Epidural anesthesia can block the negative effects of prostaglandin mediators during prostate surgery

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Introduction: *Inflammation plays a key role in the development of benign prostatic hyperplasia. Prostaglandin E2 (PGE2) is an important inflammation factor found in enlarged prostatic tissue that can be the main cause of inflammatory pain. The aim of this study was to investigate whether epidural anesthesia can block the negative effects of prostaglandin mediators during prostate surgery.*

Materials and methods: *The study included 60 patients who underwent open prostatectomy. All patients were randomly allocated to one of two study groups. The first group received general anesthesia and the second group a combination of general and epidural anesthesia. Main outcome measures were plasma concentration of PGE2, adrenaline, noradrenaline, and dopamine, before induction of anesthesia and at the time of enucleation.*

Results: *Preoperative serum concentrations of PGE2 were high in both groups. During enucleation, serum concentrations of adrenaline, noradrenaline, and dopamine increased, followed by a rise of systolic and diastolic blood pressure in the group of patients that received only general anesthesia. Serum concentration of PGE2 was at the same level as before induction of anesthesia in both groups.*

Conclusion: *Epidural anesthesia blocks transmission of painful stimulus through the spinal cord caused by prostaglandin release and prevents the rise of catecholamines and blood pressure. Open prostatectomy can become a safer procedure performed under a combination of general and epidural anesthesia. Negative intraoperative effects of inflammatory prostate mediators during other techniques for prostate surgery could also be blocked with epidural anesthesia.*

Key Words: open prostatectomy, inflammation, benign prostatic hyperplasia, prostaglandin E2, epidural anesthesia

Introduction

Benign prostatic hyperplasia (BPH) represents the most common urologic diagnosis in elderly males.[1] Despite its frequency, however, the pathogenesis of BPH is still largely unresolved. Indeed, although multiple theories have been proposed, the etiology of BPH still remains uncertain. Several mechanisms seem to be involved in the development and progression of BPH. Although aging represents the central mechanism implicated, recent findings also highlight the key role of androgens and estrogens, metabolic syndrome, and prostatic inflammation that stimulates cellular proliferation.[2,3]

During the last two decades, the role of chronic inflammation in the pathogenesis of BPH has emerged. Kohnen and Drach reported that 98% of all analyzed BPH specimens had an inflammatory infiltrate.[4,5]

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The MTOPS Medical Therapy of Prostatic Symptoms (MTOPS) study has also detected an association between prostatic inflammation and higher prostate volume, higher risk of urinary retention, and higher risk of symptomatic evolution.[6,7] In the recent decade, following these results and new insights on BPH pathogenesis and progression, numerous studies have investigated inflammatory markers in BPH. The study of Robert et al showed that patients with presence of high grade prostate inflammation had higher prostate volume than patients with low grade inflammation.[8] Patients with high grade inflammation were also more likely to undergo open prostatectomy.

The production of prostaglandins and leukotriene lipid mediators are key events in acute and chronic inflammation.[9] The most abundant derivative of prostaglandin H2 (PGH2) in prostate is the prostaglandin E2 (PGE2) which is synthesized by several PGE2 synthases.[10] The expression of PGE2 synthases has not been well studied in BPH or prostate cancer until now. A recent study confirms a correlation between PGE2 and inflammatory infiltrates, suggesting increased production of PGE2 by inflammatory cells. PGE2 levels are higher in the transitional zone when prostate volumes are higher. PGE2 and inflammation may be associated to stromal BPH whereas leukotriene B4 (LTB4) may play a role in prostate carcinogenesis.[11] PGE2 is an important inflammation factor that is associated with BPH by regulating cell proliferation, migration, and apoptosis. In BPH and prostate cancer, the production of PGE2 is significantly increased. However, the exact molecular mechanism that PGE2 regulates has not been well studied.[12] PGE2 has been implicated as playing a pivotal role in inflammatory pain by interacting with G-protein-coupled receptors on peripheral nociceptors and spinal neurons. The diversity of PGE2 actions is mediated by activation of prostaglandin E receptors that comprise subtypes EP1 to EP4 messenger ribonucleic acid (mRNAs).[13,14] In general, EP2, EP3, and EP4 are coupled to stimulation and inhibition of adenylate cyclase, and EP1 enhances Ca^{2+} mobilization. EP1, EP3, and EP4 were expressed in approximately 30%, 50%, and 20% of dorsal root ganglion neurons, respectively, and all EP receptor mRNAs are expressed in lumbar spinal cords. PGE2 induces allodynia by stimulation of orphanin FQ (N/OFQ) release in the spinal cord via EP4 receptor subtypes.[15]

Open prostatectomy represents one of the oldest surgeries to treat BPH. During the last two decades, numerous minimally invasive therapy modalities have been developed to challenge the traditional surgery of BPH.[16] Because of these options, associated with minimal anesthesia, risks, contraindications, complications, and hospital stays, the need for open prostatectomy is becoming limited today. However, open prostatectomy continues to be the treatment of choice for men with excessively large prostates, presence of bladder diverticuli or damage, and/or large stones.[17]

With an aging population and increasing morbidity of urological patients, especially with cardiovascular etiology, it is important to make this operative procedure safer for these patients. The increase of blood pressure and heart rate at the time of prostate enucleation are frequent events associated with open prostatectomy. Avoidance of serious intraoperative cardiovascular events, especially rise of blood pressure, and hence protection of patients from serious consequences is one of the primary goals of anesthesia during this procedure.

There are numerous studies confirming favorable effects of the combination of general and epidural anesthesia on perioperative morbidity. Some data suggests that regional anesthesia might reduce the incidence of malignant cell recurrence and prevent bleeding during open radical prostatectomy.[18]

The aim of this study was to investigate whether epidural anesthesia can block the negative effects of prostaglandin mediators during prostate surgery.

Material and methods

With the approval of the Ethical Committee and after obtaining informed consent, the study was carried out on 60 American Society of Anesthesiologists (ASA) physical status II patients aged 63-76 years. All patients had diagnosed BPH and were scheduled to undergo open prostatectomy at the Clinic of Urology at the Clinical Center of Serbia between November 2009 and November 2010. Patients with a history of myocardial infarction, previous cerebrovascular accident, transient ischemic attack, diabetes, obesity, and previous hypertension were excluded from the study. Also the patients with any other known acute or chronic inflammatory process were excluded. The patients were allocated to one of two groups using a computer generated randomization list manipulated by statistician in a sealed envelope.

Thirty patients who underwent open prostatectomy under general anesthesia only (GETA) comprised the first group. They were compared with 30 patients (second group) who underwent open prostatectomy under a combination of general anesthesia and epidural anesthesia (GETA+EA). Half an hour prior to induction of anesthesia, both groups received usual

premedication (midazolam 5 mg and atropine 0.5 mg i.m.). Methods of balanced general anesthesia were the same in both groups of patients. Most typically, this includes 1.5 µg/kg of fentanyl and 2 mg/kg of propofol for induction of anesthesia, and neuromuscular antagonism to facilitate tracheal intubation with 0.6 mg/kg of rocuronium bromide. General anesthesia was maintained with a mixture of sevoflurane (Fex = 0.8%), nitrous oxide, and oxygen (FiO_2 = 0.40). The neuromuscular antagonism maintenance dose was 0.15 mg/kg rocuronium bromide, which was administered when two responses to train-of-four stimuli were present. In the patients of the second (GETA) group, analgesia was maintained by intravenous injection of opiates, this included 1.0 µg/kg fentanyl bolus injection.

In the second group (GETA+EA), an epidural catheter was placed preoperatively at level Th12-L1 and a preemptive dose of local anesthetic (14 mL of levobupivacaine 0.25%) was given before the induction of anesthesia. Anesthesia was maintained by 5 mL/h of levobupivacaine 0.125% through an epidural catheter.

Intraoperative monitoring for all patients included recording a continuous five-lead electrocardiogram with special attention to ST segment, oxygen saturation by pulse oximetry, and non-invasive blood pressure, airway gas analysis, capnography, and train-of-four (TOF).

The plasma concentration of PGE2, adrenaline, noradrenaline, and dopamine were measured in the operating room just before induction of anesthesia and during the operation, at the time of prostate enucleation. The PGE2 plasma concentrations were measured using specific enzyme immunoassay kits (Prostaglandin E2 EIA Kit–Monoclonal, Cayman Chemical Company, Ann Arbor, MI, USA). The assay was performed according to the manufacturer's instructions. Normal plasma levels for PGE2 are 3-12 pg/mL. Adrenaline, noradrenaline, and dopamine were measured using specific enzyme immunoassay kits (Catecholamine-ELISA, DLD Diagnostika GmbH, Hamburg, Germany). Normal plasma levels are: adrenaline < 100 pg/mL, noradrenaline < 600 pg/mL, and dopamine < 100 pg/mL. To determine the total prostate-specific antigen (PSA), both free PSA and PSA complexed to alph-1-actichymotrypsin, the AxSYM Total PSA test (Microparticle Enzyme Immunoassay-MEIA, Abbott Labs) was used. The normal plasma level for total PSA was estimated according to age and prostate volume specific adjustment. All patients underwent complete urologic assessment including International Prostate Symptom Score (IPSS), quality of life (QoL), digital rectal examination, ultrasound, and transrectal ultrasound if necessary. Prostate weight was measured after surgical prostate enucleation.

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS version 16.0, SPSS Inc., Chicago, IL, USA). Results are presented as mean ± standard deviation. In each group, the t-test for paired samples was used to compare parameter changes before and after prostate enucleation where there were normally distributed variables while the Wilcoxon unpaired test was used for variables with persisting skewed distribution. Pearson's rank or Spearman's correlation coefficients were calculated between variables using a two-tailed significance test for variables with a Gaussian or non-Gaussian distribution, respectively. A result is considered statistically significant if $p < 0.05$.

Results

The anthropometric and biochemical parameters for all 60 patients from the study are summarized in Table 1. The preoperative serum concentration of PGE2, dopamine, and preoperative PSA were higher than reference ranges.

All patients were divided into two groups by type of anesthesia. The clinical and biochemical parameters of each group are summarized in Table 2, showing there were no statistically significant differences between groups. Blood pressure, heart rate, serum adrenaline, and noradrenaline were in normal range in both

TABLE 1. **Anthropometric and biochemical parameters for all 60 patients**

Number of patients	60
ASA physical status (score)	2
	mean ± SD
Age (years)	70 ± 6.2
Body mass index (kg/m²)	25.78 ± 2.34
Prostate-specific antigen (ng/mL)	10.01 ± 6.2
PGE2 (pg/mL)	37.3 ± 19.3
Adrenaline (pg/mL)	79.83 ± 37.32
Noradrenaline (pg/mL)	254.13 ± 122.46
Dopamine (pg/mL)	244.81 ± 197.4
Systolic blood pressure (mmHg)	132.82 ± 11.11
Diastolic blood pressure (mmHg)	78.63 ± 11.51
Heart rate (beat/min)	73.82 ± 10.81
Prostate weight after enucleation (gr)	114.17 ± 60.35

TABLE 2. **Clinical and biochemical parameters before induction of anesthesia according to the patient groups**

Clinical and biochemical parameters before induction of anesthesia	Group 1 (mean ± SD)	Group 2 (mean ± SD)
Number of patients	30	30
Age (years)	70.53 ± 6.3	69.4 ± 6.12
Body mass index (kg/m²)	25.7 ± 2.76	25.86 ± 1.88
Prostate-specific antigen (ng/mL)	10.94 ± 5.75	9.08 ± 6.58
Prostata weight after enucleation (gr)	109.33 ± 71.15	119 ± 47.97
Systolic blood pressure (mmHg)	128.93 ± 6.90	136.7 ± 13.12
Diastolic blood pressure (mmHg)	74.67 ± 9.81	82.6 ± 11.87
Heart rate (beat/min)	70.91 ± 12	76.7 ± 10.92
Adrenaline (pg/mL)	75.47 ± 39.62	84.2 ± 35
Noradrenaline (pg/mL)	221.27 ± 148.04	287 ± 79.73
Dopamine (pg/mL)	87.51 ± 40.41	402.1 ± 162.64
PGE2 (pg/mL)	49.23 ± 18.69	25.35 ± 10.73

groups. An equal number of patients were randomly assigned to one of two groups; preoperative serum concentrations of dopamine were normal in Group 1 and high in Group 2. Preoperative serum concentration of PGE2 was high in both groups. Prostate weight was measured after operative enucleation, and there were no statistically significant differences between groups.

Significant negative correlation between preoperative serum concentrations of dopamine and PGE2 (Spearman's rho ρ = -0.563, p < 0.01) was found by bivariate correlation analysis, Figure 1.

In the first group of patients, who received general anesthesia, at the time of prostate enucleation, systolic (t = 31,689, p < 0, 01) and diastolic (t = 21,095 p < 0, 01) blood pressure were statistically higher than before induction of anesthesia, and there was no statistically significant difference in heart rate. Also, the serum concentration of adrenaline (p < 0.01), noradrenaline (p < 0.05), and dopamine (p < 0.01) was statistically higher at the time of prostate enucleation without any changes in serum level of PGE2 (p > 0.05), Table 3.

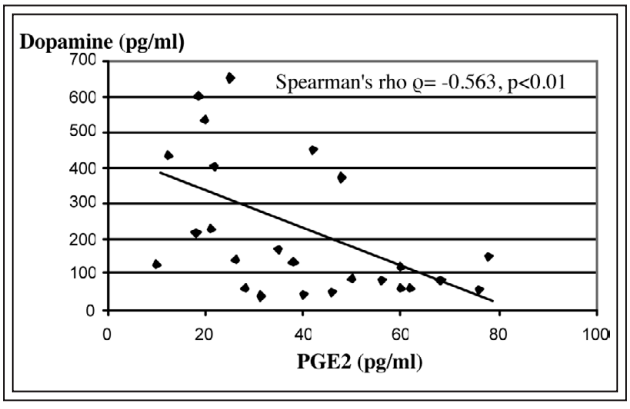

Figure 1. Correlation between preoperative serum concentrations of dopamine and PGE2 for all 60 patients.

Patients in the second group, who received general anesthesia and epidural anesthesia, had lower systolic (t = 33.05, p < 0.01) and diastolic (t = 19.27 p < 0.01) blood pressure and heart rate (t = 2.439, p < 0.01) at the time of prostate enuclation. Also, serum concentrations of adrenaline (p < 0.01), noradrenaline (p < 0.01), and dopamine (p < 0.01), were statistically lower than before induction of anesthesia while there were no changes in serum level of PGE2 (p > 0.05), Table 4.

We found that all patients preoperatively had increased prostate weight, serum PSA, and serum dopamine. During manipulation of the prostate tissue (prostate enucleation), we have noticed increased serum concentration of adrenaline, noradrenaline, and dopamine followed by rise of systolic and diastolic blood pressure, in the group of patients that received only GETA. The serum concentration of PGE2 was at the same level as before induction of anesthesia in both groups.

There were no differences in term of pathology between the groups, based on anesthesia and size of prostate. The operating time was not different. We have not detected other factors that could have made the inflammation response different.

TABLE 3. **Clinical and biochemical parameters of patients in the first group before induction of anesthesia and in the time of prostate enucleation**

Group 1	Before induction of anesthesia (mean ± SD)	In the time of prostate enucleation (mean ± SD)		
Systolic blood pressure (mmHg)	128.93 ± 6.90	146.4 ± 27.26	t = 31.689	p < 0.01
Diastolic blood pressure (mmHg)	74.67 ± 9.81	91.73 ± 20.43	t = 21.095	p < 0.01
Heart rate (beat/min)	70.91 ± 12	75.6 ± 19	t = -1.699	p > 0.05
Adrenaline (pg/mL)	75.47 ± 39.62	124.27 ± 112.23	F = -2.71	p < 0.01
Noradrenaline (pg/mL)	221.27 ± 148.04	326 ± 176.09	F = -2.52	p < 0.05
Dopamine (pg/mL)	87.51 ± 40.41	215.33 ± 183.01	F = -3.59	p < 0.01
PGE2 (pg/mL)	49.23 ± 18.69	47.84 ± 21.35	F = -0.79	p > 0.05

Discussion

Surgical treatment of BPH is increasingly focused on the use of new technologies, especially emerging laser therapy. However, in cases of management of large prostate adenomas, open prostatectomy is still very common procedure, even in developed countries. A study investigating 570 urologists in North America emphasized that the two procedures urologists continue to utilize most are open prostatectomy (78%) and monopolar TURP (73%).[17] Meanwhile, recent data on surgical treatment of BPH showed that in cases of presence of high grade inflammation, patients were more likely to be operated on by open prostatectomy.[8] For this reason, we have decided to investigate the impact of inflammatory mediators during surgical manipulation with inflammatory prostate tissue on open prostatectomy, not as a target, but as a model.

Our work is the only instance, to the best of our knowledge, in which the concentration of PGE2 in blood has been directly measured before the induction of anesthesia as well as at the time of manipulation with inflamed prostate tissue.

There were two main finding in this study. First, patients in the epidural group had significantly lower heart rate and blood pressure increase at the time of prostate enucleation than patients who received only general anesthesia. Adrenaline, noradrenaline, and dopamine levels were also significantly lower in the epidural group compared with the general anesthesia group.

As we know, major surgery is associated with acute stress response. Epidural anesthesia moderates the neuroendocrine stress response to surgery by blocking afferent neural transmission from reaching the central nervous system and activating the stress response,

TABLE 4. **Clinical and biochemical parameters of patients in the second group before induction of anesthesia and in the time of prostate enucleation**

Group 2	Before induction of anesthesia (mean ± SD)	In the time of prostate enucleation (mean ± SD)		
Systolic blood pressure (mmHg)	136.7 ± 13.12	124.3 ± 19.83	t = 33.05	p < 0.01
Diastolic blood pressure (mmHg)	82.6 ± 11.87	76.5 ± 10.92	t = 19.27	p < 0.01
Heart rate (beat/min)	76.7 ± 10.92	71.1 ± 11.16	t = 2.439	p < 0.05
Adrenaline (pg/mL)	84.2 ± 35	41.8 ± 18.8	F = -4.48	p < 0.01
Noradrenaline (pg/mL)	287 ± 79.73	138.8 ± 67.35	F = -4.79	p < 0.01
Dopamine (pg/mL)	402.1 ± 162.64	185.1 ± 147.37	F = -4.79	p < 0.01
PGE2 (pg/mL)	25.35 ± 10.73	24.33 ± 14.83	F = -0.096	p > 0.05

and by blocking descending efferent activation of the sympathetic nervous system.[19] Epidural local anesthetics also suppress perioperative epinephrine and norepinephrine production.[20,21] Postoperative plasma levels of cortisol, adrenocorticotrophic hormone, aldosterone, and glucose, and urinary cortisol levels are lower after surgery with epidural blockade than other methods of analgesia.[22]

Furthermore, surgery, anesthesia, and analgesia induce a perioperative inhibition of immune function. Regional anesthesia and analgesia may help to preserve immune function by attenuating the surgical stress response, decreasing anesthetic requirement, and diminishing the needs for opioids.[23] Local anesthetics were shown to inhibit release of inflammatory mediators and block receptors for them. The agents are also able to down regulate processes involved in immune cell trafficking like adhesion and transmigration, resulting in lesser accumulation of the cells at the injury site.[24]

Ahlers et al hypothesised that epidural anesthesia reduces intraoperative stress, thereby attenuating the inflammatory response. He showed that intraoperative use of epidural anesthesia diminishes stress reactions and thus attenuates perioperative suppression of the adaptive immune system.[22]

The second finding is that serum levels of prostaglandin E2 did not significantly change before and after manipulation with the inflamed prostatic tissue. We presumed that the PGE2 levels were in correlation with the severity of inflammation in BPH. Larre and colleagues did show in their study the positive correlation between PGE2 level, prostatic volume, inflammatory scores, and decreased glandular surface.[9] PGE2 has an important role in the direct activation and/or sensitization of sensory nerves, and there is considerable evidence for increased sympathetic nerve activation.[25,26] Shahed and Shoskes demonstrated a correlation of higher PGE2 and lower beta-endorphin in the expressed prostatic secretions of symptomatic men with chronic prostate inflammation. They proposed that inflammatory cells in the prostates of men with prostatitis produce beta-endorphin locally and that high PGE2 levels inhibit the ability of beta-endorphins to modulate pain in this setting.[27] There is a well established association between acute inflammation, prostaglandin level, and pain sensation, but the exact correlation is poorly understood.

On the other hand, significant increases in sympathetic nerve activation have been found in patients who received general anesthesia only. We documented a statistically significant increase in serum concentration of adrenaline, noradrenaline, and dopamine followed by changes in blood pressure. The increase in heart rate was not statistically significant compared with patients in the epidural group. This is in accordance with Celic-Spuzic's study, which showed that regional anesthesia with sympathetic blockade causes greater suppression of hormonal responses than general balanced anesthesia.[28]

Conclusion

Our results confirm the hypothesis that epidural anesthesia can block the negative effects of prostaglandin mediators during prostate surgery, on the model of open prostatectomy. As an association between prostatic inflammation and higher prostate volume, but also higher risk of urinary retention and symptomatic evolution in smaller prostates, are well established, negative intraoperative effects of inflammatory prostate mediators during other techniques for prostate surgery could also be blocked with epidural anesthesia. Further studies are necessary to investigate this hypothesis.

This study has a few limitations. Several other inflammatory mediators are important in benign prostatic enlargement and inflamed prostatic tissue, such as IL-6,IL-8, and IL-17. Furthermore, we did not compare PGE2 levels in our patients with PGE2 levels in others diagnosed with BPH but with significantly smaller prostate glands. And finally, as we presumed that the more inflamed prostate would cause the greater pain when manipulated, we measured only serum levels of adrenaline, noradrenaline, and dopamine as the indirect markers of severity of intraoperative pain and stress levels. □

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