THORACIC EPIDURAL ANALGESIA FOR RADICAL CYSTECTOMY IMPROVES BOWEL FUNCTION EVEN IN TRADITIONAL PERIOPERATIVE CARE: A RETROSPECTIVE STUDY IN EIGHTY-FIVE PATIENTS

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SUMMARY – Radical cystectomy is associated with significant morbidity and mortality due to complex surgery and comorbidities associated with advanced age of patients. In contrast to the surgery, which is clearly the procedure of choice for patients with invasive bladder cancer, the optimal anesthesiologic method is still under debate. Therefore, we retrospectively analyzed 85 patients having undergone radical cystectomy at our institution, either under combined epidural-general anesthesia (CEGA) or opioid based general anesthesia (GA). The intraoperative blood loss was significantly lower in CEGA group (497.37±354.13) than in GA group (742.31±403.69; p=0.006), due to induced hypotension. Consequently, blood transfusion requirements were lower in CEGA group (107.20±263.92) than in GA group (388.18±321.32; p=0.001). The incidence of postoperative ileus was also lower in CEGA group (p=0.024). There was no difference in analgesic efficacy, but a trend towards lower incidence of venous thrombosis and infection was noticed. The results of our study suggest that epidural anesthesia might have specific advantages in patients undergoing radical cystectomy.

Key words: *Cystectomy; Anesthesia, epidural; Anesthesia, general*

Introduction

Bladder cancer is three times more common in men than in women. In Europe in 2007, it was the fourth most common malignancy in men after prostate, lung and colorectal cancer, accounting for 6.6% of all cancer cases. In women, it was the ninth most common cancer accounting for 2.3% of all cancers[1]. In Croatia, 634 newly detected cases of urinary bladder carcinoma were reported in 2009, ranking it the fifth most common malignancy in male[2].

In 30% of cases, bladder carcinoma is invasive at presentation. Radical cystectomy is the optimal treatment for muscle invasive cancers, high-grade recurrent tumors and carcinoma *in situ*, which cannot be controlled by conservative therapy. The standard surgical approach to muscle-invasive bladder cancers is radical cystoprostatectomy in male and anterior pelvic exenteration in female, with *en bloc* regional pelvic lymphadenectomy. Urinary diversions performed at our institution include ureterocutaneostomy, ureteroileocutaneostomy (ileal conduit according to Bricker), sigma-rectum pouch (Mainz-pouch II), ileum and cecum augmentation (Mainz-pouch I), and orthoptic urinary diversion (ileal neobladder according to Hautmann). Although not without a substantial complication rate, orthoptic ileal neobladder is the urinary

diversion of choice in our institution. It offers better quality of life despite complications. Careful patient selection is very important in the decision-making process. Absolute contraindications include impaired renal and hepatic function, inflammatory bowel disease, and pelvic floor malfunction.

Radical cystectomy is a major surgery which is due to its complexity associated with multiple potential postoperative complications. Pouch-related complications are urine leakage with paralytic ileus, mucus hyperproduction, urosepsis and pyelonephritis. Non-pouch-related complications include diarrhea, pneumonia, deep venous thrombosis, pulmonary embolism and wound infection[3].

An additional risk factor is the patient population undergoing the procedure; the incidence of invasive bladder carcinoma peaks in the seventh decade when the coexistence of serious comorbidities is more frequent, e.g., diabetes mellitus, arterial hypertension, coronary artery and cerebrovascular disease. Due to complex surgery and the patient risk factors, the reported morbidity and mortality are still high. Postoperative morbidity, mainly due to ileus, venous thrombosis, pulmonary embolism and sepsis, ranges from 0.3% to 4.2%[4,5].

The optimal anesthesiologic technique for radical cystectomy is still under debate. Thoracic epidural anesthesia has theoretical advantage of efficacious postoperative pain control and a reduced rate of cardiac and pulmonary complications. Moreover, due to its sympaticolytic effects, the lower rate of postoperative ileus and venous embolism has been reported among patients who underwent major abdominal and vascular surgery under epidural anesthesia[6-9]. Additional potential benefit is relative hypotension which reduces intraoperative blood loss and the need of blood transfusion[10]. Clinical relevance of these potential benefits in patients undergoing radical cystectomy remains to be determined.

In our study, we retrospectively analyzed clinical course in 85 consecutive patients having undergone radical cystectomy at our institution between January 2010 and March 2011. We analyzed postoperative complications and efficacy of postoperative pain therapy according to anesthesiologic technique, i.e. general and combined general-thoracic epidural anesthesia.

Patients and Methods

Patients

Eighty-five consecutive patients with invasive urinary bladder tumor from T2 to T4 stage according to TMN classification scheduled for radical cystectomy were included in the analysis. Two anesthesiologic techniques were used: general and combined thoracic epidural and general anesthesia. The type of anesthesia was chosen according to patients' and anesthetists' preference. No accelerated perioperative care program was used, but a traditional treatment, except for thoracic epidural analgesia during surgery and 4 days postoperatively.

Methods

In the combined epidural-general anesthesia group (CEGA), epidural catheter was inserted before surgery at the T9-T10 or T10-T11 level. A test dose of 3 mL of 2% lidocaine was administered before induction of general anesthesia. All patients were administered general anesthesia using thiopental 3-5 mg/kg, fentanyl 3-5 µg/kg and pancuronium 0.1 mg/kg. Anesthesia was maintained with isoflurane 0.7-1.2 minimal alveolar concentration (MAC) and pancuronium as needed. In the group under general anesthesia (GA), fentanyl 0.1 mg was added when clinically indicated, while the CEGA group were administered an epidural bolus of 25 to 50 mg of levobupivacaine after hemodynamic stabilization. Ninety minutes after bolus, continuous epidural infusion of 0.1% levobupivacaine 10 mL, fentanyl 2 mL and epinephrine 0.1 mg in 50 mL 0.9% NaCl 7-9 mL/h was commenced. Neuromuscular blockade was antagonized using neostigmine 2.5-3.5 mg and atropine 1 mg.

In the GA group, intravenous tramadol based analgesia was administered for postoperative pain control. Morphine equivalents were calculated for the analysis of opioid consumption. CEGA group received continuous epidural analgesia consisting of 0.5% levobupivacaine 50 mg, fentanyl 0.1 mg, epinephrine 0.1 mg in 50 mL of 0.9% NaCl 4-6 mL/h[-1]. Analgesic efficacy was assessed by nurses in the intensive care unit every six hours using the Numeric Rating Scale (NRS) of 11 points. When pain intensity was over 3 points, a rescue medication of 2.5 mg morphine sulfate intravenously was administered. Metoclopramide 10 mg in-

Table 1. Demographic data and type of urinary diversion

Variable	GA group	CEGA group
Patients (n)	57	28
Mean age (yrs)	62	61.5
<59	21	10
60-69	17	9
70-79	19	7
>80	1	0
Gender: male/female	44/13	19/7
ASA category		
ASA I	2	4
ASA II	40	14
ASA III	14	6
Type of diversion		
Orthoptic ileal neobladder (operation sec Hautmann)	24	15
Ureterosigmoidostomy (Mainz-Pouch II)	3	0
Ileal conduit (operation sec Bricker)	19	11
Ureterocutaneostomy	7	5
Mean operative time (min ± SD)	283±10	270±35

GA = general anesthesia; CEGA = combined epidural-general anesthesia; ASA = American Society of Anesthesiology

travenously was given for nausea and vomiting. Ileus was defined as absence of bowel movement after the fourth postoperative day[12]. Sepsis was defined according to the American Society of Chest Physicians definition[13]. Thrombosis was objectively diagnosed using Doppler sonography.

Demographic data, intraoperative medication, blood loss and postoperative data were obtained from standardized medical documentation.

Statistical analysis

Statistical analysis was performed using the SPSS 17.0 software (SPSS Inc., Chicago, IL). Nominal scale variables were described using relative and absolute frequencies. Fisher exact test was used if matched cells were rare, i.e. less than 5. Distribution of continuous variables was tested using Smirnoff-Kolmogorov test. Parameters with normal distribution were expressed as mean ± standard deviation (SD) and analyzed using Student's t-test. Mann-Whitey test was used for analysis of two variables with non-normal distribution. The first day of peristalsis according to the type of postoperative analgesia was analyzed using t-test. The incidence of postoperative ileus, thrombosis and infection was analyzed by use of Fisher exact test.

Results

We analyzed clinical course in 85 consecutive patients having undergone radical cystectomy at our institution under either GA or CEGA. One patient operated on under GA died in the operating theater. Demographic and clinical data did not differ between the GA and CEGA groups (Table 1). Intraoperative blood loss was significantly lower in the CEGA group (Table 2). Consequently, blood transfusion requirements were significantly lower in the CEGA group.

Overall pain control was good with pain intensity below 3 points on NRS except during the first 4 hours after surgery when the mean pain score was 3.4 in the GA group.

Epidural analgesia provided superior pain control only in this period, but morphine consumption was significantly higher in the intravenous analgesia group (mean 40 mg, range 30-46 mg) than in the epidural analgesia group (mean 3.25 mg, range 0-15 mg, p<0.001). Recovery of gastrointestinal function differed statistically significantly between the two groups (Table 3). Peristalsis occurred earlier in CEGA

Table 2. Intraoperative blood loss and transfusion of red cell concentrate according to type of anesthesia

Type of anesthesia	Blood loss (mL ± SD)	Transfusion (mL ± SD)	p-value
GA	742.31 ± 403.69	388.18 ± 321.32	0.006*
CEGA	497.37 ± 354.13	107.20 ± 263.92	0.001*

GA = general anesthesia; CEGA = combined epidural-general anesthesia; *Mann-Whitney U test

Table 3. Bowel function according to type of postoperative analgesia

	GA	CEGA	p-value
First day of peristalsis (mean ± SD)	3.3 ± 3.3	2.0 ± 0.9	0.024*
Incidence of ileus (%)	7 (11.7%)	1 (3.9%)	0.024**

GA = general anesthesia; CEGA = combined epidural-general anesthesia; *t-test; **Fisher exact test

group than in GA group (p=0.024). The incidence of postoperative ileus was significantly higher in the GA group (p=0.024). Neither technique was found superior regarding analgesic efficacy (Table 4).

A higher rate of postoperative infection was found in the GA group, but the difference did not reach statistical significance. Deep venous thrombosis was diagnosed in two GA patients and none of CEGA

Table 4. Intensity of pain during 72 hours after surgery according to postoperative analgesia

	VAS (mean ± SD)		p-value*
Time after surgery	Intravenous analgesia	Epidural analgesia	
4 h	3.2±1.9	1.9±1.1	**0.009**
8 h	2.2±1.3	2.0±2.0	0.15
12 h	1.8±1.4	1.7±1.3	0.933
24 h	1.5±1.1	2.4±1.6	**0.019**
48 h	1.3±0.8	1.8±1.1	0.032
72 h	1.1±1.1	1.6±1.1	0.037

VAS = visual analog scale; *Kruskal-Wallis H test

patients. The length of hospital stay did not differ between the groups (Table 5), but this result should be interpreted with caution as our institution is a tertiary center and nonmedical reasons often influence patient discharge.

Table 5. Complications and length of hospital stay

Type of complication	GA	CEGA	Sum	p-value
Infection (%)	14 (24.6%)	4 (15.4%)	18 (21.4%)	0.39*
Deep venous thrombosis (%)	2 (3.4%)	0 (0%)	2 (2.4%)	1*
Mortality (%)	1(1.7%)	0 (0%)	1 (1.2%)	1*
Length of stay (mean ± SD)	15.9 ± 7.2	15.7 ± 3.5	15.8 ± 6.2	0.93**

GA = general anesthesia; CEGA = combined epidural-general anesthesia; *Fisher exact test; ** t-test

Discussion

Results of our analysis imply that several theoretical benefits of thoracic epidural analgesia could have clinical implications in patients undergoing radical cystectomy. One of the main findings of our study is reduction of postoperative ileus in the CEGA group. In another study on the effect of thoracic epidural analgesia (TEA) after radical cystectomy, just a trend towards earlier eating solid food was found[10]. Our results suggest that TEA might have similar beneficial effects on gastrointestinal function in patients undergoing radical cystectomy as in patients undergoing major abdominal surgery.

Postoperative ileus is one of the most frequent complications following radical cystectomy[12]. It is caused by abdominal pain, which induces sympathetic hyperactivity and systemic inflammatory reaction with cytokine production that inhibits bowel motility[13-15]. Subsequent opioid consumption is another reason for delayed gastrointestinal movement recovery. Gastrointestinal hypoperfusion is considered to have an important role in the pathophysiology of surgical stress response and postoperative complications as intestinal paralysis and loss of gut barrier function. Moreover, splanchnic hypoperfusion has been implicated as a cause of increased mortality among critically ill patients. The beneficial effect of TEA on surgery induced gastrointestinal injury has been demonstrated in experimental and clinical investigations. It has been found that TEA increases mucosal blood flow and decreases the time of intestinal paralysis after abdominal surgery. TEA also prevents decrease in gastric intramucosal pH, which reflects adequacy of intestinal perfusion in patients undergoing major abdominal surgery[16,17]. These effects are probably related to TEA induced blockade of efferent sympathetic nerves.

Considering the effects of TEA on blood transfusion, our findings are in accordance with the authors[11,18] who found the epidural analgesia related intraoperative hypotension to be associated with less bleeding and consequently with less blood transfusion requirements. As *in vitro* studies imply that blood transfusion causes immunosuppression by reducing non killer cell activity, suppressing macrophage antigen presentation, altering T cell ratio and decreasing the concentration of cytokines (tumor necrosis factor, interferon-γ and granulocyte colony stimulating factor) important for immune reaction, avoiding blood transfusion might improve immune response[19-21]. Analyzing the efficacy of pain therapy, we found that both groups had well controlled postoperative pain with pain scores of less than 3, but that GA group had substantially higher opioid consumption. Systemically administered opioids have well documented immunosuppressive actions, e.g., inhibitory effects on cellular and humoral immune responses including antibody production, natural killer cell activity, cytokine expression and phagocytic activity[22]. On the other hand, local anesthetics lack immunosuppressive activity. Moreover, thoracic epidural anesthesia with bupivacaine in an animal model of mesenteric ischemia-reperfusion injury induced antiinflammatory effects due to reduced cytokine and attenuated lipid oxidation, oxidative injury and mucosal apoptosis[23]. Local anesthetics *per se* have also been shown to have antiinflammatory effects reducing cytokine and cortisol production[24-26]. Consequently, due to lower transfusion rate and lower opioid consumption, patients under CEGA could have less pronounced immunosuppression. We found a tendency towards lower infection rate among patients under CEGA, but the difference did not reach statistical significance.

Deep venous thrombosis was diagnosed using Doppler sonography in two patients under GA. None of the CEGA patients had clinical evidence of thrombosis. Although the incidence of thrombosis in our study was low and did not reach statistical significance, the finding is consistent with a meta-analysis showing that epidural analgesia is potentially associated with a reduced incidence of postoperative venous thrombosis[27]. The antithrombotic effect of epidural analgesia is due to the direct effect on platelet function[28] and reduction in venous stasis[29].

A limitation of our study was its retrospective design and a relatively small number of patients in the CEGA group. Although our results must be interpreted with caution, we find them to justify further clinical research on the effects of thoracic epidural analgesia in the context of radical cystectomy.

Conclusion

The results of our study show that the primary advantage of the combined epidural-general anesthesia in patients undergoing radical cystectomy is more rapid recovery of gastrointestinal motility and reduction of intraoperative blood transfusion requirements, rather than superior analgesia. The suggested lower infection and thrombosis rate, while theoretically founded, clinically require further investigation.

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Sažetak

TORAKALNA EPIDURALNA ANALGEZIJA ZA RADIKALNU CISTEKTOMIJU POSPJEŠUJE FUNKCIJU CRIJEVA I U TRADICIONALNOJ PERIOPERACIJSKOJ SKRBI

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Radikalna cistektomija je praćena značajnom smrtnošću i pobolom zbog složenog kirurškog zahvata i komorbiditeta povezanog sa starijom dobi bolesnika. Za razliku od kirurškog zahvata koji je bez dvojbe metoda izbora za invazivni karcinom mokraćnog mjehura, optimalna metoda anestezije još je predmet rasprave. Stoga smo retrospektivno analizirali 85 bolesnika koji su u našoj ustanovi podvrgnuti zahvatu radikalne cistektomije u kombiniranoj torakalnoj epiduralnoj i općoj anesteziji ili u općoj anesteziji baziranoj na opioidima. Intraoperacijski gubitak krvi bio je značajno niži u skupini na kombiniranoj torakalnoj epiduralnoj i općoj anesteziji (497,37±354,13) nego u skupini na općoj anesteziji baziranoj na opioidima (742,31±403,69, p=0,006). Posljedično, količina transfundirane krvi bila je značajno niža u skupini koja je imala torakalnu epiduralnu anesteziju (107,20±263,92) nego u skupini na općoj anesteziji (388,18±321,32, p=0,001). Incidencija poslijeoperacijskog ileusa također je bila niža u skupini na kombiniranoj anesteziji (p=0,024). Nije uočena razlika u analgetskoj učinkovitosti, ali je zabilježen trend prema nižoj incidenciji venske tromboze i poslijeoperacijskih infekcija u skupini na kombiniranoj anesteziji. Rezultati naše studije impliciraju da bi torakalna epiduralna analgezija mogla imati specifične prednosti kod bolesnika podvrgnutih zahvatu radikalne cistektomije.

Ključne riječi: *Cistektomija; Anestezija, epiduralna; Anestezija, opća*