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THE IMPACT OF ANAESTHESIA ON HYPERALGESIA, TESTOSTERONE, CORTISOL, C-REACTIVE PROTEIN, AND GLUCOSE LEVELS AFTER SPINE SURGERY: PROSPECTIVE RANDOMISED CONTROLLED TRIAL

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Abstract

Background: *A large number of spinal deformities with severe pain are treated with complex and traumatic spinal surgeries. The objectives of our study were to test the hypotheses that bilateral erector spinae plane block (BESPB) as a component of combined anaesthesia for spinal surgeries decreases the quantity of opioid analgesic used and reduces hyperalgesia in comparison with general anaesthesia. We additionally proposed the use of serum testosterone, cortisol, C-reactive protein (CRP), and glucose levels as laboratory markers for hyperalgesia.*

Methods: *Fifty-two patients who underwent posterior transpedicular fixation of the spine were randomly assigned to either general anaesthesia – control group (CG) – or combined anaesthesia with BESPB – study group (SG). The main outcomes sought were quantity of opioid analgesic perioperatively; hyperalgesia measured with mechanical pain thresholds; and testosterone, cortisol, CRP, and glucose serum levels before and after surgery.*

Results: *The quantity of fentanyl and morphine was lower in SG in comparison with CG. There was no difference in mechanical pain thresholds in the SG cohort as opposed to CG, where mechanical pain thresholds were lower on the fifth day after surgery. No difference was found before and after surgery in testosterone, cortisol, CRP, and glucose levels in SG. In the CG, the level of testosterone was significantly lower than baseline; the levels of cortisol, CRP, and glucose were significantly higher than baseline on the fifth day after surgery.*

Conclusion: *Bilateral erector spinae plane block as a component of combined anaesthesia for spinal surgeries reduces the quantity of opioid analgesic used and hyperalgesia. Also, we can propose to use the serum testosterone, cortisol, CRP, and glucose levels as the laboratory markers of hyperalgesia.*

Keywords

erector spinae plane block • hyperalgesia • testosterone • cortisol • C-reactive protein

Introduction

The incidence of chronic postoperative pain in Europe 12 months after surgery is 11.8%. Severe pain occurs in 2.2% of those patients – when the intensity of pain reaches more than 6 points on the visual analogue scale (VAS). Signs of neuropathic pain were recorded in 35.4% of patients with severe pain and 57.1% of patients with moderate pain. Mild pain (VAS 1–2) was diagnosed in 17.4% of patients twelve months after spinal surgery. The percentage of patients with moderate-to-severe pain (VAS 3–5) reached 39.1%. Effective treatment of pain is critically important precisely on the first day after surgery, because prolonged severe postoperative pain is a risk factor for chronic postoperative pain [1].

It is important to detect the development of hyperalgesia and possible chronisation of the pain at an early stage. A pain complaint itself is a subjective criterion for assessing pain intensity. The characteristics of pain relayed by the patient are not always sufficient to determine hyperalgesia and chronic pain. The cornerstone of pain treatment is its objective assessment. Von Frey monofilaments are one of the ways to diagnose hyperalgesia [2]. Maximilian von Frey in the late nineteenth century proposed to use different diameter horsehairs to assess sensitivity [3]. Since then, monofilaments have been named after him. However, instrumental methods do not suffice to assess hyperalgesia and predict the development of chronic postoperative pain.

Every syndrome has its own specific patient complaints, clinical signs, and laboratory markers that determine and establish the final diagnosis and treatment. Subsequently, laboratory markers are used to assess the effectiveness of the treatment and patient recovery.

The diagnosis of hyperalgesia and chronisation of acute pain has its own laboratory markers [5, 14, 52] which can be

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assessed at the beginning of the disease, during treatment, and after patient recovery. Evaluation of laboratory markers of hyperalgesia allows us to change treatment and prevent chronic pain from developing. We propose using serum cortisol, testosterone, C-reactive protein (CRP), and glucose levels as laboratory markers of hyperalgesia.

Testosterone is synthesised by Leydig interstitial cells in the testes (testiculi) and controlled by luteinizing hormone–releasing factor of the hypothalamus. In women, testosterone synthesis occurs in the same manner in the ovaries (ovarium) [4]. The impact of testosterone on hyperalgesia and the perception of pain have been studied in animals. Thus, orchiectomy and further decrease in testosterone levels in male mice caused prolonged hyperalgesia. Subsequent administration of exogenous testosterone to these males significantly reduced hyperalgesia and returned it to preoperative levels [5]. Another study made a credible case that testosterone plays a protective role for pain perception in rats [6]. Moreover, low testosterone levels are likely to result in a widening pain field and neuronal plasticity which can turn into entrenched chronic pain states, which was found in fibromyalgia patients [7].

Cortisol is synthesised in the adrenal glands under control of corticotropin-releasing hormone in the hypothalamus. The main task of cortisol is to ensure the supply of energetic material to the body during the stress response, as quickly as possible. Therefore, activation of the hypothalamic–pituitary–adrenal system significantly increases serum cortisol level. Due to its high level, amino acids in the liver are metabolised to glucose. Cortisol also inhibits the absorption and use of glucose by all cells in the body, which counteracts the effect of insulin, causing an increase in serum glucose levels.

Hyperalgesia associated with hyperactivity of the hypothalamic–pituitary axis of the adrenal glands can be assessed employing adrenocorticotropic hormone and cortisol plasma concentrations [8]. In the study of the effects of nocebo on the activity of the hypothalamic–pituitary axis of the adrenal glands, cortisol was used as a marker of hyperalgesia as well [9].

It should be taken into consideration that hyperactivity of the hypothalamic–pituitary adrenal gland and constant rise in serum cortisol, due to constant pain and worry about its occurrence, leads to chronisation of pain [10, 11, 12]. However, not only pain influences serum testosterone and cortisol levels. Stress additionally decreases testosterone and increases cortisol levels in people who do not experience physical pain [13].

C-reactive protein is an acute-phase protein that is synthesised in hepatocytes. Most of the damaging processes in body tissues (infections, inflammatory diseases, malignant neoplasms, injury, or surgery) are associated with a pronounced acute-phase response of C-reactive protein and other acute-phase reactants. After the onset of the acute phase response, the concentration of C-reactive protein expands rapidly and significantly; its changes can be observed within 6 to 8 hours, and the peak value might be reached within 24 to 48 hours. The half-life of C-reactive protein is only a few hours, making it an ideal marker for clinical observations.

Recently it has been found that the intensity of acute pain is associated with increased concentrations of C-reactive protein. This elevation might be explained by inflammation of local soft tissues leading to pain and excessive C-reactive protein serum levels [14, 15]. Other studies have shown an association between inflammation and increased C-reactive protein with enlarged pain sensitivity and hyperalgesia [16, 17]. The association of elevated C-reactive protein serum levels with hyperalgesia and chronisation of pain may be explained by determining levels of cold pain activation in brain regions including the anterior insula, posterior parietal cortex, caudate nucleus, and thalamus [18].

Determining the glucose level is necessary to define the stress response. Also, serum glucose levels are used by researchers to compare the effectiveness of analgesia in various surgeries [19, 20] and even in the assessment of chronic pain [21].

The primary objective of our study was to test the hypothesis that bilateral erector spinae plane block (BESPB) as a component of combined anaesthesia for spinal surgeries would decrease the quantity of opioid analgesic and reduce hyperalgesia in comparison with general anaesthesia. The secondary objective was to test the hypothesis that the serum testosterone, cortisol, CRP, and glucose levels can be used as laboratory markers of hyperalgesia.

Materials and Methods

The study was carried out in 2021 at the Yuriy Semenyuk Rivne Regional Clinical Hospital and supervised by the Rivne Regional Council in the Department of Anaesthesiology and Intensive Care and the Rivne affiliate of the Department of Anaesthesiology and Intensive Care, Faculty of Postgraduate Education, Danylo Halytsky Lviv National Medical University. Ethical approval for this study (protocol № 5-1B/1612) was granted by the Commission of Ethics and Bioethics at the Yuriy Semenyuk Rivne Regional Clinical Hospital and was supervised by Rivne Regional Council (chairman V. Tkach), 16 December 2020.

All participants provided written informed consent to participate in the study. The study was registered on ClinicalTrials.gov (identification number NCT04697498). Study design: open, prospective, controlled, randomized, allocation ratio 1:1.

Randomisation assignments were generated using an internet-based randomisation software (https://www.random.org) and was performed after the patient was administered general anaesthesia and was intubated. With patient in prone

position, before skin incision the researcher staff randomly assigned the patient to the control or study group. The control group (CG) included patients who underwent surgery under general anaesthesia. In this group no regional techniques were performed. The study group (SG) included patients who underwent surgery under general anaesthesia with a BESPB. In this group, before skin incision the anaesthesiologist performed BESPB. The skin puncture site for blockade was close to the incision and so small that no additional bandages were needed in the postoperative period; therefore, the patient did not know whether he was in the BESPB group. Anaesthesia providers were not blinded to group allocation, but patients and the assessors collecting the outcome data were. The control and study groups were further divided into two subgroups each depending on the sex: control group male (CGM), control group female (CGF), study group male (SGM), study group female (SGF); and age of the patients: control group male 20–49 years old (CGM1), control group male ≥50 years old (CGM2), control group female 20–49 years old (CGF1), control group female ≥50 years old (CGF2), study group male 20–49 years old (SGM1), study group male ≥50 years old (SGM2), study group female 20–49 years old (SGF1), study group female ≥50 years old (SGF2).

Primary outcome: hyperalgesia measured with the mechanical pain threshold assessed with Von Frey monofilaments.

Secondary outcomes were measures of serum testosterone, cortisol, and C-reactive protein levels before surgery and on the fifth day after surgery; serum glucose levels before surgery and 6 hours after surgery; and the quantity of opioid analgesic used intra- and postoperatively. Patients' testosterone, cortisol, C-reactive protein, and glucose serum samples were taken a few days before surgery, along with standard patient blood sampling between 8 and 9 am; patients were fasted for 8–12 hours before to get the most accurate results. Glucose levels were assessed 6 hours after surgery during the postoperative period. Serum samples of testosterone, cortisol, and C-reactive protein were collected on the fifth postoperative day between 8 and 9 am, patients were fasted for 8–12 hours before as well. Fentanyl was administered intraoperatively to all patients in both groups before tracheal intubation and skin incision. Furthermore, fentanyl administration differed in both groups, and depended on changes in heart rate and blood pressure. In addition, the administration of fentanyl depended on the phase of the surgery. The administration of morphine in the postoperative period depended on the intensity of pain on the VAS. Nonsteroidal anti-inflammatory drugs were taken every 6 hours postoperatively in both groups. Estimation of fentanyl quantity during surgery was performed by μg/kg-1h-1. Estimation of morphine quantity was performed after surgery by total milligrams for one patient.

To determine the mechanical pain threshold before surgery and on the fifth day after surgery Von Frey monofilaments were used. The set consists of 20 nylon filaments of different thicknesses in ascending order. Patients were asked to lie down on their backs, close their eyes and inform the doctor when they felt a clear point of contact with the skin. Monofilaments were pressed against the skin of the middle third of the palmar surface of the forearm at an angle of 90 ° until the filament bent for 2 seconds. Monofilaments were used in ascending order, with an interval of 10 seconds.

Measurement of serum testosterone and cortisol levels was performed on an immune-electro-chemiluminescent photometer analyser, Cobas E411; measurements of serum C-reactive protein and glucose were performed on a biochemical analyser-photometer, Cobas Integra 400 Plus, in the Department of Clinical Laboratory Diagnostics at the Yuriy Semenyuk Rivne Regional Clinical Hospital. The reference values of serum testosterone, cortisol, C-reactive protein, and glucose levels are shown in Table 1.

The inclusion criteria were as follows: informed consent of the patient to participate in the study, scoliosis or other spinal deformities that require surgical correction, and the absence of known allergies to local anaesthetics.

Exclusion criteria included refusal to participate in the study both at the beginning of the study and at any stage of the study, type I or II diabetes, acute spinal cord injury, physical status according to the ASA III, and more, oral contraceptives, oestrogen therapy, prednisolone or methylprednisolone before surgery, age less than 12 and more than 70 years old. Body mass index (BMI) more than 40 kg/m^2. Chronic analgesic therapy, those with a history of opioid dependence, those receiving anticoagulation or experiencing any bleeding disorder, or those who were unable to communicate with the investigators. In addition, all patients who required repeated surgical interventions due to surgical complications (infectious or neurological) during this case of hospitalisation were excluded as well.

All the patients in the operating room received paracetamol, dexketoprofen, ondansetron, dexamethasone, and tranexamic

Table 1: Reference values of serum testosterone, cortisol C-reactive protein, and glucose levels.

TESTOSTERONE	
Men 20–49 years	8.64–29.0 nmol/l
Men ≥50 years	6.68–25.7 nmol/l
Women 20–49 years	0.290–1.67 nmol/l
Women ≥50 years	0.101–1.42 nmol/l
CORTISOL	
AM 7:00–10:00	171–536 nmol/l
PM 16:00–20:00	64–327 nmol/l
C-REACTIVE PROTEIN	
<5 mg/ml	
GLUCOSE	
4.11–6.05 mmol/l	

acid. Anaesthesia was induced using propofol, fentanyl, and atracurium besylate. After preoxygenation, tracheal intubation was performed in an improved position, and the patient was rotated to the abdomen with specific placement to prevent abdominal compression. Lung protective ventilation was conducted with supporting driving pressure of 12–14 cm H^2O. After induction of anaesthesia, general anaesthesia was maintained with sevoflurane and dexmedetomidine. Standard intraoperative monitoring included: electrocardiography; respiratory rate; body temperature; systolic, diastolic, mean blood pressure; heart rate; and SpO^2. For postoperative analgesia, patients in both groups received paracetamol in combination with dexketoprofen every six hours. Thromboprophylaxis was administered based on the risk of thromboembolic complications.

Patients in the SG underwent BESPB, after intubation of the trachea, in prone position, before the skin incision. To identify the required level of blockade the extent of transpedicular fixation was discussed before surgery with the surgeon, and the blockade was performed bilaterally as close as possible to the screw implantation sites. A solution with bupivacaine 0.375%, dexamethasone 0.02% and epinephrine 0.00018% was used for blockade. The erector spinae and transverse vertebral processes were identified using a linear ultrasound probe at a frequency of 7 MHz. At the required level of the spine, 3 cm lateral to the spinous process, using ultrasound contrast needle 22G, a local anaesthetic with adjuvants was administered bilaterally under the erector spinae muscle. Observation of the patients who underwent spine surgery proceeded until discharge from the hospital.

All data were tested appropriately for normality of distribution and expressed as means (95% CI). The significance of deviations in the mean values was assessed according to the criteria of Student or Mann-Whitney. A *P*-value less than 0.05 was taken as statistically significant.

Results

This study involved 103 patients who underwent posterior transpedicular fixation of the spine for scoliosis and other spinal deformities. Sample size was determined using a statistical power calculation. Prior to the randomisation phase, 38 patients were excluded from the study (nine patients received opioid analgesic before surgery, six patients received oral contraceptives, five patients had diabetes, three patients had spinal cord injury, one patient received oestrogen therapy, and one patient received methylprednisolone, and 13 patients refused to participate in this study). The remaining 65 patients were randomly assigned to the SG and CG (SG – 32 patients; CG – 33 patients). At the stages of allocation 31 patients received allocated intervention and one patient refused to participate in the study in SG. In the CG, 31 patients received allocated intervention and two patients refused to participate in the study. One patient was lost to follow-up because the method of surgery was changed in the SG; in the CG, three patients were lost to follow-up because the method of surgery was also changed. At the stages of analysis, three patients were excluded from analysis because of unsuccessful blood sampling in the SG, and two patients were excluded from the CG because of the same reason. Data from 53 patients was analysed (27 patients in SG and 26 patients in CG). Because testosterone synthesis in both sexes is different, and the reference values depend not only on sex but also on the age of patients, to obtain reliable values of testosterone levels in both study groups patients were further divided into four subgroups (men aged 20–49 years old, men over the age of 50 years old, women aged 20–49 years old, women over the age of 50 years old). A CONSORT follow-up diagram is shown in Figure 1. The baseline characteristics of patients (age, sex, ASA, body mass index) showed no significant statistical deviations and are shown in Table 2.

The result of the comparison of the impact of the method of anaesthesia on laboratory markers of hyperalgesia after spinal surgery revealed statistically significant deviations ($P<0.05$) in mechanical pain thresholds, testosterone, cortisol, C-reactive protein, and glucose levels after surgery in the CG. In the SG no statistically significant deviations were found in mechanical pain thresholds nor in any of the laboratory markers studied. The quantity of fentanyl used during surgery and morphine used after surgery was significantly lower ($P<0.05$) in SG.

Opioid analgesic. The quantity of fentanyl administered during surgery in the SG was significantly lower (1.68 CI 95% 1.4–2 μg/kg-1h-1) than in the CG, where the quantity of intraoperative fentanyl was 4.7 (CI95% 4 to 5.4) μg/kg-1h-1. In the postoperative period in the SG, only five patients, once, received morphine hydrochloride at a dose of 10 mg due to exceeded intensity of pain up to 7 points on the VAS. Quite opposite results were obtained in the CG, where morphine hydrochloride was administered to 23 patients from the beginning of sixth postoperative hour and re-administrated every 24 hours for 3 days after surgery, because the intensity of pain reached up to 7 points on a visual analogue scale. A graphical representation of the statistical ranges of administered fentanyl and morphine hydrochloride in the study groups are shown in Figure 2.

Mechanical pain thresholds. In the CG, patients before the surgery felt a clear touch of the monofilament at a pressure of 21.45 (95% CI 18.80–24.10) g/mm^2, but on the fifth postoperative day the feeling of a clear touch appeared at a monofilament pressure of only 4.75 (95% CI 4.13–5.38) g/mm^2. In the SG, preoperative indicators of clear pressure did not differ significantly ($p<0.05$) from postoperative and

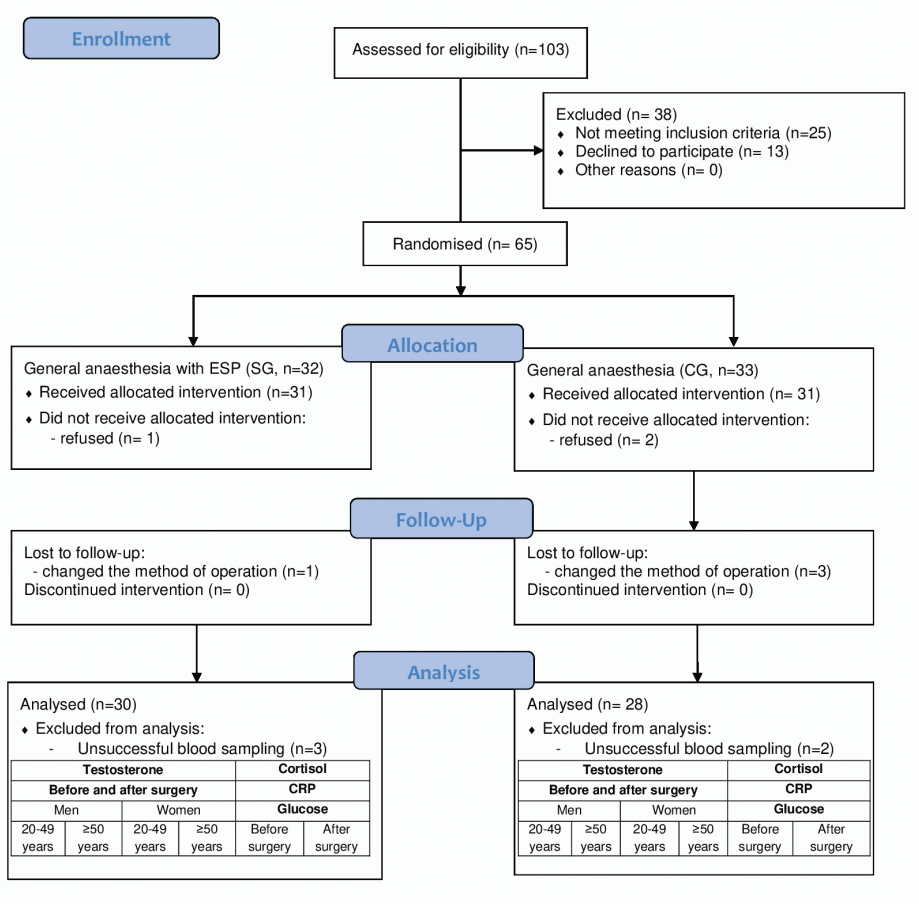


Figure 1. CONSORT follow-up diagram.

Table 2: The baseline characteristics of patients.

	SG (n=27)	CG (n=26)
	Men (n=26)	
Age 20–49 years old (n)	7	7
Age ≥50 years old (n)	7	6
	Women (n=24)	
Age 20–49 years old (n)	6	8
Age ≥50 years old (n)	7	5
	ASA	
I (n)	11	9
II (n)	16	17
BMI (kg/m^2)	26.6 (CI 95% 23.4–29.7)	26.6 (CI 95% 23.4–29.7)

were 14.49 (95% CI 10.72–25.21) g/mm^2 and 16.70 (95% CI 13.02–20.57) g/mm^2, respectively. The average mechanical pain thresholds in CG and SG before surgery and after surgery are shown in Table 3. A graphical representation of the statistical ranges of mechanical pain thresholds are shown in Figure 3.

Testosterone. In the SG, the level of testosterone after surgery did not differ significantly from baseline. The average testosterone levels in SG before surgery and after surgery are shown in Table 4. A graphical representation of the statistical ranges of testosterone levels in SG is shown in Figure 4.

In contrast to SG, patients in CG had significantly lower testosterone levels on the fifth postoperative day. The average testosterone levels in CG before surgery and after surgery are shown in Table 5. A graphical representation of the statistical ranges of testosterone levels in CG is shown in Figure 5.

Cortisol. The level of cortisol has statistically the same values before and after surgery in the SG in contradistinction to the CG, where the level of cortisol was significantly higher after surgery in comparison with baseline. The average cortisol levels in SG and CG before and after surgery are shown in Table 6. A graphical representation of the statistical ranges of cortisol levels in the studied groups is shown in Figure 5.

C-reactive protein. In the SG, the level of C-reactive protein after surgery also did not differ statistically from baseline. In the CG, patients had significantly higher levels of C-reactive protein on the fifth postoperative day. The average C-reactive protein levels

in SG and CG before and after surgery are shown in Table 7. A graphical representation of the statistical ranges of CRP levels in the studied groups is shown in Figure 6.

Glucose. The glucose level after surgery did not differ statistically from the baseline in SG. Patients in CG had significantly higher levels of glucose on the fifth postoperative day. The average glucose levels in SG and CG before and after surgery are shown in Table 8. A graphical representation of the statistical ranges of the glucose levels in the studied groups is shown in Figure 7.

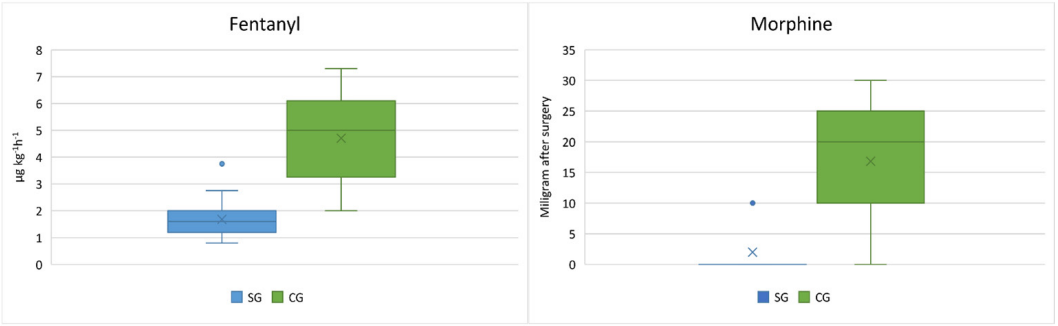


Figure 2. A graphical representation of the statistical ranges of administered fentanyl and morphine hydrochloride in the study groups: (a) fentanyl during surgery in SG and CG; (b) morphine hydrochloride total amount after surgery in SG and CG.

Table 3: The average mechanical pain thresholds in SG and CG before surgery and after surgery.

	Before Surgery	After Surgery
SG	14.49 (95% CI 10.72–25.21) g/mm^2	16.70 (95% CI 13.02–20.57) g/mm^2
CG	21.45 (95% CI 18.80–24.10) g/mm^2	4.75 (95% CI 4.13–5.38) g/mm^2

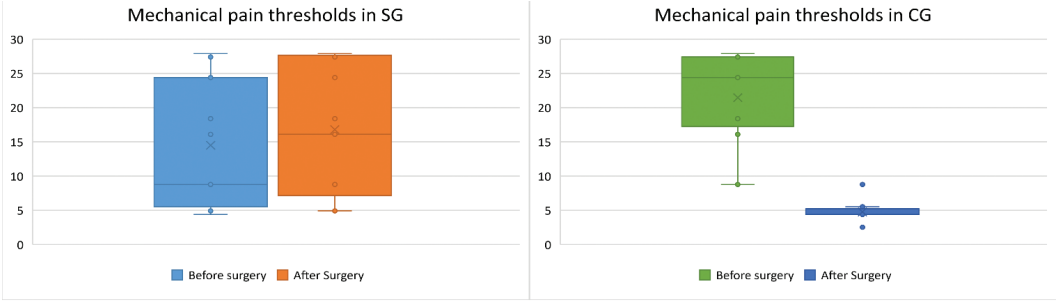


Figure 3. A graphical representation of the statistical ranges of mechanical pain thresholds: (a) in study group; (b) in control group.

Table 4: The average testosterone levels in SG before surgery and after surgery.

General anaesthesia with BESPB (SG)		
	Before Surgery	**After Surgery**
Men 20–49 years old	20.73 (95% CI 19.07–22.38)	21.11 (95% CI 20.00 –22.23)
Men 20–49 years old	19.38 (95% CI 13.11–25.65)	16.35 (95% CI 8.21–24.49)
Women 20–49 years old	0.65 (95% CI 0.20–1.16)	0.62 (95% CI 0.11–1.13)
Women ≥50 years old	0.55 (95% CI 0.04–1.07)	0.71 (95% CI 0.07–1.35)

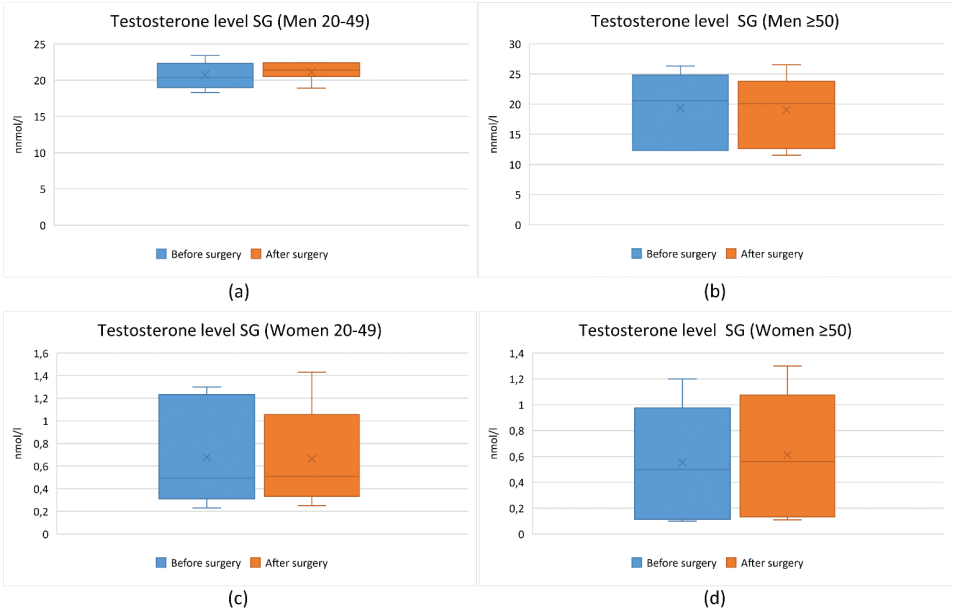


Figure 4. A graphical representation of the statistic ranges of testosterone levels in SG: (a) Men 20–49 years old; (b) Men ≥50 years old; (c) Women 20–49 years old; (d) Women ≥50 years old.

Table 5: The average testosterone levels in CG before surgery and after surgery.

General anaesthesia without BESPB (CG)		
	Before Surgery	**After Surgery**
Men 20–49 years old	26.94 (95% CI 25.37–28.52)	6.79 (95% CI 5.28–8.29)
Men 20–49 years old	17.67 (95% CI 14.23–21.1)	2.63 (95% CI 0.88–4.39)
Women 20–49 years old	1.09 (95% CI 0.85–1.32)	0.11 (95% CI 0.08–0.14)
Women ≥50 years old	1.15 (95% CI 0.82–1.48)	0.1 (95% CI 0.1–0.1)

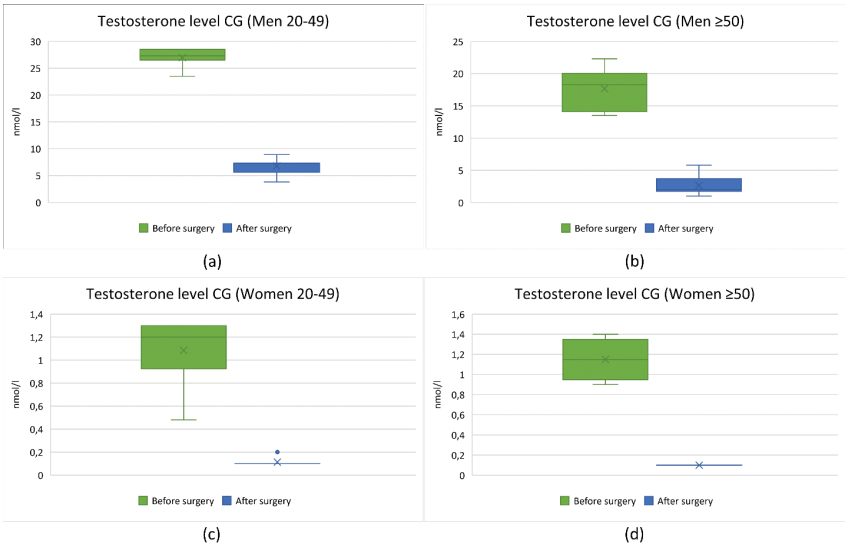
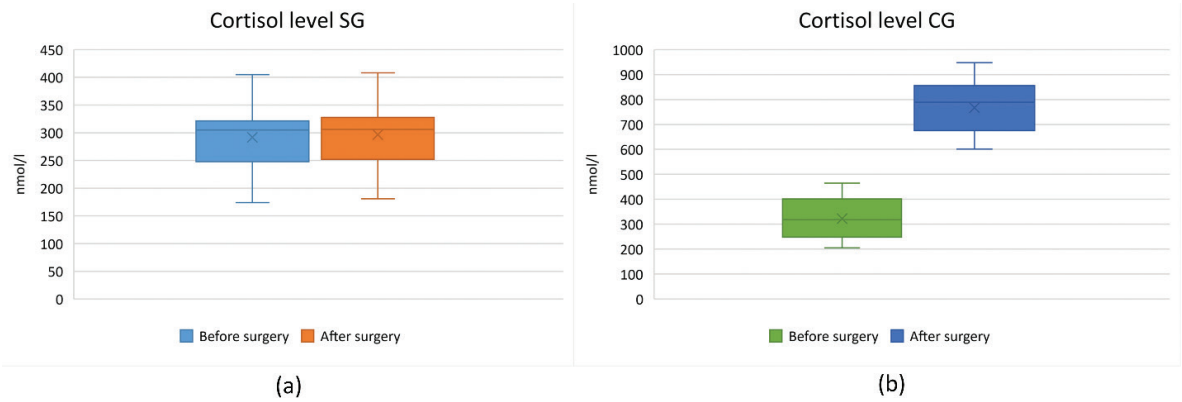


Figure 5. A graphical representation of the statistic ranges of testosterone levels in CG: (a) Men 20–49 years old; (b) Men ≥50 years old; (c) Women 20–49 years old; (d) Women ≥50 years old.

Table 6: The average cortisol levels in Groups 1 and 2 before and after surgery.

	Before Surgery	After Surgery
SG	291.6 (95% CI 265.74–317.46)	322 (95% CI 290.35–353.65)
CG	296.4 (95% CI 270.8–567.2)	767.24 (95% CI 720.02–814.46)

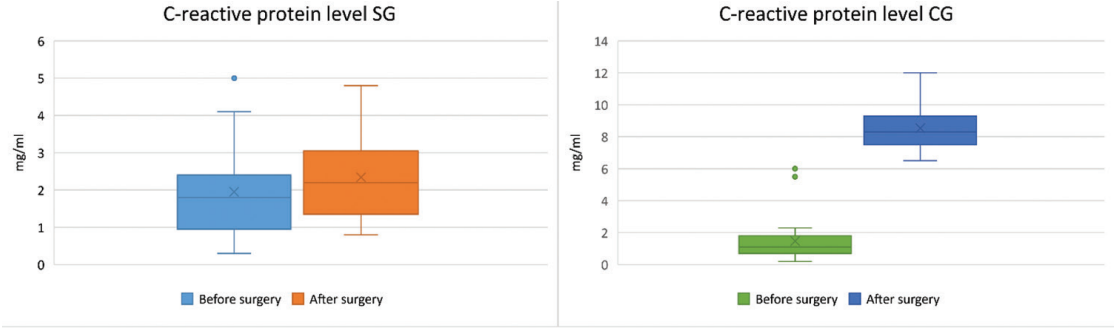


(a) (b)

Figure 6. A graphical representation of the statistical ranges of cortisol levels in the studied groups: (a) in SG; (b) in CG.

Table 7: The average C-reactive protein levels in Groups 1 and 2 before and after surgery.

	Before Surgery	After Surgery
SG	1.95 (95% CI 1.48 to 2.42)	2.34 (95% CI 1.88 to 2.81)
CG	1.48 (95% CI 0.89 to 2.06)	8.54 (95% CI 8 to 9.1)



(a) (b)

Figure 7. A graphical representation of the statistical ranges of CRP levels in the studied groups: (a) in SG; (b) in CG.

Table 8: The average glucose levels in SG and CG before and after surgery.

	Before Surgery	After Surgery
SG	5.09 (95% CI 4.88–5.3)	6.06 (95% CI 5.83–6.3)
CG	5.2 (95% CI 4.9–5.5)	9.23 (95% CI 8.63–9.83)

Discussion

Even small doses of opioid analgesic for pain relief before orthopaedic surgery cause hyperalgesia prior to intervention. As a result, the quantity of analgesics used after surgery is increased because of the development of tolerance to opiates [22]. We excluded all patients who received opioid analgesic before surgery. The results of serum testosterone and cortisol tests can be affected by the administration of oral contraceptives [23, 24] and oestrogen therapy [25, 26]. The results of serum cortisol tests could also be affected by the administration of prednisolone or methylprednisolone before surgery [27], therefore, we excluded all patients from the study who received the same therapy before surgery.

The use of regional anaesthesia methods reduces the quantity of opioid analgesic used perioperatively, reduces the intensity of postoperative pain and subsequent development of hyperalgesia. Our study clearly showed that general anaesthesia without ESPB reduces pain threshold and causes the development of hyperalgesia in patients who underwent spine surgery. Use of Von Frey monofilaments allowed us to investigate the opiates' effects on hyperalgesia [28] and to predict chronisation of the pain [29].

In the results of our study, we found that the use of the BESPB did not affect the serum testosterone levels in patients who underwent spinal surgery due to less analgesic use before and after surgery. In contrast, in the general anaesthesia group, the quantity of opioid analgesic used was significantly higher and testosterone levels after surgery were significantly lower.

Opioid analgesics in different hospitals still are the gold standard for pain management. However, we must keep in mind that short-term opiate therapy may lead to their long-term use, at least in some patients [30]. According to studies carried out in Europe and the United States in 2009 and 2012, respectively, the number of patients taking opioid analgesics before elective orthopaedic surgery (hip or knee arthroplasty) ranged from 16% to 32%, and 22% to 56% of patients continued to take opiates postoperatively. As a result, 32% to 68% of patients had pain at the site of surgery for 30 days after surgery; moreover, 32% of patients after 713 days had pain in various localisations [31, 32]. These results may indicate hyperalgesia and chronic postoperative pain.

Despite the effectiveness of opiates in pain therapy, their influence on organs and systems of the human body is often ignored. One of the systems most vulnerable to routine drug use is the endocrine system [33]. Symptoms of hypogonadism are observed in patients who have made long-term use of opioid analgesics for chronic pain treatment [34]. The mechanism of development of such complications consists of suppression of gonadotropin-releasing hormone in the hypothalamus [35]. In addition, opiates reduce the sensitivity of the anterior pituitary gland to sex and gonadotropin-releasing hormones. Inhibition of luteinizing hormone-releasing factor synthesis reduces testosterone production.

Testosterone therapy also demonstrates the importance of the endocrine system in the development of chronic pain and hyperalgesia. Exogenous testosterone is especially effective in patients with long-term opioid analgesic use. Pain was reduced, and energy, motivation, and libido were improved [36]. Testosterone therapy in opiate-induced male hypogonadism also maximised lean body mass and decreased total fat mass (body composition was measured by dual X-ray absorptiometry scan) [37]. Therefore, low testosterone levels after spinal surgery may be a predictor of hyperalgesia and can be used in the early diagnosis of chronic postoperative pain.

The regional component of anaesthesia in the surgical correction of spinal deformities reduces the body's stress response to surgical trauma. Stress not only suppresses the hypothalamic–pituitary–gonadal axis (resulting in decreased serum testosterone levels) but also stimulates the hypothalamic–pituitary–adrenal axis and cortisol synthesis [38]. Cortisol levels obtained after surgery indicated a reduction in the body's stress response to surgery if the BESPB was used.

Cortisol is also an effective marker of stress response to surgical trauma. Frequently used by various researchers, this marker had already demonstrated the effects of anaesthesia on the stress response to surgery in adults [39] and children [40, 41]. In addition, cortisol was an effective marker of stress even in pregnant women in a study with intrathecal sufentanil in the first period of labour [42]. In addition, serum cortisol levels were used to compare two different surgeries on different parts of the body to determine the effect of surgical trauma on the stress response [43]. Cortisol is no less important than testosterone as a marker of chronic pain. A study by Forest Tennant and Laura Hermann in 2002 showed that morning serum cortisol levels can be not only useful biological markers of chronic pain but also an effective marker for treating chronic pain [44].

C-reactive protein is another important marker not only of the body's inflammatory response but also of chronic pain. The results of our study clearly demonstrate the impact of the method of anaesthesia on C-reactive protein levels after surgery. In patients who underwent BESPB, the level of C-reactive protein after surgery did not differ statistically from baseline, indicating that the use of regional anaesthesia reduces the body's inflammatory response to surgical trauma compared to the group of patients who underwent surgery only under general anaesthesia. However, it is not entirely clear why this effect is observed, either because of a reduction in the quantity of opioid analgesic or because of the action of a local anaesthetic, which can act as an anti-inflammatory agent [45].

Intraoperative tissue trauma causes a neuroendocrine stress response that primarily involves the hypothalamic–pituitary–adrenal axis and parasympathetic nervous system,

with the synthesis of acute phase proteins of inflammation in the liver. Physiological studies of the effect of prolonged blockade of peripheral nerves for knee joint arthroplasty clearly shed light on the deuteration of the inflammatory response to surgical trauma [46]. Postoperative analgesia also affects the inflammatory response. The use of long-term epidural infusion reduces the level of C-reactive protein in the postoperative period compared with morphine analgesia [47]. Elevated C-reactive protein levels after surgery may also be a marker of chronic acute postoperative pain [48]. Elevated C-reactive protein levels after non-cardiac surgery in patients with myocardial damage are associated with an increase in one-year and 30-day mortality after discharge from the hospital [49]. Similar to the mean nociceptive response index during surgery, C-reactive protein level is likely correlated with serious complications after gastrointestinal surgery under general anaesthesia [50].

Glucose levels are probably the simplest and most effective way to diagnose the body's stress response to surgical trauma in patients who do not have diabetes or who are not taking high doses of steroids. Glucose levels are routinely measured in the perioperative period [51]. In our study, the result of comparing glucose levels after surgery obtained statistically significant results; in patients who did not receive the blockade, glucose levels were significantly higher. This is another indicator of the effectiveness of regional anaesthesia in reducing the body's stress response to surgery.

A few limitations should be mentioned. First, this was a single-centre study with patients that received only transpedicular fixation of the spine without spinal cord surgery. Second, it should also be noted that we did not use placebo (saline) for injection in the general anaesthesia group without the regional component, as it can play a role in the analgesic component. Third, the heterogeneity of the spine surgeries performed should be considered. The number of segments operated varied from 2 to 15 and the duration of surgery ranged from 65 to 360 min, which probably can result in different intensity of postoperative pain, limited by the randomisation. Besides, despite the fact that we stratified patients by age to determine testosterone levels, mechanical pain threshold and hyperalgesia in younger patients may differ from older patients. Finally, we did not analyse the serum testosterone, cortisol, C-reactive protein, and glucose levels after discharge from the hospital. Additionally, we did not evaluate the chronicity of pain several months after the surgery and we did not investigate its relationship with the performed spinal surgery. Therefore, we are limited in the conclusion that those laboratory and instrumental indicators obtained during the patient's stay at the hospital can indicate the chronisation of acute pain.

Thus, regional anaesthesia is not the only effective and safe method for reducing intra- and postoperative pain. Employing BESPB reduces the quantity of opioid analgesic after surgical correction of spinal deformities. Due to the elimination of the negative effects of pain and opiates on the neuroendocrine regulation of endogenous hormones and anti-inflammatory cytokine synthesis, BESPB not only reduces the body's stress response to surgical trauma but also does not trigger the mechanism of hyperalgesia and, possibly, chronisation of acute postoperative pain.

Conclusion

Employing bilateral erector spinae plane block as a component of general anaesthesia for spine surgery reduces the incidence of hyperalgesia and the quantity of opioid analgesics used during surgery and in the postoperative period**.** We can propose to use the serum testosterone, cortisol, C-reactive protein, and glucose levels as the laboratory markers of hyperalgesia, but further research is necessary.

Author Contributions

Conceptualisation – Barsa M.; methodology – Barsa M.; software – Barsa M.; formal analysis – Barsa M.; investigation – Barsa M.; resources – Barsa M.; data curation – Barsa M; writing – original draft preparation Barsa M.; writing – review and editing Filyk O.; visualisation – Barsa M.; supervision – Filyk O.; project administration – Filyk O.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Commission of Ethics and Bioethics of Yuriy Semenyuk Rivne Regional Clinical Hospital, supervised by Rivne Regional Council (protocol code 5-1B/1612 and date of approval 16 December 2020).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The study was registered on ClinicalTrials.gov (ID number: NCT04697498).

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Fletcher D, Stamer UM, Pogatzki-Zahn E, Zaslansky R, Tanase NV, Perruchoud C, et al. Chronic postsurgical pain in Europe. Eur J Anaesthesiol 2015; 32(10): 725–34. https://doi.org/10.1097/EJA.0000000000000319

[2] Joly V, Richebe P, Guignard B, Fletcher D, Maurette P, Sessler D, et al. Remifentanil-induced Postoperative hyperalgesia and its prevention with small-dose ketamine. Anesthesiology 2005; 103: 147–155. https://doi.org/10.1097/00000542-200507000-00022

[3] Leal P, Sakata RK. Methods for the assessment of opioid-induced hyperalgesia in the perioperative period. Revisa Dor 2014; 15(4): 296–299. https://doi.org/10.5935/1806-0013.20140064

[4] Schmidt R, Thews G. Human Physiology. 3rd edition. Moskwa: Mir 2005: 64–66.

[5] Lesnak JB, Inoue S, Lima L, Rasmussen L, Sluka KA. Testosterone protects against the development of widespread muscle pain in mice. Pain 2020; 161(12): 2898–2908. https://doi.org/10.1097/j.pain.0000000000001985

[6] Gaumond I, Arsenault P, Marchand S. Specificity of female and male sex hormones on excitatory and inhibitory phases of formalin-induced nociceptive responses. Brain Research 2005; 1052(1): 105–111. https://doi.org/10.1016/j.brainres.2005.06.011

[7] White H, Robinson T. A novel use for testosterone to treat central sensitization of chronic pain in fibromyalgia patients. Int Immunopharmacol 2015; 27(2): 244–248. https://doi.org/10.1016/j.intimp.2015.05.020

[8] Benedetti F, Amanzio M, Vighetti S, Asteggiano G. The biochemical and neuroendocrine bases of the hyperalgesic nocebo effect. J Neuro 2006; 26(46): 12014–12022. https://doi.org/10.1523/JNEUROSCI.2947-06.2006

[9] Colloca L, Benedetti F. Nocebo hyperalgesia: how anxiety is turned into pain. Curr Opin Anaesthesiol 2007; 20(5): 435–439. https://doi.org/10.1097/ACO.0b013e3282b972fb

[10] Hannibal K, Bishop M. Chronic stress, cortisol dysfunction, and pain: A psychoneuroendocrine rationale for stress management in pain rehabilitation. Phys Ther 2014; 94(12): 1816–1825. https://doi.org/10.2522/ptj.20130597

[11] Van Uum S, Sauvé B, Fraser L, Morley-Forster P, Paul T, Koren G. Elevated content of cortisol in hair of patients with severe chronic pain: A novel biomarker for stress. Stress 2008; 11(6): 483–488. https://doi.org/10.1080/10253890801887388

[12] Vachon-Presseau E, Roy M, Martel M-O, Caron E, Marin M-F, Chen J, et al. The stress model of chronic pain: evidence from basal cortisol and hippocampal structure and function in humans. Brain 2013; 136(3): 815–827. https://doi.org/10.1093/brain/aws371

[13] Choi J, Chung M, Lee Y. Modulation of pain sensation by stress-related testosterone and cortisol. Anaesthesia 2012; 67(10): 1146–1151. https://doi.org/10.1111/j.1365-2044.2012.07267.x

[14] Sturmer T. Pain and high sensitivity C reactive protein in patients with chronic low back pain and acute sciatic pain. Ann Rheum Dis 2005; 64(6): 921–925. http://dx.doi.org/10.1136/ard.2004.027045

[15] Chi C-H, Shiesh S-C, Chen K-W, Wu M-H, Lin X-Z. C-reactive protein for the evaluation of acute abdominal pain. Am J Emerg Med 1996; 14(3): 254–256. https://doi.org/10.1016/S0735-6757(96)90169-2

[16] Schistad E, Stubhaug A, Furberg A-S, Engdahl BL, Nielsen CS. 2017. C-reactive protein and cold-pressor tolerance in the general population. Pain 2017; 158(7): 1280–1288. https://doi.org/10.1097/j.pain.0000000000000912

[17] Dmytriiev D. PO-0914 Postoperative hyperalgesia in children after oncology surgery correlates with raised level of cortisol, interleukin 6 (il6), il8 and C-reactive protein. Arch Dis Childh 2014; 99 (Suppl2): A549.1–A549. http://dx.doi.org/10.1136/archdischild-2014-307384.1535

[18] Sterling M, Head J, Cabot PJ, Farrell M. Serum C-reactive protein levels predict regional brain responses to noxious cold stimulation of the hand in chronic whiplash associated disorders. Scand J Pain 2016; 11(1): 19–26. https://doi.org/10.1016/j.sjpain.2015.11.003

[19] Rademaker BMP, Kalkman CJ, Odoom JA, De Wit L, Ringers J. Intraperitoneal local anaesthetics after laparoscopic cholecystectomy: Effects on postoperative pain, metabolic responses and lung function. Brit J Anaesth 1994; 72(3): 263–266. https://doi.org/10.1002/14651858.CD007337.pub4

[20] Møller IW, Dinesen K, Søndergård S, Knigge U, Kehlet H. Effect of patient-controlled analgesia on plasma catecholamine, cortisol and glucose concentrations after cholecystectomy. Brit J Anaesth 1998; 61(2): 160–164. https://doi.org/10.1093/bja/61.2.160

[21] Mäntyselkä P, Miettola J, Niskanen L, Kumpusalo E. Chronic pain, impaired glucose tolerance and diabetes: A community-based study. Pain 2008; 137(1): 34–40. https://doi.org/10.1016/j.pain.2007.08.007

[22] Hina N, Fletcher D, Poindessous-Jazat F, Martinez V. Hyperalgesia induced by low-dose opioid treatment before orthopaedic surgery. Eur J Anaesthesiol 2015; 32(4): 255–261. https://doi.org/10.1097/EJA.0000000000000197

[23] Edwards DA, O'Neal JL. Oral contraceptives decrease saliva testosterone but do not affect the rise in testosterone associated with athletic competition. Horm Behav 2009; 56(2): 195–198. https://doi.org/10.1016/j.yhbeh.2009.01.008

[24] Graham CA, Bancroft J, Doll HA, Greco T, Tanner A. Does oral contraceptive-induced reduction in free testosterone adversely affect the sexuality or mood of women? Psychoneuroendocrinology 2007; 32(3): 246–255. https://doi.org/10.1016/j.psyneuen.2006.12.011

[25] Kocoska-Maras L, Hirschberg AL, Byström B, Schoultz BV, Rådestad AF. Testosterone addition to estrogen therapy: Effects on inflammatory markers for cardiovascular disease. Gynecol Endocrinol 2009; 25(12): 823–827. https://doi.org/10.3109/09513590903056134

[26] Herrera AY, Hodis HN, Mack WJ, Mather M. Estradiol therapy after menopause mitigates effects of stress on cortisol and

working memory. J Clin Endocrinol Metabol 2017; 102(12): 4457–4466. https://doi.org/10.1210/jc.2017-00825

[27] Niedermeyer HP, Zahneisen G, Luppa P, Busch R, Arnold W. Cortisol levels in the human perilymph after intravenous administration of prednisolone. Audiol Neurotol 2003; 8(6): 316–321. https://doi.org/10.1159/000073516

[28] Leal PC, Salomão R, Brunialti MKC, Sakata RK. Evaluation of the effect of ketamine on remifentanil-induced hyperalgesia: A double-blind, randomized study. J Clin Anesth 2015; 27(4): 331–337. https://doi.org/10.1016/j.jclinane.2015.02.002

[29] Hay JL, White JM, Bochner F, Somogyi AA, Semple TJ, Rounsefell B. Hyperalgesia in Opioid-Managed Chronic Pain and Opioid-Dependent Patients. J Pain 2009; 10(3): 316–322. https://doi.org/10.1016/j.jpain.2008.10.003

[30] Steyaert A, Lavand'homme P. Postoperative opioids. Eur J Anaesthesiol 2013; 30(2): 50–52. https://doi.org/10.1097/EJA.0b013e32835b9db2

[31] Carroll I, Barelka P, Wang CKM, Wang BM, Gillespie MJ, McCue R, et al. A Pilot Cohort Study of the Determinants of Longitudinal Opioid Use After Surgery. Anesth Analges 2012; 115(3): 694–702. https://doi.org/10.1213/ANE.0b013e31825c049f

[32] Andersen LØ, Gaarn-Larsen L, Kristensen BB, Husted H, Otte KS, Kehlet H. Subacute pain and function after fast-track hip and knee arthroplasty. Anaesthesia 2009; 64(5): 508–513. https://doi.org/10.1111/j.1365-2044.2008.05831.x

[33] Tennant F. The physiologic effects of pain on the endocrine system. Pain Ther 2013; 2(2): 75–86. https://doi.org/10.1007/s40122-013-0015-x

[34] Katz N, Mazer NA. The impact of opioids on the endocrine system. Clin J Pain 2009; 25(2): 170–175. https://doi.org/10.1097/AJP.0b013e3181850df6

[35] Seyfried O, Hester J. Opioids and endocrine dysfunction. Brit J Pain 2012; 6(1): 17–24. https://doi.org/10.1177/2049463712438299

[36] Tennant F, Lichota L. Testosterone replacement in chronic pain patients. Practical Pain Management 2010; 10: 12–15.

[37] Glintborg D, Vaegter HB, Christensen LL, Bendix E, Graven-Nielsen T, Andersen PG, et al. Testosterone replacement therapy of opioid-induced male hypogonadism improved body composition but not pain perception: a double-blind, randomized, and placebo-controlled trial. Eur J Endocrinol 2020; 182(6): 539–548. https://doi.org/10.1530/EJE-19-0979

[38] Choi JC. Testosterone and cortisol modulate pain sensation: 14AP7-9. Eur J Anaesthesiol 2012; 29: 209–210.

[39] Ismail S, Ahmed A, Hoda MQ, Asghar S, Habib A, Aziz A. Bilateral mid-axillary transversus abdominis plane block does not attenuate stress response to total abdominal hysterectomy. Eur J Anaesthesiol 2021; 38(7): 768–776. https://doi.org/10.1097/eja.0000000000001413

[40] Oleshchenko I, Cok OY, Iureva T, Zabolotskii D, Kripak A. Effect of pterygopalatine blockade on perioperative stress and inflammatory outcomes following paediatric cataract surgery. Reg Anesth Pain Med 2020; 45(3): 204–208. http://dx.doi.org/10.1136/rapm-2019-100823

[41] Çnar SÖ, Kum Ü, Cevizci N, Kayaoglu S, Oba S. Effects of levobupivacaine infiltration on postoperative analgesia and stress response in children following inguinal hernia repair. Eur J Anaesthesiol 2009; 26(5): 430–434. http://dx.doi.org/10.1097/EJA.0b013e32832974fc

[42] Stocche R. Effects of intrathecal sufentanil on plasma oxytocin and cortisol concentrations in women during the first stage of labor. Reg Anesth Pain Med 2001; 26(6): 545–550. http://dx.doi.org/10.1053/rapm.2001.27851

[43] Naito Y, Tamai S, Shingu K, Shindo K, Matsui T, Segawa H, et al. Responses of plasma adrenocorticotropic hormone, cortisol, and cytokines during and after upper abdominal surgery. Anesthesiology 1992; 77(3): 426–431. https://doi.org/10.1097/00000542-199209000-00004

[44] Tennant F, Hermann L. Normalization of serum cortisol concentration with opioid treatment of severe chronic pain. Pain Med 2002; 3(2): 132–134. https://doi.org/10.1046/j.1526-4637.2002.02019.x

[45] Cassuto J, Sinclair R, Bonderovic M. Anti-inflammatory properties of local anesthetics and their present and potential clinical implications. Acta Anaesthesiol Scand 2006; 50(3): 265–282. https://doi.org/10.1111/j.1399-6576.2006.00936.x

[46] Bagry H, Delacuadrafontaine J, Asenjo J, Bracco D, Carli F. Effect of a continuous peripheral nerve block on the inflammatory response in knee arthroplasty. Reg Anesth Pain Med 2008; 33(1): 17–23. https://doi.org/10.1016/j.rapm.2007.06.398

[47] Kristek G, Radoš I, Kristek D, Kapural L, Nešković N, Škiljić S, et al. Influence of postoperative analgesia on systemic inflammatory response and postoperative cognitive dysfunction after femoral fractures surgery: a randomized controlled trial. Reg Anesth Pain Med 2019; 44(1): 59–68. http://dx.doi.org/10.1136/rapm-2018-000023

[48] Hashimoto K, Tsuji A, Takenaka S, Ohmura A, Ueki R, Noma H, et al. C-reactive protein level on postoperative day one is associated with chronic postsurgical pain after mastectomy. Anesthesiol Pain Med 2018; 8(4): e79331. http://dx.doi.org/10.5812/aapm.79331

[49] Oh AR, Park J, Lee S-H, Kim J, Lee JH, Min JJ, et al. Elevated high-sensitivity C-reactive protein concentrations may be associated with increased postdischarge mortality in patients with myocardial injury after noncardiac surgery. Eur J Anaesthesiol 2021; 38(1): 33–40. http://dx.doi.org/10.1097/EJA.0000000000001409

[50] Ogata H, Matsuki Y, Okamoto T, Ueki R, Kariya N, Tatara T, et al. Intra-operative nociceptive responses and postoperative major complications after gastrointestinal surgery under general anaesthesia. Eur J Anaesthesiol 2021; 38(12): 1215–1222. http://dx.doi.org/10.1097/EJA.0000000000001505

[51] Miles ME, Rice MJ. Recent advances in perioperative glucose monitoring. Curr Opin Anaesthesiol 2017; 30(6): 718–722. http://dx.doi.org/10.1097/ACO.0000000000000521

[52] Tennant F, Hermann L. Normalization of serum cortisol concentration with opioid treatment of severe chronic pain. Pain Med 2002; 3(2): 132–134. http://dx.doi.org/10.1046/j.1526-4637.2002.02019.x