood loss and blood replacement were similar in both groups (Table 3). The patients' weight changes are summarized in Fig 3. A significant weight increase ( $p<0.001$ ) compared to the preoperative weight occurred in both groups on Day 1 EPI 3.1 (-2.4 – 7.5) kg vs. IV 2.6 (-0.5 – 4.4 kg), respectively; ns). Although the total colloid/crystalloid

administration during the first 24 h was higher in the EPI group, there were no apparent differences in the postoperative weight changes between the groups. From Day 1, the patient weights gradually decreased in both groups until Day 4.

Dopamine was more often used intraoperatively, i.e. to restore cardiac output and maintain MAP > 60mmHg, in the EPI group, whereas ephedrine, dobutamine, and norepinephrine were utilized to a similar extent in both groups (Table 3). Fifteen patients in the EPI group compared to one patient in the IV group (ns) experienced postoperative atrial fibrillation without any correlation to patient age, and fluid volume during the first 24 hours from start of anesthesia.

Thirty-five patients (17%) were treated more than 48 hours postoperatively in the ICU (EPI 27/166 vs. IV 8/35; ns), (Table 4). Nine patients with prolonged ICU stay had circulatory, 22 respiratory, 3 infectious, and 8 miscellaneous complications. Six patients had more than one complication. The circulatory group included four patients with atrial fibrillation, three with unspecified arrhythmias, and two with circulatory instability. The 22 patients with respiratory complications and prolonged ICU stay include 16 patients with respiratory failure (average ICU stay 5.6 days), one patient with pneumothorax, one with delayed extubation due to an endotracheal metastasis, two patients with aspiration, and two patients with pleural effusion. However, our data also show that only 5 patients had to be reintubated.

Infectious complications included three patients with sepsis. The miscellaneous group included one patient with necrotic gastric tube, two patients with anastomotic leakage, three patients with bleeding, one patient with renal failure, and one patient with insufficient analgesia. The patient with pneumothorax and two of the patients with bleeding were brought



back to the operating room for early reoperation. Three of the patients with prolonged postoperative ICU stay were readmitted to the ICU.

The overall in-hospital mortality was 0.5 % (1/201). The patient was previously treated for pulmonary tuberculosis, and died intraoperatively due to uncontrollable intrathoracic blood loss. Another patient died 153 days following esophagectomy due to recurrent cancer while still in the hospital. The long-term mortality did not differ between the groups. The one-year survival for patients with esophageal cancer was 67% and the five-year survival was 37 %. In addition, we found no difference in tumor classification between the groups (Table 1).

## Discussion

The present prospective study of 201 patients undergoing thoraco-abdominal esophagectomy demonstrates that the choice of anesthetic technique and postoperative analgesic method influence pain relief, the incidence of opioid related adverse effects, and fluid replacement. However, no impact on prolonged postoperative ICU stay and hospitalization time could be referred to group assignment. Only one patient died within 30 days following esophagectomy.

Adequate analgesia following esophagectomy is important for early postoperative mobilization, and may reduce the frequency of cardio-pulmonary complications (3). The patients treated with intra- and postoperative epidural analgesia in the present study experienced better pain relief at rest and during mobilization than patients treated with IV morphine. We found that the 0.25 % bupivacaine/0.005 % morphine epidural mixture is useful even with an infusion rate set as low as 3-5 ml/h for several days. The analgesic dose can be reduced over time with maintained pain relief which is in accordance with Tiippana et al. (20). Factors such as early onset analgesia preventing wind up phenomenon, little or no tachyphylaxis due to the mixture of epidural local anesthetics and opioids, and decreasing pain intensity over time, may all contribute to this finding. However, we also observed a similar decrease over time in IV morphine treated patients.

A drawback with the epidural regimen, however, was that in one third of the patients in the epidural group the treatment was stopped earlier than planned due to insufficient analgesia and/or catheter displacement. Rigg et al. (21) showed that 42% of the epidural catheters were removed before the stipulated 72 h. Tiippana et al. (20) showed that 24% of the epidural treatments were terminated earlier than planned, although only 19% was due to catheter

displacement. By inserting 4-6 cm of the catheter into the epidural space, and applying a proper catheter dressing (22), the frequency of catheter dislocation can be diminished (23). Our observation underscores the importance of adequate handling with correct catheter placement, dosage and follow-up to provide a beneficial analgesic regimen following an advanced surgical procedure in high-risk patients.

Lower extremity motor blockade and orthostatic reactions during mobilization may also limit the use of postoperative epidural analgesia. Utilizing a higher vertebral interspace for the catheter placement can prevent such drawbacks. Since three patients in our study experienced motor blockade even with the epidural catheter placed at Th 7-8 or 8-9, a less concentrated local anesthetic solution may resolve the lower extremity weakness in such instances.

Opioid related side effects such as sedation, hallucination, confusion and respiratory depression were more common in the iv morphine group, and mental disturbance was the main reason for interrupted iv treatment. Our previous study of 2,696 patients demonstrated a higher incidence of sedation, confusion, hallucinations, and nightmares when intravenous morphine PCA was used compared to epidural analgesia (15). This finding is important to bear in mind, since the awareness of opioid related complications in the postoperative period is more focused on late respiratory depression induced by epidural opioids.

Moderate fluid administration has been recommended in the perioperative period (24;25), whereas others advocate larger fluid volumes (26) to improve patient outcome. The crucial issue is to calculate the individual fluid requirements. Commonly, monitoring of hemodynamic variables and simple algorithms for fluid replacement are used. For obvious reasons transesophageal echocardiography cannot be used during esophagectomy, and pulmonary catheter placement may be associated with serious complications with little

evidence that the use of the catheter will impact patient outcome (27;28). We found that larger amounts of colloids and crystalloids were administered the first 24 h in the EPI group compared to patients receiving general anesthesia and postoperative IV morphine analgesia. Previous studies have shown that the fluid load is higher in patients with regional blockades (29-31). Thoracic epidural anesthesia usually induces a sympathetic blockade reflected in lower blood pressure and regional blood flow. At our institution we commonly counteract the diminished sympathetic activity by combining a low dose of an inotropic drug, such as dopamine (16), with crystalloids and colloids to maintain systemic perfusion pressure. The desired goal is to restore the mean arterial pressure to 60-80 mmHg and keep the cardiac output around 4-5 l/min combined with a low vascular resistance to maintain adequate regional blood flow. During an extensive thoracic epidural anesthetic a dopamine infusion rate at 2-4 µg/kg/min is sufficient to achieve this goal. The technique may limit an otherwise extensive fluid load to restore hemodynamic stability, and Neal et al. demonstrated low postoperative morbidity when a multimodal approach including intraoperative fluid restriction was utilized (32).

A useful and important method to monitor postoperative fluid balance is to obtain a daily patient weight. The goal at our institution is to normalize the preoperative weight within three to four days, aiming at a negative fluid balance by using furosemide. Although there was a difference in perioperative fluid administration between the groups, there was no difference in the daily postoperative weight. In addition, the postoperative weight increase was moderate and transient over a three-day period.

Thirty-five patients had one or more complications that prolonged the ICU stay with readmission of three patients. The most common complication was respiratory failure

followed by circulatory complications. This is in agreement with Whooley et al. (4). Tsiu et al. (3) reported postoperative respiratory failure in 13% of the patients, while Tandon et al. (33) reported 24 % in their study. Different patient characteristics and clinical practice may contribute, since Tandon et al. reported an average ICU stay of 17 days due to respiratory failure compared to 6 days among our patients, and an early mortality rate of 27 % compared to our <1 %. Another reason for the different outcomes could be our use of two-lung ventilation with a standard single-lumen endotracheal tube during surgery. At our hospital the non-dependent lung is manually and intermittently retracted for surgical access. The airway pressures may remain lower than during one-lung ventilation with a lesser risk of barotrauma and need for high oxygen partial pressures (34). High FiO<sub>2</sub> and airway pressures are well-known causes of lung injury during mechanical ventilation (35-37), and one-lung ventilation may induce lung tissue injury by an ischemia/reperfusion mechanism by collapsing and re-expanding the non-dependent lung (33). However, Tachibana et al. (38) did not find any difference in respiratory complications between one- and two-lung ventilation during esophagectomy. In the present study we found no difference in postoperative respiratory complications between the groups, and there was no correlation to the extent of perioperative fluid administration. Adequate pain relief, moderate perioperative fluid therapy, and active postoperative dehydration in both groups may have minimized postoperative respiratory complications.

Thirty-four patients were extubated immediately after surgery, and the rest of the patients had a median postoperative intubation time of nine hours. Caldwell et al. advocate early extubation compared to extubation 24 h after esophagectomy. They found fewer cardiac complications, shorter ICU stay, and lower 90-day mortality (39). Chandrashekar et al. recommend early extubation and a brief period with one-lung ventilation to minimize lung

trauma (40). Our low incidence of respiratory complications may be related to the intraoperative two-lung ventilation and early extubation once the patient is normothermic, pain free, and awake with stable hemodynamics.

Atrial fibrillation often occurs after thoracic surgery (11). Whooley et al. (4) reported an incidence of 23% after esophagectomy. In our study sixteen patients (10%) suffered from atrial fibrillation postoperatively. There was no significant difference between the EPI and IV group, and no correlation to fluid administration or patient age, although Scott et al (11) have found that thoracic epidural anesthesia may diminish the incidence of supraventricular arrhythmias. Our perioperative regimen with early return to preoperative body weight could explain our generally low incidence of atrial fibrillation. Hypothetically, an even more restricted fluid therapy may further diminish the incidence of atrial fibrillation in patients treated with epidural analgesia following esophagectomy.

The average time for surgery (10.5 h) in our study is high compared to other studies (3;38). The surgical approach at our institution with an en-bloc resection of the esophagus and atraumatic handling of the tissues with extensive lymph node dissection may explain the longer surgical duration. Most likely the patients in our cohort benefit from this approach with a very low (0.5%) in-hospital mortality rate, and high (37%) five-year survival rate. In comparable reports the in-hospital mortality is 3 - 23 % (2-4;40-44) and the five-year survival 16-40% (42;43;45;46).

In conclusion, we found that irrespective of analgesic regimen, esophagectomy resulted in low morbidity/mortality rates and similar hospital stay. Thoracic epidural analgesia provides more efficient pain relief and less opioid related side effects than intravenous analgesia,

although the epidural technique was associated with more technical difficulties. Although patients in the epidural group received more crystalloids/colloids during the first 24 hours we found similar distribution of complications, ICU/hospital stay and mortality. In our opinion thoracic epidural analgesia provides a better analgesic therapy following thoraco-abdominal esophagectomy than intravenous opioids.

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**Table 1: Demographic data.**

	<b>EPI group</b>	<b>IV group</b>	<b>p</b>
<b>Age, yrs, median (range)</b>	65 (27-86)	65 (37-82)	ns
<b>Gender, % (n)</b>			
<b>Male</b>	73 (121)	69 (24)	ns
<b>Female</b>	27 (45)	31 (11)	ns
<b>Preoperative weight, kg</b>	72 (40-119)	71 (49-125)	ns
<b>Height, cm</b>	173 (148-189)	174 (158-194)	ns
<b>ASA classification, % (n)</b>			
<b>I</b>	30 (50)	14 (5)	ns
<b>II</b>	59 (98)	66 (23)	
<b>III</b>	11 (18)	20 (7)	
<b>Diagnosis % (n)</b>			
<b>Cancer of the esophagus</b>	95 (157)	91 (32)	ns
Stage 0	10 (16)	20 (7)	ns
Stage I	5 (8)	3 (1)	
Stage IIA	15 (25)	11 (4)	
Stage IIB	7 (11)	14 (5)	
Stage III	32 (54)	29 (10)	
Stage IV	8 (13)	3 (1)	
No staging available	18 (30)	11 (4)	
<b>Non-malignant disease</b>	5 (9)	9 (3)	ns
<b>Medical history, % (n)</b>			
<b>Previous MI</b>	7 (12)	6 (2)	ns
<b>Hx of CHF</b>	2 (4)	0	ns
<b>Hx of angina pectoris</b>	4 (6)	14 (5)	ns
<b>Hx of COPD</b>	11 (18)	3 (1)	ns
<b>Diabetes mellitus</b>	7 (12)	3 (2)	ns
<b>Medication, % (n)</b>			
<b>Insulin</b>	2 (3)	0	ns
<b>Beta-blockers</b>	11 (19)	14 (5)	ns
<b>Digoxin</b>	1 (2)	11 (4)	<0,01
<b>ACE-inhibitors</b>	4 (6)	3 (1)	ns
<b>Bronchodilators</b>	7 (11)	0	ns



**Table 2: Postoperative analgesia. Drugs and side effects.**

	<b>EPI group</b>	<b>IV group</b>	<b>P</b>
<b>Patients (n)</b>	166	35	
<b>Drugs</b>			
<b>Morphine, mg/h</b>	0.2 (0-0.6)	1.5 (0.8-3,1)	0.001
<b>Bupivacaine, mg/h</b>	9.6 (1-29)	--	
<b>Total morphine, mg</b>	25 (5-73)	245 (41-740)	0.001
<b>Total bupivacaine, mg</b>	1250 (228-3625)	--	
<b>Treatment duration, h</b>	140 (11-480)	144 (17-648)	ns
<b>Side effects, % (n)</b>			
<b>Sedation</b>	1(2)	17(6)	<0.001
<b>Pruritus</b>	4 (6)	0 (0)	ns
<b>Nausea/Vomiting</b>	2 (3)	3 (1)	ns
<b>Respiratory depression</b>	0 (0)	6 (2)	0.03
<b>Orthostatism</b>	6 (10)	3 (1)	ns
<b>Nightmares</b>	0 (0)	3 (1)	ns
<b>Hallucinations</b>	2 (4)	11 (4)	0.03
<b>Confusion</b>	0 (0)	11 (4)	0.001
<b>Catheter displacement</b>	18 (30)		
<b>Motor blockade</b>	4 (7)		
<b>Insufficient analgesia,% (n)</b>	21 (35)	26 (9)	ns
<b>Early termination, % (n)</b>	37 (62)	26 (9)	ns
<b>Altered analgesia, % (n)</b> <b>(EPI→IV vs. IV→EPI)</b>	10 (17)	3 (1)	<0.01

**Table 3: Intra- and postoperative data.**

	<b>EPI group</b>	<b>IV group</b>	<b>p</b>
<b>Surgery time, h</b>	10.0 (5.8-17.7)	10.6 (7.1-15.5)	ns
<b>Blood loss, L</b>	0.9 (0.2-22.0)	0.9 (0.2-2.0)	ns
<b>Fluid replacement first 24 h</b>			
<b>Crystalloids, L</b>	7.0 (0.5-13.0)	6.0 (4.0-13.0)	ns
<b>Colloids, L</b>	2.3 (0-8.0)	2.0 (0.5-4.0)	0.03
<b>Crystalloids + Colloids, L</b>	9.0 (2.3-16.5)	8.0 (5.5-16.5)	0.01
<b>Packed blood, units</b>	2 (0-48)	2 (0-4)	ns
<b>Inotropic support, % (n)</b>			
<b>Ephedrine</b>	64.5 (107)	48.6 (17)	ns
<b>Dopamine</b>	50.0 (83)	14.3 (5)	<0.001
<b>Dobutamine</b>	1.2 (2)	0 (0)	ns
<b>Norepinephrine</b>	0.6 (1)	0.9 (1)	ns
<b>Anesthesia time, h</b>	11.8 (7-20)	11.9 (9-15)	ns
<b>Postoperative intubation, h</b> (n=(EPI/IV) 137/30)	9.4 (1-65)	9.3 (1-67)	ns
<b>ICU stay, h</b>	20 (10-377)	19 (13-160)	ns
<b>Postoperative atrial fibrillation,</b> <b>% (n)</b>	10 (15)	3 (1)	ns
<b>Postoperative respiratory</b> <b>complications, % (n)</b>	14 (22)	17 (6)	ns
<b>Chest tubes, days</b>	9.0 (5-24)	8.0 (5-15)	ns
<b>Hospital stay, days</b>	15 (9-148)	14 (9-55)	ns

**Table 4. Prolonged ICU stay and ICU readmission.**

	<b>EPI group</b>	<b>IV group</b>	<b>p</b>
<b>Patients, % (n)</b>	16 (27)	23 (8)	ns
<b>Age, yrs (range)</b>	65 (44-86)	60 (37-79)	ns
<b>ICU stay, h (range)</b>	113 (58-377)	100 (60-160)	ns
<b>Circulatory complications, n</b>	8	1	ns
<b>Respiratory complications, n</b>	17	5	ns
<b>Tracheal reintubation, n</b>	4	1	ns
<b>Infectious complications, n</b>	2	1	ns
<b>Other complications, n</b>	4	4	ns
<b>Readmission, n</b>	2	1	-
<b>ICU readmission stay, h</b>	25 vs.127	791	-

## Legends to figures

Figure 1:

Postoperative NRS-scoring for pain in the epidural (EPI) and intravenous (IV) groups during rest (A) and mobilization (B). The graph presents box-plots as determined by Tukey. The box represents the interquartile range containing 50% of the value, and the horizontal line indicates the median value. The whiskers show the largest observed value within 1.5 box-lengths from the upper (75% percentile) or lower (25% percentile) border of the box. NRS scoring was significant lower in the EPI group, both at rest and mobilization, compared with the IV group on postoperative day 1.

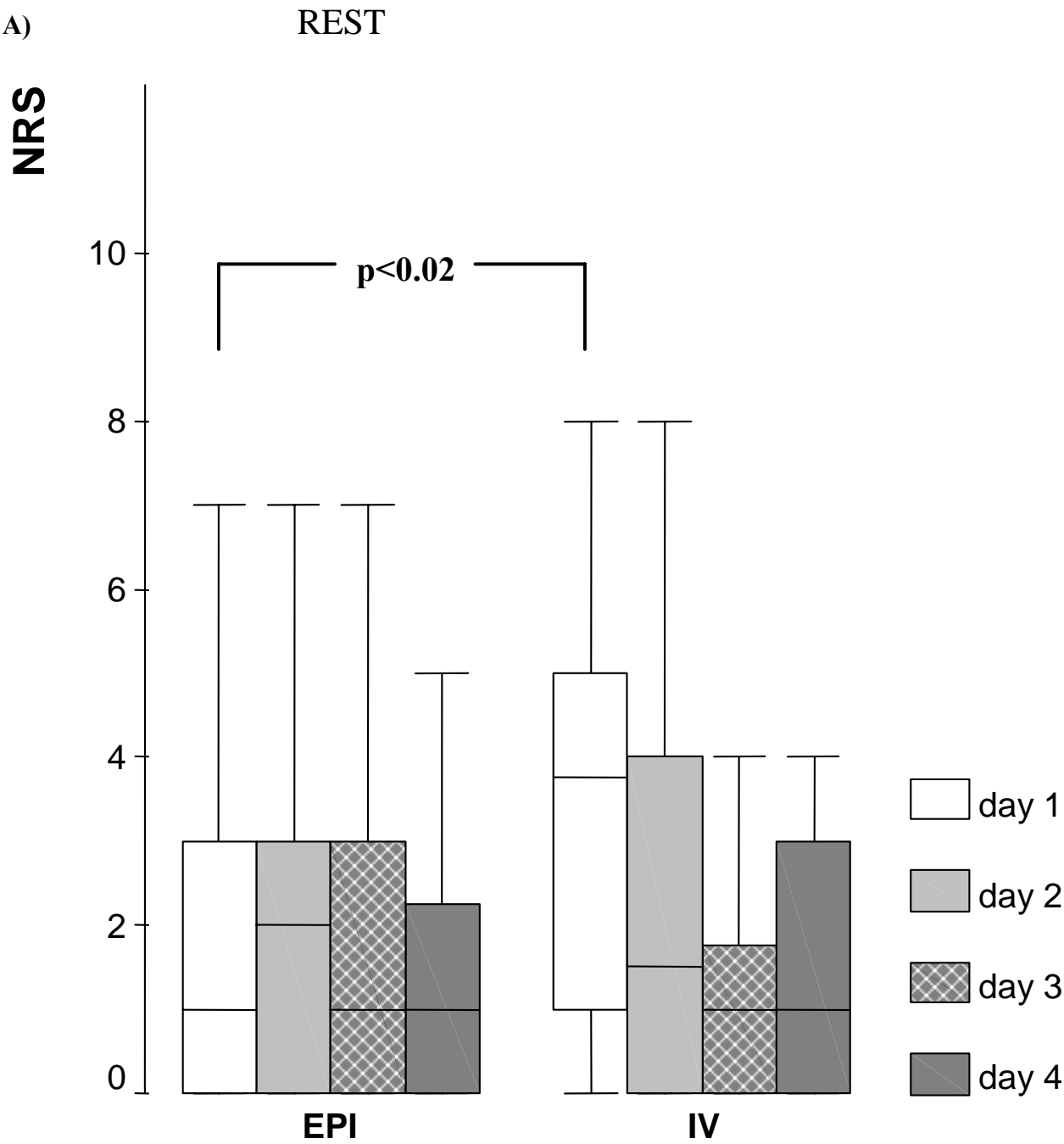
Figure 2

Analgesic infusion rate (ml/h) on day 0 (day of surgery) until postoperative day 6 in the epidural (EPI; 0.25% bupivacaine/0.005% morphine) and intravenous (IV; morphine 0.1%) groups. The background infusion decreased over time in both groups ( $p < 0.001$ ). The graph presents box-plots as determined by Tukey. The box represents the interquartile range containing 50% of the values, and the horizontal line across the box indicates the median value. The whiskers show the largest observed value within 1.5 box-lengths from the upper (75% percentile) or lower (25% percentile) border of the box. The background infusion decreased significantly over time in both groups ( $p < 0.001$ ).

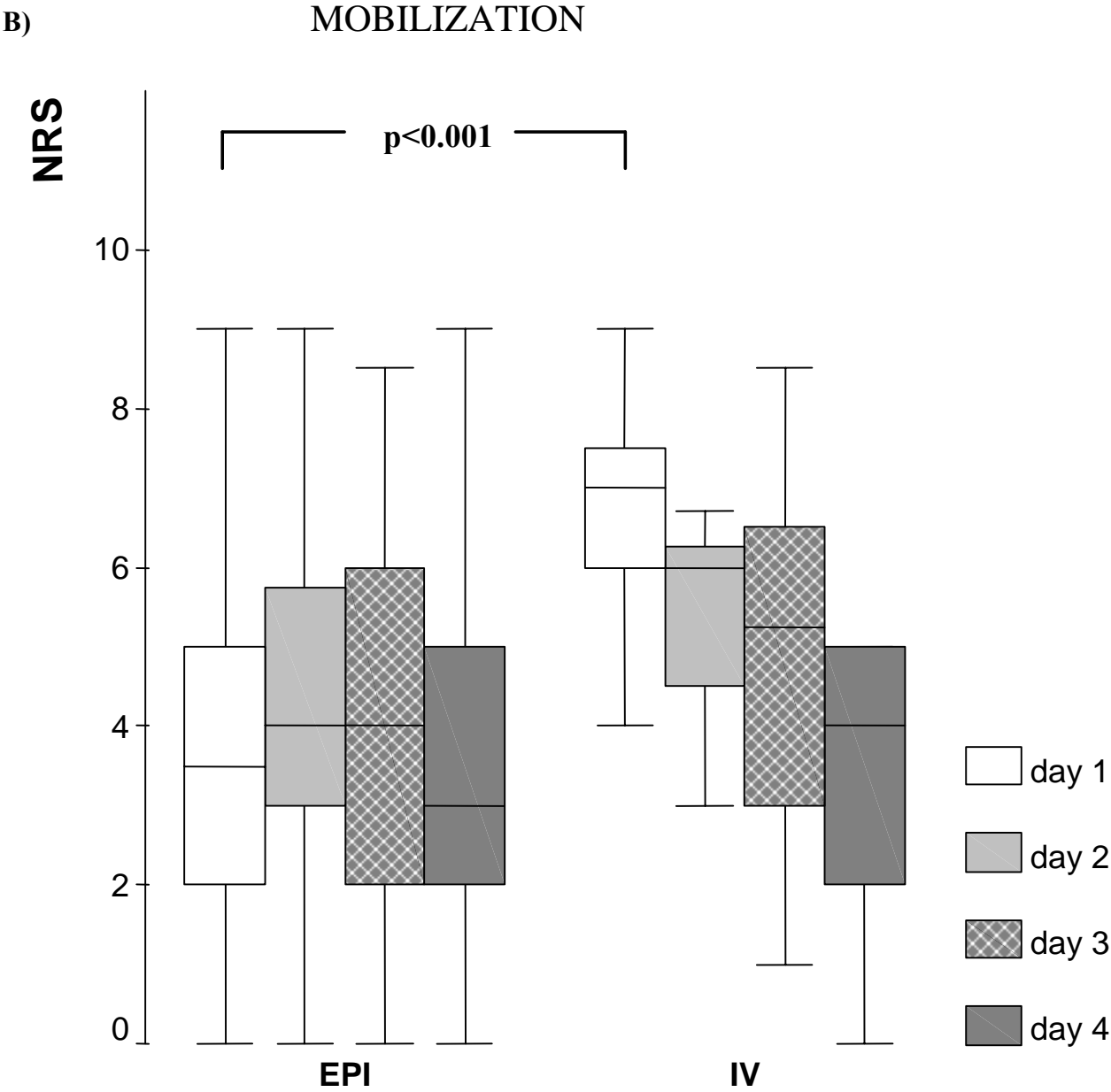
Figure 3:

Postoperative weight changes for patients in the epidural (EPI) and intravenous (IV) groups. The graphs present box-plots as determined by Tukey. The box represents the interquartile range, containing 50% of the values, and the horizontal line indicates the median value. The whiskers show the largest observed value within 1.5 box-lengths from the upper (75% percentile) or lower (25% percentile) border of the box. A significant weight increase in both groups occurred on day 1, compared to the postoperative weight (day 0) ( $p < 0.001$ ).

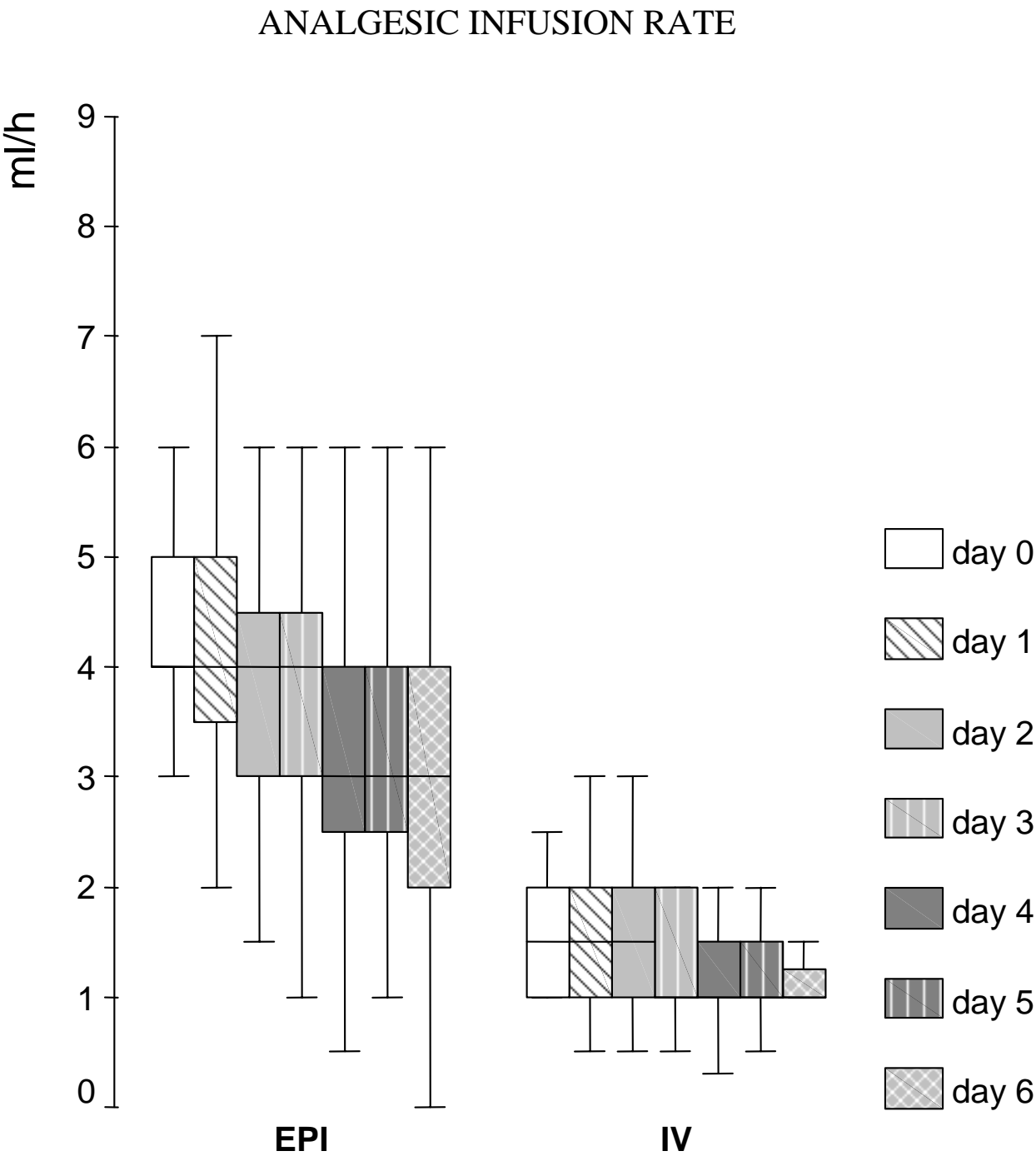
**FIGURE 1**



**FIGURE 1**



**FIGURE 2**





**FIGURE 3**

