Доклади на Българската академия на науките
Comptes rendus de l'Académie bulgare des Sciences
*Tome 76, No 1, 2023*

*MEDICINE*
*Clinical medicine*

# RADICAL CYSTECTOMY AS A CAUSE OF AN INCREASED NEUROENDOCRINE RESPONSE

**Petya Hubenova, Plamen Krastev*,#, Atanas Temelkov**

*Received on March 16, 2020*
*Presented by D. Damianov, Member of BAS, on May 26, 2020*

**Abstract**

The present study compared the neuroendocrine response in patients undergoing conventional cystectomy with two postoperative pain management techniques: epidural analgesia (EA) and intermittent opioid analgesia (IOA) on adrenocorticotropic hormone (ACTH), cortisol, glucose levels for 48 hours. We hypothesize that appropriate analgesic regime can attenuate stress response reaction. Forty-four patients scheduled for radical conventional cystectomy were assigned to one of the two study groups: group A ($n = 22$) with EA, group B ($n = 22$) with IOA. The surgical stress factor induced significant hypothalamic-pituitary-adrenal (HPA) axis responses in both groups. The ACTH and cortisol levels were higher than baseline for both groups, but more significantly in group B. Blood glucose level was elevated few hours after the surgical intervention and was back to baseline level by the following morning. The results suggest that EA might have more advantages associated with reduced postoperative pain and attenuated neuroendocrine response when open access is the preferred operative technique. There is a need of randomized multicentre trials to evaluate the quality of life, the survival and the role of pain management at least 12 months after radical cystectomy.

**Key words:** stress response, urological surgery, neuroendocrine response, pain management, biomarker

**Introduction.** In recent years, innovations in surgical technology have greatly changed anaesthesia practice. The standard treatment of invasive urinary bladder carcinoma includes preoperative radiotherapy, radical surgical removal of the

#Corresponding author.
DOI:10.7546/CRABS.2023.01.13

tumour with derivation of the urine and postoperative chemotherapy. Conventional open radical cystectomy is still the most frequent surgical approach in Bulgaria.

The stress response to surgery involves neuroendocrine, metabolic, and inflammatory processes in the organism. Neuroendocrine effects are induced by activation in the HPA axis [1]. Surgical stress can be attenuated by preoperative assessment, individualized approach, intra- and postoperative pain management techniques. Prolongation of the stress response can worsen outcomes. Regardless of the progress of medical technology after radical cystectomy, a part of the patients entering the intensive care unit need prolonged intensive care.

ACTH, somatotropin and prolactin secretion from the anterior pituitary gland are increased under stress. ACTH stimulates cortisol production in the adrenal cortex. Cortisol secretion increases several minutes after surgery and reaches a maximum at 4–6 hours after surgery, depending on the severity of tissue damage. A feedback mechanism operates so that the increased concentrations of circulating cortisol inhibit the secretion of ACTH by the putiutary gland. Cortisol promotes protein breakdown, glycogenolysis and gluconeogenesis in the liver as well as inhibits the use of glucose by cells. These effects lead to an increased blood glucose (BG) concentrations [1]. Hyperglycemia, defined as BG levels greater than 9.99–11.1 mmol $L^{-1}$, is associated with poor clinical outcomes including increased postoperative complications, perioperative mortality, hospital length of stay [2].

Postoperative pain is a potent trigger for stress response. Epidural local anaesthetics (LA) block afferent stimuli and reduce neuroendocrine metabolic responses [3]. Their administration results in an effective pain relief [4]. Continuous epidural analgesia (EA) with early nutrition and mobilization suggests an attenuated stress response and improved recovery [5].

Epidurally applied ropivacaine and morphine are more effective than each agent applied alone [6].

The surgical stress response triggers a cascade of neuroendocrine responses. The combination of epidural opioids and local anaesthetic provides synergisic effect. Nonetheless, the relationship between quality of analgesia and postoperative outcomes remains ill defined.

**Materials and methods.** Radical cystectomy with ureterocutaneostomy was performed in 44 patients. A prospective design was used. All patients had clinically, endoscopically and histologically verified bladder adenocarcinoma and had signed informed consent.

On the day before surgery patients were made familiar with the use of a numerical rating scale (NRS; 0 = no pain, 10 = worst pain imaginable) [7]. Anaesthesia was induced in both groups using propofol 2–3 mg $kg^{-1}$ i.v., fentanyl 1–1.5 µg $kg^{-1}$ i.v., and atracurium 0.6 mg $kg^{-1}$ i.v. It was maintained with isoflurane 1–2% end-tidal concentration. Intermediate bolus doses of 0.5–1 µg $kg^{-1}$ i.v. fentanyl were given when needed.

Surgery was performed via a midline lower laparotomy. Epidural analgesia is defined as the postoperative use of a local anaesthetic and an opioid. An epidural catheter (18 gauge Perifix Complete Set, B. Braun) was inserted via a midline approach at the L1-L2 interspace using the loss of resistance technique in patients assigned to group A.

On arrival in the postanaesthesia care unit patients of group A were given an initial loading dose of 10 ml of a mixture of 3 mg $ml^{-1}$ ropivacaine and 0.1 mg $ml^{-1}$ morphine. This analgesic regime was continued 48 h at a speed of 3–5 ml $h^{-1}$. Patients of group B received an initial dose of morphine 3 mg i.v. followed by 3 mg i.v. if needed to relieve intensity of pain to maximum 10 mg morphine within 30 min.

Pain scores on a NRS were obtained at rest and after movement (changing position, coughing) and recorded by trained nurses.

Neuroendocrine stress responses were assessed by measuring plasma concentrations of ACTH, cortisol, and glucose before surgical incision (baseline), 4 h after surgery, after 12 h, on the 1st and 2nd postoperative morning. Blood samples for plasma ACTH and cortisol were collected in 10 ml tubes treated with ethylenediamine tetraacetic acid (EDTA). Plasma ACTH and serum cortisol were measured by radioimmunoassay. ACTH values in the laboratory were 7.2–63.3 pg $ml^{-1}$, and cortisol values were 133.0–537.0 nmol $L^{-1}$. Glucose concentrations were determined by a routine glucose oxidase method (Glucose, Granutest 250; Merck) with a reference range of 3.9–5.6 mmol $L^{-1}$.

The sample size of 44 patients was estimated to show a clinically useful difference (at least 25%) in mean morphine consumption over 48 h. Statistical analyses were carried out using SPSS v.22 and MS Excel. Methods include means comparison, Student's *t*-test for normal data and Mann–Whitney U-test for skewed data. Significance level was set at 0.05. 95% confidence intervals were calculated.

**Results.** Demographic and physical status variable between the two groups are expressed as mean +/–SEM (Table 1). There were no significant differences between groups.

Table 1

Demographic data and patient physical status characteristic

| Group | Number *n* | Sex male | Sex female | Age (y) x±Sx | Weight (kg) x±Sx | Height (cm) x±Sx |
|---|---|---|---|---|---|---|
| Group A | 22 | 15 | 7 | 65.18±5.5 | 80.82±6.42 | 173.55±3.58 |
| Group B | 22 | 16 | 6 | 67.32±2.87 | 77.95±4.21 | 174.14±2.86 |
| ASA (American Society of Anaesthesiologists) | | | | | Group A | Group B |
| ASA II | | | | | 7 | 5 |
| ASA III | | | | | 15 | 17 |
| Total: | | | | | 22 | 22 |

The mean duration of surgery and consumption of fentanyl were similar in both groups. Hemodynamic parameters, oxygen saturation, respiratory rate were monitored. The mean value of systolic blood pressure in group A was 122.59 (SD±21.97) and 139.00 (SD±11.5) in group B. The mean value of the heart rate in group A was 83.27 (SD±11.24) and 81.36 (SD±13.41) in group B, $p > 0.05$. There were no cases of bradypnea, defined as respiratory rate below 8 $\min^{-1}$.

The baseline concentrations of ACTH, cortisol, and glucose were similar in the two groups. In the earliest postoperative period ACTH mean level in group A was 42.44 pg $ml^{-1}$ (SD±13.18) and 51.99 pg $ml^{-1}$ (SD±15.42) in group B. At the end of the study period the mean ACTH plasma level in group A was 16.8 pg $ml^{-1}$ (SD±6.26) and 16.11 pg $ml^{-1}$ (SD±6.87) in group B (Fig. 1).

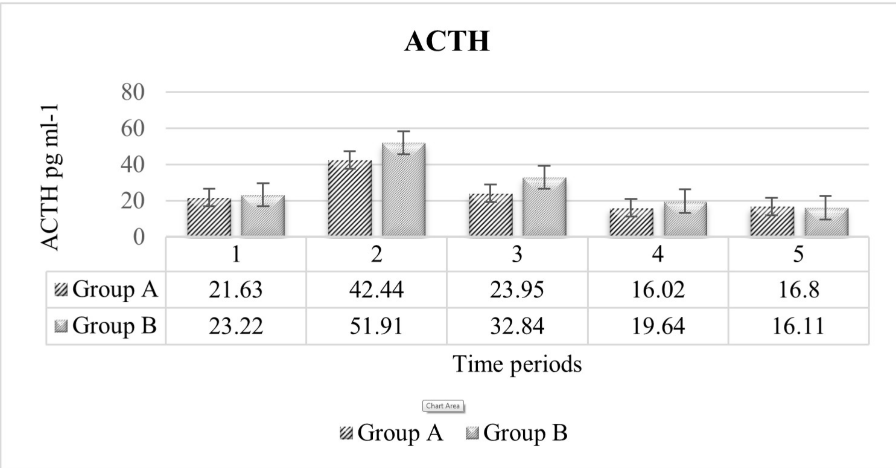


Fig. 1. Mean plasma concentration of ACTH, time periods: 1 – before surgical incision, 2 – 4 h after surgery, 3 – after 12 h, 4 – 1st postoperative day, 5 – 2nd day

At 4 h after surgery the mean cortisol level was 433.31 nmol $l^{-1}$ (SD±139.55) in group A and 556.38 nmol $l^{-1}$ (SD±104.60) in group B (Fig. 2). At the end of the study period mean serum cortisol level in group A was 229.96 nmol $L^{-1}$ (SD±115.27) and 334.36 nmol $L^{-1}$ (SD±67.48) in group B.

At 4 h after surgery the mean level of glucose in group A was 10.42 mmol $L^{-1}$(SD±1.05) and 13.82 mmol $L^{-1}$ (SD±0.47) in group B. At the second post-operative morning the mean level of blood glucose in group A was 5.08 mmol $L^{-1}$ (SD±1.21) and 5.67 mmol $L^{-1}$ (SD±0.87) in group B (Fig. 3).

The scores of the NRS in rest (NRS-R) and mobilization (NRS-M) in group A were lower than in group B during the study period. The total mean dose of morphine required in group A was 9.54 mg (SD±2.21) vs. 34.09 mg (SD±6.43) in group B. The difference is more than 25% and it is statistically significant ($p < 0.05$).

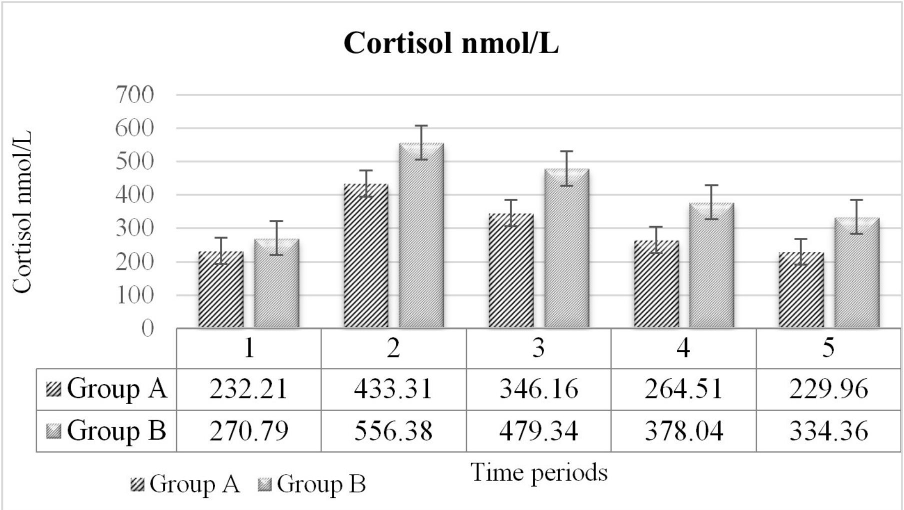


Fig. 2. Mean plasma concentration of cortisol, time periods: 1 – before surgical incision, 2 – 4 h after surgery, 3 – after 12 h, 4 – 1st postoperative day, 5 – 2nd day

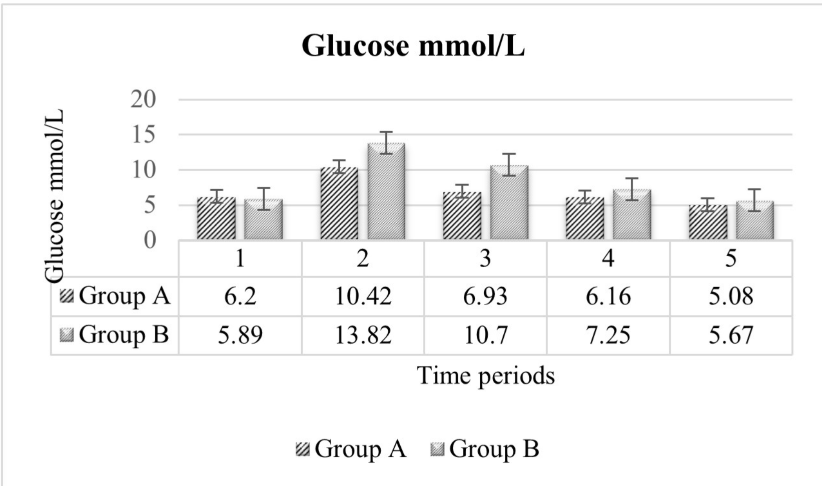


Fig. 3. Mean plasma concentration of glucose, time periods: 1 – before surgical incision, 2 – 4 h after surgery, 3 – after 12 h, 4 – 1st postoperative day, 5 – 2nd day

**Discussion.** In this study, EA was superior to IOA. Throughout the observation period (48 h), patients in group A had significantly lower pain score and were more satisfied than patients in group B.

The optimal analgesic regime for open urologic surgery in the lower abdominal cavity is a subject of debate. EA has gained widespread acceptance in providing postoperative analgesia for major abdominal surgery [8]. On the other hand with the advancement of minimally invasive operative techniques regional analgesia there is almost no place.

EA is effective in attenuating the surgical stress response when open access is needed. It has an impact on decreasing complications following abdominal surgery. It can reduce postoperative systemic neuroendocrine reaction, opioid consumption, and possibly to improve patient survival [9]. We have shown that epidurally administered ropivacaine and morphine decrease pain sensitivity for patients in group A and reduce ACTH and cortisol concentrations to a certain level, provide stable blood glucose level though not statistically significant due to small sample size. Our findings confirmed the data obtained in previous studies [1,10]. The plasma levels of ACTH and cortisol are increased during surgery, at 24 and 48 h their concentration decreases and stays higher than the baseline, but changes are less when EA is used. We have registered more stable postoperative blood glucose levels in group A without extremely high or low concentrations. Stable BG level is beneficial for patients susceptible to alter pancreatic function and higher risk of insulin resistance due to the stress response.

It is well established that surgical intervention can modulate the activity of the endocrine and immune systems [11]. It has been reported that surgery induced immunosuppression is directly linked to the extent of the perioperative trauma [3]. If the stress respose is prolonged, it results in decreased resistance, increased morbidity and longer hospitalization [12].

Numerous studies have demonstrated that EA reduces postoperative physiologic responses in addition to providing pain relief [2,13]. We have shown that EA has certain benefits regarding neuroendocrine response. However, effects of epidural analgesia on postoperative morbidity remain controversial. Most studies to date do not have sufficient power to detect clinically significant differences.

Regardless of the progress of medical technology, a part of the patients after open radical cystectomy need prolonged intensive care, because of postoperative complications. However, in Bulgaria statistical data is lacking for long-term follow up after successful treatment. The results of a study evaluating the quality of life and the survival of patients after cardiac surgery in Bulgaria show that they fully recover within 6 and 12 months after sucessful treatment [14]. Patients who have survived after cardiac surgery and prolonged ICU stay have worse quality of life than those with a normal stay [15]. Determining the factors that affect the length of hospital stay after cystectomy is of special importance in planning the intervention and the resources needed for recovery.

The multifactorial nature of the stress response makes it difficult to determine and eliminate the reasons that triger it. Preoperative conversation with the patient and detailed explanation could be beneficial.

**Conclusion.** Our results support the presumption that through the pain management strategy and individual approach stress response can be modulated when open radical cystectomy is the treatment of choice. The appropriate application of modern technology in compliance with the current situation in Bulgaria can facilitate patient recovery and improved survival. EA was proposed as a beneficial technique for patients undergoing open radical cystectomy.

## REFERENCES


[1] J. P. Desborough (2000) The stress response to trauma and surgery, BJA, **85**(1), 109–117.

[2] Carli F. (2015) Physiologic considerations of Enhanced Recovery After Surgery (ERAS) programs: implications of the stress response, Can. J. Anesth./J. Can. Anesth., **62**, 110–119.

[3] Holte K., H. Kehlet (2002) Epidural anaesthesia and analgesia – effects on surgical stress responses and implications for postoperative nutrition, Clin. Nutr., **21**, 199–206.

[4] Guay J., M. Nishimori (2016) Epidural local anaesthetics versus opioid-based analgesic regimens for postoperative gastrointestinal paralysis, vomiting and pain after abdominal surgery, Cohrane, `https://doi.org/10.1002/14651858.CD001893.pub2`.

[5] Nelson G., A. D. Altman, A. Nick, L. A. Meyer et al. (2016) Guidelines for postoperative care in gynecologic/oncology surgery: Enhanced Recovery After Surgery (ERAS®) Society ecommendations—Part II, Gynecol. Oncol., **140**(2), 323–332.

[6] Kuthiala G., G. Chaudhary (2011) Ropivacaine: A review of its pharmacology and clinical use, Indian journal of anaesthesia, **55**(2), 104–110, doi:10.4103/0019-5049.79875.

[7] Farrar J. T., Y. L. Pritchett, M. Robinson (2010) The Clinical Importance of Changes in the 0 to 10 Numeric Rating Scale for Worst, Least, and Average Pain Intensity, The Journal of Pain, **11**(2), 109–118.

[8] Cerantola Y. , M. Valerio (2013) Guidelines for perioperative care after radical cystectomy for bladder cancer: Enhanced Recovery After Surgery (ERAS®) society recommendations, Clinical Nutrition, **32**(6), 879–887.

[9] Cummings III K. C., T. D. Kou, A. Chak, M. D. Schluchter, S. Margevicius (2019) Surgical approach and the impact of epidural analgesia on survival after esophagectomy for cancer: A population-based retrospective cohort study, PLoS One, **22; 14**(1):e0211125. doi: 10.1371/journal.pone.0211125.

[10] Akural E. I., T. E. Salomaki, A. H. Tekay, A. H. Bloigu, S. M. Alahuhta (2002) Pre-emptive effect of epidural sufentanil in abdominal hysterectomy, Br. J. Anaesth., **88**, 803–808.

[11] Kehlet H., J. B. Dahl (2003) Anaesthesia, surgery, and challenges in postoperative recovery, Lancet, **362**, 1921–1928.

[12] Moawad H. El S., E. M. Mokbel (2014) Postoperative analgesia after major abdominal surgery: Fentanyl–bupivacaine patient controlled epidural analgesia versus fentanyl patient controlled intravenous analgesia, Egyptian Journal of Anaesthesia, **30**(4), 393–397.

[13] Privado M. S., A. M. Issy, V. L. Lanchote (2010) Epidural versus intravenous fentanyl for postoperative analgesia following orthopedic surgery: randomized controlled trial, Sao Paulo Med. J., **128**(1), 5–9.

[14] Abedinov F., N. Bakalova., P. Krastev, I. Petrov, R. Marinova, G. Tzatyanski (2019) Survival and Quality of Life of Patients with a Prolonged Stay in the Intensive Care Unit after Cardiac Surgeries – Remote Results, C. R. Acad. Bulg. Sci., **72**(8), 1130–1136.

[15] Abedinov F., P. Krastev, I. Petrov, R. Iliev, K. Tsvetanova (2018) Risk Factors for Prolonged Length of Stay in the ICU Following Cardiac Surgery, International Journal of Science and Research, **7**(3), 67–71.

*Clinic of Anaesthesiology and Intensive Care*
*University Hospital "Alexandrovska"*
*1 Georgi Sofiiski St*
*1431 Sofia, Bulgaria*
*e-mail*: petya.hubenova@gmail.com
atemelkov@abv.bg

**Cardiology Clinic*
*University Hospital "St. Ekaterina"*
*52A, P. Slaveykov Blvd*
*1431 Sofia, Bulgaria*
*e-mail*: plamenkr@mail.bg