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Stress Response Measured by Cortisol and Adrenocorticotropic Hormone in Bupivacaine 0.5% Epidural Versus General Anesthesia During the Different Prostate Surgery

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Abstract : The study intended to evaluate the levels of adrenocorticotropic hormone (ACTH) and cortisol as a general markers of stress response in patients undergoing radical prostatectomy and transvesical adenectomy in bupivacaine administered epidural versus general anesthesia. This study was prospective, interventional and included a total of 120 patients from Urological Clinic of Clinical Centre of University of Sarajevo, that were stratified into 4 groups of 30 participants, based on inclusion criteria for 2 different operative methods for prostate related diseases. Both methods that were applied had a group of patients receiving epidural versus the group receiving the general anaesthesia. The stress response was evaluated through cortisol levels and 24-hour urine and ACTH in plasma samples. Study showed an increase of ACTH intraoperatively with both types of applied anaesthesia, but with significantly larger increase in patients subjected to general anaesthesia $F(2.115) = 56.75$, $p<0.05$. Also, it showed cortisol increase during the surgical procedure with both types of applied anaesthesia, but significantly higher increase in patients subjected to general anaesthesia $U=1220$, $Z=-3.05$, $p<0.01$, $r=-0.28$, and cortisol in urine increase regardless of the type of anaesthesia with significantly higher increase in patients subjected to the general anaesthesia. It is evident that epidural bupivacaine-based anesthesia has more favorable profile in terms of stress response indicators irrelevant of methodology of surgical procedure or baseline indication. Values of ACTH and cortisol (blood and urine) should be considered as relevant indicators in a patient recovery after application of different modalities of anesthesia.

Keywords: *ACTH, cortisol, anaesthesia, adenomectomy*

I. INTRODUCTION

General magnitude of the stress response in the patient is greatly dependent on type of the applied anaesthesia, as well as the anesthesiologist's expertise [1-4]. Stress is defined by series of negative noxious substances

affecting the patient's organism resulting in decrease of immune defences, increase of mortality rate and prolongation of hospitalization [1,5,6].

The magnitude of stress response depends on several factors, such as length and potency of the surgical trauma, patient's age, volume of blood loss during surgical procedure, pain, type of anaesthesia and surgical techniques [7].

Activation of the sympathetic nerve system increases the secretion of adrenocorticotropic hormone (ACTH) by sending afferent impulses through hypothalamus and anterior lobe of pituitary gland. ACTH increases the secretion of antidiuretic hormone (ADH) and catecholamines, with which it compensates for hypovolemia and loss of arterial pressure [8].

Periventricular nuclei of pituitary gland play central role in discharge of stress hormones as well as regulation of autonomic nerve system activities [9]. Funcke et al. (2021) described the relationship between the extent of nociception and variation in serum cortisol concentrations, depending on if very low or higher doses of anesthetic medication were used [10].

The aim of the study is to evaluate the changes in cortisol concentration in serum and urine, and ACTH in serum in patients undergoing radical prostatectomy (RP) and transvesical adenectomy (TA) under epidural and general anaesthesia (GA).

By observing hormonal changes in surgeries performed under epidural and general anaesthesia, this study aims to provide results which would benefit to more efficacious clinical work and provide better recommendations for balancing of type and technique of applied anesthesia [11,12]. According to the available literature, this is the first study in our country with such an aim and opens opportunities for further, more intensive research.

II. MATERIALS AND METHOD

2.1. Patients and study design

Study was designed as an open, interventional, randomized and stratified comparative trial conducted at Clinical Centre of University of Sarajevo in period 2013-2015. A total sample of 120 patients from Urological Clinic underwent RP or TA surgical procedure for 18 months. They were randomized into following four groups of 30 participants: participants subjected to TA performed under epidural anesthesia; participants subjected to TA performed under general anesthesia; participants subjected to RP performed under epidural anesthesia and participants subjected to RP performed under general anesthesia.

Third and fourth group included patients with clinical organ – limited carcinoma.

Epidural anaesthesia was performed by administration of bupivacaine 0.5% dosed per body surface, and GA was administered per guided scheme that involved droperidole (DHBP) 0.02 – 0.07 mg/kg, fentanyl 3 μg/kg IV, plus oxygenation with 100% O2. For introduction it has been administered propofol in 1.5 mg/kg, for intubation relaxant atracurium besilat in 0.3-0.6 mg/kg. Further on GA has been continued with gases and with addition of sevoflurane 0.8–2.2%, depending on age. Study population was selected based inclusion criteria's including confirmation of diagnosis by medical history, digital rectal exam, transrectal ultrasound of the prostate, measurements of residual urine, urine flow and analysis, values of PSA in serum and prostate biopsy.

All adult patients who were diagnosed with MM and went to Clinical University Center of Sarajevo as an outpatient and/or inpatient were included in this study. Patients who entered the study had to meet several criteria: to have monoclonal plasma cells in the bone marrow, to have monoclonal protein present in the serum and/or urine and to have evidence of lytic bone lesions. Exclusion criteria for this study were: previous or

concomitant other malignancies, primary or secondary thrombocytopenia and chronic anti-inflammatory medication users. In this retrospective study we have used data from 90 MM patients who were divided into three groups: patients who were newly diagnosed; those at steady state of MM and those who were in relapse state - 30 patients in each group. On the other hand, all of them have been classified by MM International Staging System (ISS), using relevant parameters to do so.

2.2. Methods

This study used sampling of ACTH in serum, cortisol in serum and urine and creatinine clearance as its research instrument. Sampling of adrenocorticotropic hormone was performed at three time points: at 8.00 a.m. prior to anaesthesia application, intraoperatively, during the enucleation of glandular prostatic tissue or complete removal of prostate including vesicles, and at 10.00 a.m., 24 hours, postoperatively.

Sampling of cortisol was performed at six different time points: during the first day at 8.00 a.m., intraoperatively at 9.00 a.m., postoperatively at 10 a.m., at 4.00 p.m. and at 11.00 p.m. The last sample was obtained on the day after procedure at 10.00 a.m.

Sampling of cortisol in urine was done in the 24-hour urine on the day before surgical procedure, and the urine samples were collected at 7.00 a.m. on the same day and on the following day. Afterwards, container was replaced, and cortisol was tracked in the urine during the 24-hour period on the day of the surgical procedure from 7.00 a.m., preoperatively, intraoperatively and postoperatively, until 7.00 a.m. on the following day.

Assessment of ACTH in plasma was done in the Central Biochemical Laboratory at the Clinical Centre on by the method of Electro Chemical Illuminescence Immuno Assessment (ECLIA). Assessment of cortisol in plasma and urine was done in the Central Biochemical Laboratory, measured with enhanced chemiluminescent immunoassay.

2.3. Statistical analysis

Data was presented through classical methods of descriptive statistics, through tables and graphs. Corresponding comparisons of arithmetic medians were tested with Mann-Whitney or Kruskal-Wallis, depending on number of cohorts. Relations of hormonal variations were assessed using MANOVA. Surface under the curve was calculated in assessing individual sampling time points. Statistical significance was set at $p<0.05$.

III. RESULTS

Total quantity of secreted ACTH (extrapolated from three measurements) is on average M=2137.46 pg/ml, SD=1806.62 pg/ml, spanning from 170.20 to 10217.10 pg/ml. Average value of secreted ACTH in procedures performed under general anaesthesia is Mdn=1973.70 pg/ml with average range of 67.62. In procedures performed under epidural anaesthesia value is Mdn=1115.55 pg/ml, with average range of 53.38. The difference is statistically significant: U=1373, Z=-2.24, $p<0.05$, r=-0.20 (Figure 1).

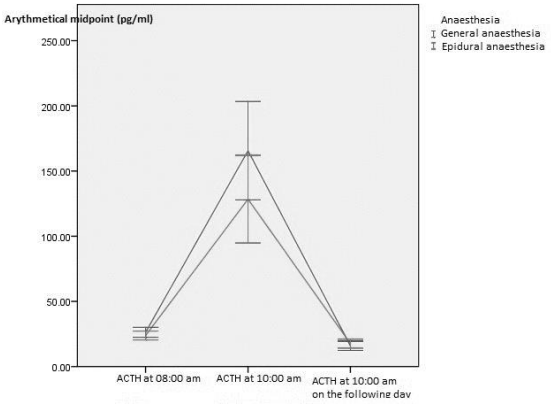

Figure 1. Changes of ACTH in three measurements in relation to applied anaesthesia. Columns represent intervals with 95% accuracy.

Total quantity of secreted cortisol (extrapolated from six assessments) is on average M=15510.02 nmol/L, SD=5265.45 nmol/L, spanning from 7834.5 to 28653 nmol/L. Average value of secreted cortisol in procedures performed under general anaesthesia is Mdn=15768 nmol/L with average range of 70.17, and in procedures performed under epidural anaesthesia Mdn=12806 nmol/L, with average range of 50.83. The difference is statistically relevant: U=1220, Z=-3.05, p<0.01, r=-0.28 (Figure 2).

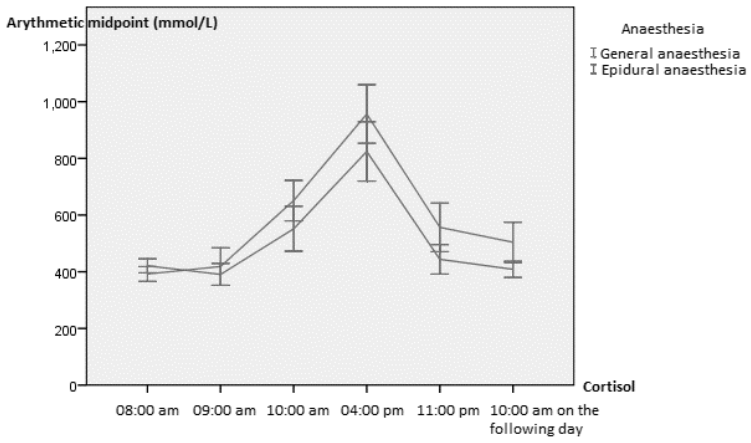

Figure 2. Changes related to the levels of cortisol measured in six instances regarding the applied anaesthesia. Columns represent intervals with 95% accuracy.

Differences between values measured at different time points are significant (MANOVA): F(5,112) = 48.94, p<0.05 and among the groups: F(15,342) = 5.68, p<0.05.

Post-hoc testing was used to establish that the differences are statistically significant (Bonferroni) amongst the following three groups: Adenoma with epidural anaesthesia – Adenoma with general anaesthesia; Adenoma with epidural anaesthesia – Carcinoma with general anaesthesia; Adenoma with epidural anaesthesia – Carcinoma with epidural anaesthesia.

Post-hoc tests were used for determination of existence of statistically significant differences between the following pairs (Bonferroni): Adenoma with general anaesthesia – Adenoma with epidural anaesthesia; Adenoma with epidural anaesthesia – Carcinoma with general anaesthesia; Adenoma with epidural anaesthesia – Carcinoma with epidural anaesthesia.

Post-hoc test (Bonferroni) shows that the differences are significant in the following pairs: Carcinoma with general anaesthesia – Adenoma with general anaesthesia; Carcinoma with general anaesthesia – Carcinoma with epidural anaesthesia.

Total quantity of secreted cortisol in urine (extrapolated from two measurements) is on average M=261.51 nmol/daily urine, SD=114.77 nmol/daily urine, ranging from 102.5 to 707 nmol/daily urine. Average value of secreted cortisol in procedures performed under general anaesthesia is Mdn=266.5 nmol/daily urine with average range of 54.28 (Figure 3). Difference signifying the change in cortisol levels in urine during different times of measurement has been statistically significant: U=1426.5, Z=-1.96, $p<0.05$, r=-0.18.

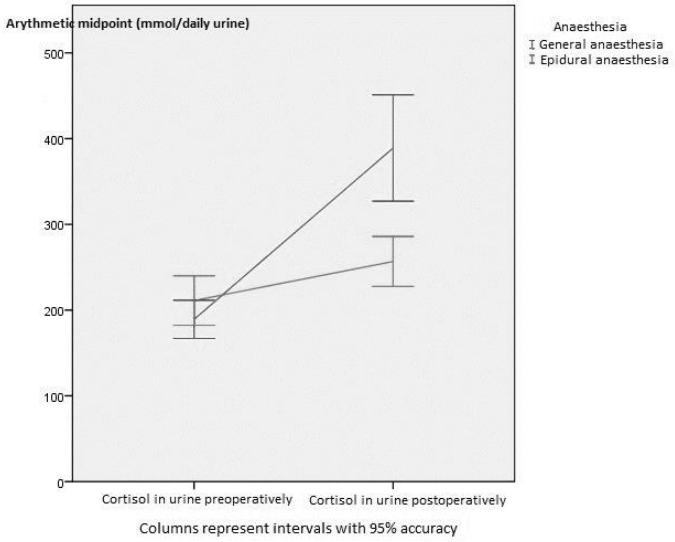

Figure 3. Changes of cortisol levels in urine during two measurements considering the applied anaesthesia. Columns represent intervals with 95% accuracy.

IV. DISCUSSION

ACTH has significant role in stress response to the surgical procedure. Prete et al. (2018) states that secretion of cortisol from the pituitary gland increases quickly from the start of the surgical procedure because of ACTH stimulation [1]. Our study confirmed the increase of ACTH intraoperatively with both types of applied anaesthesia, but with significantly larger increase in patients subjected to general anaesthesia. Values of ACTH return to their approximate preoperative values within the time of 24 hours postoperatively, with both types of applied anaesthesia.

The physiological feedback functions in a way that the increase in concentration of the circulating cortisol inhibits further creation of ACTH. This control mechanism becomes ineffective in period of several hours after the surgical procedure, and the concentration levels of both hormones remain high [1]. Khoo et al. (2017) also pointed out positive correlation of surgical severity with observed peak serum cortisol, suggesting that the more severe the operation, the greater the provoked stress cortisol response; this effect appears to overcome any inhibitory effect of opiate analgesia post-operatively [13].

Surgical severity can be depicted in type of surgery, as either conventional open surgery or minimally invasive surgery. Lesser stress response is expected with smaller incisions, reduced intraoperative bleeding, and lesser postoperative pain; however, minimally invasive surgery may also result in increased trauma due to factors such

as increased intra-abdominal pressure. Most commonly reported type of anesthesia used in both TA and RA was general anesthesia, regardless of type of procedure. Several researches indicated that propofol anesthesia significantly attenuated the increase in IL-6, TNF-α, CRP and NO levels during minimally invasive procedure, suggesting stronger stress response [13]. On the other hand, some newest research indicates that spinal epidural anesthesia seems to be more suitable and efficient technique for patients undergoing open RP [14-16].

Similar results are noted with cortisol values, with increase during the surgical procedure with both types of applied anaesthesia, but significantly higher increase in patients subjected to general anaesthesia. Values of cortisol reach their peak at 4.00 p.m. on the day when the surgical procedure is performed at every control group of patients. More prominent increase in cortisol levels has been registered at patients with diagnosed carcinoma.

The increase of cortisol is not limited only to period during the surgical procedure, but there is further increase after the surgical procedure which persists for several hours after the procedure. Values started to decrease in evening hours and eventually returned to their referential range.

Normal basal values are ~400 nmol/litre-1, and the research shows that the same values can reach over 1500 nmol/litre-1 within 4-6 hours from the start of larger surgical procedure [2].

This advantageous adaptive process of immune modulation of adrenal glucocorticoid secretion as a stress response, unfortunately has the potential to become maladaptive, especially in cases of chronic inflammatory disease [17]. Relative perioperative cortisol deficiency is an under-recognized contributor to perioperative organ injury, which was avoided by excluding the patients older than 75 years of age and with values of selected hormones in referential range during the preoperational stage [9].

Statistically significant increase in values of cortisol in urine after surgical procedure have been recorded. Values of cortisol in urine increase regardless of the type of anaesthesia used, with significantly higher increase in patients subjected to the general anaesthesia compared to patients subjected to the epidural anaesthesia. Increased values of cortisol in urine are additional indicator of higher cortisol secretion in patients subjected to general anaesthesia and its cumulative effect.

V. CONCLUSION

It is evident that epidural bupivacaine-based anesthesia has more favorable profile in terms of stress response indicators irrelevant of methodology of surgical procedure or baseline indication.

REFERENCES

[1] Prete A, Yan Q, Al-Tarrah K, Akturk HK, Prokop LJ, Alahdab F, Foster MA, Lord JM, Karavitaki N, Wass JA, Murad MH, Arlt W, Bancos I. The cortisol stress response induced by surgery: A systematic review and meta-analysis. Clin Endocrinol (Oxf) 2018; 89(5):554-67.
[2] Kelliher LJS, Scott M. Modifying the Stress Response - Perioperative Considerations and Controversies. Anesthesiol Clin 2022; 40(1):23-33.
[3] Du YT, Li YW, Zhao BJ, Guo XY, Feng Y, Zuo MZ, Fu C, Zhou WJ, Li HJ, Liu YF, Cheng T, Mu DL, Zeng Y, Liu PF, Li Y, An HY, Zhu SN, Li XY, Li HJ, Wu YF, Wang DX, Sessler DI; Peking University Clinical Research Program Study Group. Long-term Survival after Combined Epidural-General Anesthesia or General Anesthesia Alone: Follow-up of a Randomized Trial. Anesthesiology 20211;135(2):233-45.
[4] Ljungqvist O, Scott M, Fearon KC. Enhanced Recovery After Surgery: A Review. JAMA Surg 2017; 152(3):292-8.
[5] Bonhomme V, Staquet C, Montupil J, Defresne A, Kirsch M, Martial C, Vanhaudenhuyse A, Chatelle C, Larroque SK, Raimondo F, Demertzi A, Bodart O, Laureys S, Gosseries O. General Anesthesia: A Probe to Explore Consciousness. Front Syst Neurosci 2019;13:36
[6] Cusack B, Buggy DJ. Anaesthesia, analgesia, and the surgical stress response. BJA Educ 2020; 20(9):321-8.

[7] Manou-Stathopoulou V, Korbonits M, Ackland GL. Redefining the perioperative stress response: a narrative review. British journal of anaesthesia 2019; 123.5:570-83.
[8] Hou BJ, Du Y, Gu SX, Fan J, Wang R, Deng H, Guo DX, Wang L, Wang YY. General anesthesia combined with epidural anesthesia maintaining appropriate anesthesia depth may protect excessive production of inflammatory cytokines and stress hormones in colon cancer patients during and after surgery. Medicine (Baltimore) 2019; 98(30):e16610.
[9] Dobson GP. Trauma of major surgery: A global problem that is not going away. Int J Surg 2020; 81:47-54.
[10] Funcke S, Pinnschmidt HO, Brinkmann C, Wesseler S, Beyer B, Fischer M, Nitzschke R. Nociception level-guided opioid administration in radical retropubic prostatectomy: a randomised controlled trial. Br J Anaesth 2021; 126(2):516-24.
[11] Lusty AJ, Hosier GW, Koti M, Chenard S, Mizubuti GB, Jaeger M, Siemens DR. Anesthetic technique and oncological outcomes in urology: A clinical practice review. Urol Oncol 2019; 37(12):845-52.
[12] Koo CH, Ryu JH. Anesthetic considerations for urologic surgeries. Korean J Anesthesiol 2020; 73(2):92-102.
[13] Khoo B, Boshier PR, Freethy A, Tharakan G, Saeed S, Hill N, Williams EL, Moorthy K, Tolley N, Jiao LR, Spalding D, Palazzo F, Meeran K, Tan T. Redefining the stress cortisol response to surgery. Clin Endocrinol (Oxf) 2017; 87(5):451-8.
[14] Georgiades F, Konstantinou K, Kouriefs C. Robotic assisted laparoscopic radical prostatectomy following open trans-vesical adenomectomy: A single centre experience and review of the literature. Urologia 2021; 88(2):135-9.
[15] Roh GU, Song Y, Park J, Ki YM, Han DW. Effects of propofol on the inflammatory response during robot-assisted laparoscopic radical prostatectomy: a prospective randomized controlled study. Sci Rep 2019; 9(1):5242.
[16] Kofler O, Prueckner S, Weninger E, Tomasi R, Karl A, Niedermayer S, Jovanovic A, Müller HH, Stief C, Zwissler B, von Dossow V. Anesthesia for Open Radical Retropubic Prostatectomy: A Comparison between Combined Spinal Epidural Anesthesia and Combined General Epidural Anesthesia. Prostate Cancer 2019; 2019:4921620.
[17] Lightman SL, Birnie MT, Conway-Campbell BL. Dynamics of ACTH and Cortisol Secretion and Implications for Disease. Endocr Rev 2020; 41(3):bnaa002.