



Surgical stress response following hip arthroplasty regarding choice of anesthesia and postoperative analgesia

Izbor anestezije i postoperativne analgezije i sistemski odgovor na hirurški stres nakon aloartroplastike kuka

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Abstract

Background/Aim. Significant surgical stress response consisting of hormonal, metabolic and inflammatory changes can be initiated by the hip replacement surgery. Appropriate choice of anesthesia and postoperative analgesia should provide diminution of surgical stress response and may reduce number of perioperative complications. Surgical stress response after peripheral nerve blocks has not been studied extensively in patients who underwent hip replacement. The aim of the study was to investigate whether continuous lumbar plexus block can significantly reduce surgical stress response in comparison to other types of postoperative analgesia – continuous epidural analgesia and intravenous patient controlled analgesia (PCA) with morphine. **Methods.** Prospective study included 60 patients, scheduled for total hip arthroplasty. The patients were randomized into 4 groups: group CNB (central nerve block - epidural), group PNB (Peripheral nerve block - lumbar plexus block), SAM (Spinal anesthesia- PCA (anesthesia) morphine) and GAM (General anesthesia + PCA with Morphine). Serum levels of cortisol, thyroid hormones (T3, T4) and thyroid stimulating hormone (TSH), insulin, glucose and C-reactive protein (CRP) were measured in all groups – preoperatively, as well as 4 h, 12 h and 24 h after surgery. **Results.** The study showed that average serum cortisol levels were significantly lower 4 h after the operation in the groups where methods of regional anesthesia were performed intraoperatively (SAM, CNB, PNB); ($F = 19.867$; $p < 0.01$). Groups with postoperative continuous catheter analgesia (CNB, PNB) had significantly lower serum cortisol levels 12 h af-

ter the operation ($F = 8.050$; $p < 0.01$). The highest serum insulin levels were detected 4 h postoperatively in the CNB and PNB group, while the lowest were in the GAM group ($F = 5.811$; $p < 0.05$). Twelve hours after the operation, the lowest values of insulin were measured in the SAM group ($F = 5.052$; $p < 0.05$), while 24 h postoperatively, the lowest values were found in the SAM and GAM group ($F = 6.394$; $p < 0.05$). T3, T4 and TSH levels showed slight reduction in comparison to preoperative values without statistical significance. Blood glucose levels were significantly different among the groups 4 h after surgery with the highest values recorded in the GAM group and the lowest ones in the SAM group ($F = 10.084$; $p < 0.01$). On the other hand, 12 h after the operation significant rise in blood glucose levels was detected in the SAM group ($F = 7.186$; $p < 0.01$). Levels of CRP increased remarkably 12 h and 24 h after the surgery, but without significant difference among the groups. **Conclusion.** Administration of postoperative analgesia using continuous lumbar plexus block following hip arthroplasty reduces significantly stress response in comparison to postoperative PCA with morphine and has comparable effects on hormone release to epidural analgesia. Spinal anesthesia provides the best diminution of surgical stress response in the early postoperative period in comparison with other types of intraoperative analgesia.

Key words:

anesthesia, general; analgesia; anesthesia, spinal; anesthesia, conduction; intraoperative period; hydrocortisone; insulin; biological markers.

Apstrakt

Uvod/ Cilj. Zamena totalne proteze kuka može izazvati značajan sistemski odgovor na hirurški stres, koji uključuje hormone, metaboličke i zapaljenske promene. Odgovarajući izbor anestezije i postoperativne analgezije bi trebalo da obezbedi

slabljenje ovog odgovora i da utiče na smanjenje broja postoperativnih komplikacija. Istraživanja u oblasti sistemskog odgovora na hirurški stres, kod bolesnika kod kojih je primenjen periferni nervni blok nakon ugradnje totalne proteze kuka, nisu brojna. Cilj studije bio je da se ispita da li kontinuirani blok lumbalnog pleksusa može značajno da umanji sistemski odgo-

vor na hirurški stres u poređenju sa drugim vrstama postoperativne analgezije – kontinuiranom epiduralnom analgezijom i intravenskom PKA (pacijent kontrolisanom analgezijom) morfinom. **Metode.** U prospektivnu studiju bilo je uključeno 60 bolesnika, predviđenih za aloartroplastiku kuka. Bolesnici su bili raspoređeni u četiri grupe u zavisnosti od primenjene vrste anestezije i postoperativne analgezije: grupa CNB (centralni neuroblok - epidural), grupa PNB (periferni neuroblok - blok lumbalnog pleksusa), SAM grupa (spinalna anestezija + PKA morfinom) i OAM (opšta anestezija + PKA morfin). Vrednosti kortizola, tiroidnih hormona (T3, T4) i tiroidni stimulišući hormon (TSH), kao i vrednosti insulina, glukoze i C-reaktivnog proteina (CRP) u serumu merene su kod svih grupa, 4 h, 12 h i 24 h u serumu nakon operacije. **Rezultati.** Istraživanje je pokazalo da su prosečne vrednosti kortizola u serumu bile značajno niže 4 h postoperativno u grupama gde je intraoperativno primenjena regionalna anestezija (SAM, CNB, PNB), ($F = 19.867$; $p < 0.01$). U grupama u kojima je primenjena kontinuirana analgezija preko katetera (CNB, PNB), nivo kortizola u serumu bio je značajno niži 12 h posle operacije; ($F = 8.050$; $p < 0.01$). Najveći porast nivoa insulina u serumu detektovan je 4 h postoperativno u grupama CNB i PNB, a najmanji u grupi OAM; ($F = 5.811$; $p < 0.05$). Dvanaest sati nakon operacije, najniže

vrednosti insulina izmerene su u grupi SAM; ($F = 5.052$; $p < 0.05$), dok su nakon 24 h njegove najniže vrednosti bile u grupama SAM i GAM, ($F = 6.394$; $p < 0.05$). Nivoi T3, T4 i TSH bili su blago sniženi u odnosu na preoperativne vrednosti, 4 h, 12 h i 24 h nakon operacije. Vrednosti glikemije su se statistički značajno razlikovale među grupama, 4 h posle operacije, a najviše vrednosti su zabeležene u grupi OAM, dok su najniže bile u grupi SAM; ($F = 10.084$; $p < 0.01$). Nasuprot tome, 12 h nakon operacije, značajan porast u nivou glukoze u serumu detektovan je u grupi SAM, ($F = 7.186$; $p < 0.01$). Vrednosti CRP-a su приметно rasle 12 h i 24 h postoperativno, ali bez statistički značajne razlike između grupa. **Zaključak.** Primena kontinuiranog bloka lumbalnog pleksusa nakon aloartroplastike kuka značajno smanjuje sistemski odgovor na stres u poređenju sa postoperativnom PKA morfinom i po hormonskom odgovoru može se porediti sa epiduralnom analgezijom. Spinalna anestezija obezbeđuje najveće smanjenje sistemskog odgovora na hirurški stres u ranom postoperativnom periodu u poređenju sa drugim vrstama anestezije.

Ključne reči:

anestezija, opšta; analgezija; anestezija, spinalna; anestezija, provodna; intraoperativni period; hidrokortizon; insulin; biološki pokazatelji.

Introduction

Significant surgical stress response consisting of hormonal, metabolic and inflammatory changes can be initiated by the hip replacement surgery¹. Triggering of this reaction is caused by surgical incision and includes release of local tissue activators from damaged tissue, such as interleukins, tumor necrosis factor (TNF), serotonin, kinins and some intracellular proteins. These local mediators may influence activation of complex autonomic, endocrine and biochemical response. Local tissue activators increase the sensitivity of nociceptors. Pain sensation is carried from nociceptors to spinal cord via fine unmyelinated C and myelinated A δ nerve fibers. Afferent impulses are transmitted throughout spinal cord and reach reticular formation and limbic system. Impulses also travel to hypothalamus and cerebral cortex².

Activation of the neuroendocrine and immune system includes stimulation of hypothalamo-pituitary-adrenal axis, resulting in secretion of "stress hormones", predominantly adrenocorticotrophic hormone (ACTH), cortisol and catecholamines. Increase in cortisol level represents the key result of the excitation of hypothalamus and secretion of ACTH. It is known that serum concentration of cortisol is doubled two hours after the surgical incision, while maximum of cortisol level (around 35 $\mu\text{g/dL}$) is reached eight hours after surgery. Thereafter, serum concentration of cortisol starts to decline, reaching 22 $\mu\text{g/dL}$, 24 h postoperatively, and remains stable within the seven following days³. Production of thyroid hormones, thyroxine (T4) and tri-iodothyronine (T3) is affected by cortisol and catecholamines. Concentrations of total and free T3 decrease few days after surgery, while TSH levels fall within 2 h postoperatively^{1,4}.

Secretion of insulin is significantly impaired during the operation and immediately after surgery, caused by α -

adrenergic inhibition of β cell secretion. The plasma concentration of insulin, the key anabolic hormone, tends to decrease due to predominance of catabolic hormones (cortisol, glucagon and catecholamines). Period of reduced insulin secretion is followed by the period of the impairment of cellular sensitivity to insulin. This phenomenon, called "insulin resistance", starts on the day of surgery and may last up to three weeks after the operation^{3,5,6}.

Increase in blood glucose levels is the main metabolic consequence of gluconeogenesis and hepatic glycogenolysis, stimulated by cortisol and catecholamines. Furthermore, the rate of glucose utilization is impaired by reduced peripheral sensitivity to insulin⁷⁻¹⁰.

Level of C-reactive protein (CRP), an acute phase protein, is expected to rise following hip arthroplasty, reaching its maximum 24 h postoperatively. It can be used as non-specific marker of inflammatory response in these patients¹¹.

Influence of anesthesia on stress response to surgery has been well established in patients scheduled for major abdominal and cardiac surgery¹²⁻¹⁴. General anesthesia cannot diminish completely activation of hypothalamo-adrenal axis. Some of the medications, used for general anesthesia, e.g. propofol, sevoflurane and beznodiazepines are found to attenuate release of catabolic hormones¹.

On the contrary, regional techniques, such as spinal and epidural anesthesia cease the nociceptive signals from surgical wound, preventing their transfer to central nervous system. As the result, release of pituitary hormones is significantly attenuated. Blocking of efferent signals, caused by regional anesthesia is also an important factor of preventing hormonal release from the target organs². Extensive use of anticoagulant therapy concomitantly with hip surgery during the past decades, raised the risk of spinal and epidural hematoma associated with neuraxial blockade in orthopedic

surgery¹⁵. Therefore, peripheral nerve blocks have gained the popularity, providing adequate analgesia with less side effects and complications^{16–18}. Surgical stress response after peripheral nerve blocks, such as 3-in-1 block and lumbar plexus block, was not studied extensively in patients who underwent hip replacement. Intraoperatively, spinal anesthesia can be used as single method of anesthesia. Epidural anesthesia and peripheral blocks are more often used in combination with general anesthesia intraoperatively, whilst as single method for continuous postoperative analgesia via the epidural or peripheral catheter. In the early postoperative period, up to 24 h following general or spinal anesthesia, intravenous administration of narcotics, especially morphine, is the method of choice in the absence of peripheral or epidural catheters. Morphine should be used via patient controlled analgesia (PCA) pump, which enables precise delivery on patient's demand with the least side effects^{19,20}.

Patients scheduled for hip replacement surgery are often elderly people, with significant comorbidity and chronic use of anticoagulant therapy. Therefore, appropriate choice of anesthesia and postoperative analgesia should provide decrease of surgical stress response and may reduce perioperative complications, such as myocardial infarction, stroke and organ dysfunction^{21–23}.

The aim of the study was to investigate whether continuous lumbar plexus block can significantly reduce surgical stress response in comparison with other types of postoperative analgesia – continuous epidural analgesia and intravenous PCA with morphine.

Methods

This prospective, randomized study was conducted in 60 patients [American Society of Anesthesiologists ((ASA) physical status II-III)], with hip osteoarthritis, scheduled for unilateral total hip arthroplasty, after obtaining Ethical Committee approval.

No significant differences were found among the groups, regarding age, gender, body mass index, type of implant prosthesis, duration of surgery and postoperative blood loss in 24 h.

Before inclusion, written informed consent was obtained from each patient. Exclusion criteria were: known allergy to local anesthetics and opioids, diabetes, chronic use of corticosteroids and opioids, neurological disorders and contraindications to central or peripheral nerve block (local skin infections, coagulation disorders). The patients were randomized into 4 groups of 15 patients each: the CNB group (central nerve block - epidural), the PNB group (peripheral nerve block - lumbar plexus block), the SAM group (spinal anesthesia + IV morphine) and the GAMa group (general anesthesia + IV morphine).

All patients received midazolam 0.03 mg/kg i.v. 20 min before planned surgery. Preoperatively, in the CNB group, epidural space was identified with normal saline, using an 18G epidural needle. Thereafter, the epidural catheter 20G (Braun, Meslungen, Germany) was inserted. Bolus of 3 mL chirocaine 0.5%, and fentanyl 50 µg was administered via

epidural catheter before anesthesia induction. Intraoperatively, boluses of 5 mL levobupivacaine 0.5% were added on a regular basis, every 30 min. Anesthetic induction was performed using propofol 2 mg/kg, fentanyl 100 µg and rocuronium 0.6 mg/kg. Following endotracheal intubation, anesthesia was maintained using sevoflurane 1–2% in a 50%/50% mixture of oxygen and nitrous oxide (N₂O). Postoperative analgesia was maintained via epidural catheter during the first 24 h, by continuous infusion of a mixture - 0.1% levobupivacaine and fentanyl 2 µg/mL, 8–15 mL/h.

In the PNB group, lumbar plexus was identified by the nerve stimulator according to Capdevila's approach²⁴, using a 15 cm long needle for peripheral block. Contractions of quadriceps muscle ("dancing patella sign") were obtained using an initial current of 1–2 mA. After twitches were observed, the current was reduced to 0.5 mA. The peripheral catheter (Braun, Meslungen, Germany) was inserted into psoas compartment where lumbar plexus is situated. A total of 20 mL levobupivacaine 0.25% was administered. Following the catheter insertion, general anesthesia was performed in the same way as in the group CNB. Postoperative analgesia was maintained via the peripheral catheter during the first 24 h, by continuous infusion of 0.25% levobupivacaine, 5–10 mL/h. Initial titration was performed postoperatively, using a 10 cm visual analog scale (VAS) and providing pain score lower than 3 cm.

In the GAM group, all patients received general anesthesia, using the same protocol as it was used for the patients from the CNB and PNB group. Average duration of general anesthesia was 135 ± 52 min and did not differ significantly among the groups (CNB, PNB and GAM). Preoperatively, the patients included into the SAM and GAM group were informed about postoperative pain management using the PCA devices. In a recovery room, the patients from the SAM and GAM groups received initial intravenous boluses of morphine hydrochloride (5 mg doses at 5 min intervals), titrated manually until their pain score was lower than 3 on a 10 cm VAS. Thereafter, PCA was initiated. The PCA pump (µSP 6000, Arcomed ga, Switzerland) was connected and delivered 1 mg doses of morphine i.v. with a 7 min lockout period and a maximum dose of 20 mg over 4 h.

After surgery, the patients from all groups were transferred to the post-anesthesia care unit (PACU), and after a two-hour observation period to the orthopedic ward.

In the SAM group, all the patients received spinal anesthesia in sitting position, using 25G, 88 mm Quincke tip needles (Braun, Meslungen, Germany). A total of 12.5 – 17.5 mg of hyperbaric bupivacaine 0.5% was administered into subarachnoidal space at L3-4 spinous level. Postoperative analgesia was administered intravenously using the PCA pump.

All operations were performed in the morning, taking into consideration circadian rhythm of hormone release. Serum levels of cortisol, thyroid hormones (T3, T4) and TSH, insulin, glucose and CRP were measured in all groups preoperatively, as well as 4 h, 12 h, and 24 h after surgery. Electrochemiluminescence immunoassay was used to determine serum concentrations of cortisol, thyroid hormones

(T3, T4) TSH and insulin. To estimate blood glucose levels, glucose oxidase enzymatic method was used. The CRP levels were determined by immunoturbidimetric assay. Non-invasive intermittent blood pressure monitoring was performed intraoperatively using measurements at 5 minute intervals. Postoperatively, arterial blood pressure was measured hourly. Episodes of hypotension were recorded if arterial pressure was below 100/70 mmHg.

Statistics

The methods of descriptive statistics were applied. The numerical variables were presented as: mean value, minimum, maximum, standard deviation, while the categorical ones as proportions (percentages). Dependence of the parameters in order to check the differences was analyzed using Pearson's χ^2 test and Fisher's exact test. The differences were considered to be significant if $p < 0.05$.

Results

Data analysis showed that preoperative serum levels of cortisol did not differ significantly among the studied groups. Average value was within the normal range (around 18.0 $\mu\text{g/dL}$; $F = 2.011$; $p > 0.05$). However, 4 h after the operation, average values of serum cortisol level rose significantly, especially in the GAM group ($F = 19.867$; $p < 0.01$). The lowest serum levels of cortisol, still in normal range, were observed in the SAM group. The levels of serum cortisol in the PNB group were nearby the levels in the GAM group, whilst the values of cortisol in the CNB group were similar to the values from the SAM group.

Furthermore, 12 h after the operation, the average serum cortisol levels were significantly different among the

groups. The highest values were observed in the GAM group, while the lowest were found in the CNB group ($F = 8.050$; $p < 0.01$). The serum levels of cortisol tended to decrease 12 h postoperatively when compared to values 4 h after the operation, except in the SAM group, where they were doubled.

Finally, 24h after the surgery, the serum cortisol levels returned to the preoperative values, except in the GAM group and this difference was significant ($F = 3.894$; $p < 0.05$). In the CNB group, the serum cortisol level was even lower compared with preoperative values, but still within the normal range (7–28 $\mu\text{g/dL}$) (Table 1).

The preoperative values of insulin in the serum did not show any significant difference among studied groups and the average value in each group was around 10 mIU/L; ($F = 1.511$; $p > 0.05$). After the operation, the serum levels of insulin were significantly changed. Four hours postoperatively, the highest serum insulin levels were detected in the CNB and PNB group, while the lowest ones were in the GAM group; ($F = 5.811$; $p < 0.05$). Twelve hours after the operation, the average serum levels of insulin showed significant differences among the groups, ($F = 5.052$; $p < 0.05$). The highest values were also observed in the CNB group, while the lowest one was found in the SAM group. The serum insulin levels in the PNB and GAM group were close to the levels in the CNB group. Twenty four hours after the surgery, there was a remarkable drop in the serum insulin levels in all groups. The CNB group had still the highest values, while the lowest ones were found in the SAM and GAM groups and this difference was statistically significant, ($F = 6.394$; $p < 0.05$) (Table 2). T3, T4 and TSH levels in the serum showed slight reduction 4 h, 12 h and 24 h postoperatively without statistical significance.

The preoperative values of blood glucose showed

Table 1
Serum cortisol levels in the CNB, PNB, SAM and GAM group preoperatively, and 4 h, 12 h and 24 h after the operation

Group	Mean serum cortisol level \pm SD ($\mu\text{g/dL}$)				Average [†]
	Preoperatively	4 h	12 h	24 h	
CNB	18.70 \pm 1.14	22.34 \pm 2.21	19.17 \pm 1.90	14.89 \pm 1.26	18.77 \pm 1.23
PNB	19.97 \pm 1.51	29.94 \pm 1.95	21.51 \pm 1.43	19.10 \pm 1.51	22.63 \pm 1.60
SAM	15.83 \pm 1.02	15.59 \pm 0.99	33.39 \pm 2.25	18.94 \pm 1.41	20.93 \pm 1.67
GAM	19.09 \pm 1.26	33.66 \pm 1.82	27.14 \pm 2.77	22.03 \pm 1.65	25.48 \pm 1.92

[†]Average values of serum cortisol within the group; SD – standard deviation; CNB – central nerve block (epidural); PNB – peripheral nerve block (lumbar plexus block); SAM – spinal anesthesia + intravenous (i.v.) morphine; GAM – general anesthesia + i.v. morphine.

Table 2
Serum insulin levels in the CNB, PNB, SAM and GAM group preoperatively, and 4 h, 12 h and 24 h after the operation

Group	Mean serum insulin \pm SD (mIU/L)				Average [†]
	Preoperatively	4 h	12 h	24 h	
CNB	9.11 \pm 4.84	17.08 \pm 13.49	22.00 \pm 18.38	19.04 \pm 23.26	16.80 \pm 13.22
PNB	12.36 \pm 6.64	17.73 \pm 7.17	20.35 \pm 9.34	18.49 \pm 10.42	17.23 \pm 8.17
SAM	9.16 \pm 4.51	11.21 \pm 6.20	13.86 \pm 4.30	12.04 \pm 3.79	11.56 \pm 5.11
GAM	9.27 \pm 3.51	15.63 \pm 9.14	20.06 \pm 8.63	14.36 \pm 5.59	14.83 \pm 5.74

Note: For abbreviations see under Table 1.

normoglycemia, with similar results in all studied groups (around 5.5 mmol/L) ($F = 0.967$; $p > 0.05$). However, 4 h after the surgery, highly significant differences were found among the groups. The highest values were recorded in the GAM group, the lowest in the SAM group, while values in the CNB and PNB group were a bit higher than those from the SAM group; ($F = 10.084$; $p < 0.01$). On the other hand, 12 h after the operation significant rise in the blood glucose levels was detected in the SAM group, while these levels remained stable in the CNB and PNB group. The GAM group showed drop in the blood glucose levels; ($F = 7.186$; $p < 0.01$) Lowering of the blood glucose levels was noticed 24 h after the operation in all groups, with average values varied from 6.4–7.4 mmol/L, ($F = 2.246$; $p > 0.05$) (Table 3).

The CRP levels were found to be within normal range preoperatively in all groups, without significant differences. Postoperatively, 4 h after the operation, CRP showed slight increase in all groups. The level of CRP continued to increase remarkably in all groups 12 h after surgery. Twenty four hours postoperatively, the level of CRP became 10-20-fold higher, when compared with preoperative values, but without significant difference among the groups (Table 4).

The number of episodes of hypotension did not differ significantly among groups; 4 h ($\chi^2 = 3.057$; $p > 0.05$); 12 h ($\chi^2 = 2.243$; $p > 0.05$) and 24 h after the operation (0% in all groups) (Table 5).

and the mode of postoperative analgesia. The present study revealed that the markers for assessing surgical stress response were significantly lower if techniques of regional anesthesia and analgesia were performed.

Cortisol, also called “the stress hormone”, has been extensively investigated in order to find the best choice of anesthesia and postoperative analgesia, capable of reducing the stress response. Some of intravenous anesthetics, such as propofol (1.5–2.5 mg/kg) may diminish release of cortisol after induction in anesthesia. Opioids (fentanyl and morphine) are also found to have significant influence on reduction of cortisol levels, but less than regional techniques²⁵. Postoperative epidural analgesia is found to be extremely efficacious in prevention of increase in cortisol and catecholamine levels²⁶. Our study confirmed that immediately after the operation, patients from the CNB, PNB and SAM group, where regional anesthesia techniques were performed, had significantly lower cortisol levels when compared to the GAM group. Especially in the SAM group, as long as spinal anesthesia lasted (around 4–5 h), cortisol levels were even lower than preoperatively. After recovering from spinal anesthesia, there was a sharp increase of the serum cortisol levels. Values were even higher than the cortisol values in the GAM group, 12 h after the operation. Only if postoperative analgesia was continued using regional anesthesia techniques, significant increase in the cortisol levels was

Table 3
Serum glucose levels in the CNB, PNB, SAM and GAM group preoperatively, and 4 h, 12 h and 24 h after the operation

Group	Mean serum glucose levels \pm SD (mmol/L)				
	Preoperatively	4 h	12 h	24 h	Average [†]
CNB	5.61 \pm 0.63	7.50 \pm 1.78	6.74 \pm 1.24	6.60 \pm 1.03	6.61 \pm 1.14
PNB	5.33 \pm 0.48	8.08 \pm 1.24	7.08 \pm 0.85	6.32 \pm 0.62	6.70 \pm 0.72
SAM	5.24 \pm 0.60	6.49 \pm 0.86	9.65 \pm 2.61	6.85 \pm 0.62	7.05 \pm 1.14
GAM	5.38 \pm 0.75	10.44 \pm 3.36	8.45 \pm 2.42	7.38 \pm 1.90	7.91 \pm 2.08

Note: For abbreviations see under Table 1.

Table 4
CRP levels in the CNB, PNB, SAM and GAM group preoperatively, and 4 h, 12 h and 24 h after the operation

Group	Mean CRP values \pm SD (mg/L)				
	Preoperatively	4 h	12 h	24 h	Average [†]
CNB	2.65 \pm 2.30	3.08 \pm 3.22	14.85 \pm 8.67	81.45 \pm 38.34	25.50 \pm 12.84
PNB	2.88 \pm 1.38	2.82 \pm 2.53	15.46 \pm 8.57	78.72 \pm 26.63	24.97 \pm 10.09
SAM	4.57 \pm 1.60	5.66 \pm 1.80	21.28 \pm 11.21	94.19 \pm 34.88	31.42 \pm 11.42
GAM	3.65 \pm 2.20	4.39 \pm 3.80	19.10 \pm 8.80	84.92 \pm 21.39	28.01 \pm 9.17

CRP – C reactive protein.

Note: For other abbreviations see under Table 1.

Table 5
Incidence of hypotension 4 h and 12 h after the hip replacement

Group	Number (%) of patients with postoperative hypotension	
	4 h	12 h
CNB	5 (33.33)	3 (20)
PNB	3 (20)	1 (6.67)
SAM	1 (6.67)	1 (6.67)
GAM	1 (6.67)	0 (0)

Discussion

Surgical stress response depends on type of surgery and can be modulated by anesthetic technique intraoperatively

prevented (the CNB and PNB group). Rodgers et al.²⁷ in an extensive meta-analysis showed reduction in overall postoperative mortality in surgical patients undergone regional anesthesia in comparison to general anesthesia. They found out

reduction in mortality rate of 30% in the regional anesthesia group, due to pulmonary embolism, pneumonia, stroke, wound infections and cardiac events. The great majority of mortality causes were supposed to be connected to inability to diminish surgical stress response. When spinal and epidural anesthesia were compared, the differences in mortality were inconclusive. Mortality rate was low, whether spinal or epidural anesthesia was continued postoperatively or not. Kehlet et al.²¹ recently confirmed that a lack of properly designed prospective studies, which compared modern general and regional anesthesia for hip and knee arthroplasty, enabled setting of recommendations and the anesthesia protocols for this type of surgery.

Donatelli et al.²⁸ investigated insulin resistance in 60 patients underwent hip and knee arthroplasty under epidural anesthesia/postoperative analgesia or general anesthesia followed by intravenous PCA. The insulin resistance was estimated using the homeostatic model assessment (HOMA) score. HOMA score was calculated in the following way - fasting insulin (microU/mL) x fasting glucose (mmol/L)/22.5. The authors did not find significant difference in insulin resistance in any group of patients who were not previously insulin resistant. We found significant differences in the serum insulin levels among our studied groups 4 h and 12 h postoperatively, with the highest insulin concentration in the CNB and PNB group. Despite the elevation of serum insulin concentrations, the blood glucose levels were above normal range in all groups, confirming the theory that peripheral utilization of insulin is impaired after normalization of insulin secretion. According to our results, neuraxial block (epidural and spinal anesthesia) can positively influence insulin secretion, but does not affect the insulin resistance, which was present in all studied groups.

Hyperglycemia induced by the insulin resistance may influence a surgical outcome after hip replacement significantly, leading to a higher risk of wound infections, sepsis and organ failure²⁹⁻³¹. In spite of the large body of evidence that has confirmed negative effects of the insulin resistance following surgery, Hahn and Ljunggren³² found out reduction in number of early side effects after hip replacement under spinal anesthesia in non-diabetic patients, estimated as the insulin resistant preoperatively, using the oral glucose tolerance test (OGTT). Therefore, episodes of nausea, vomiting and hypotensive events (systolic arterial pressure < 80 mmHg) were recorded. The patients with the preoperative insulin resistance were found to have significantly lower number of early side effects – nausea and vomiting ($p < 0.04$) and hypotension ($p < 0.05$). Our study showed higher number of hypotensive episodes (systolic arterial pressure < 100 mmHg) in the patients with spinal and epidural anesthesia. The highest percentage of episodes of hypotension was recorded in the CNB group, 4 h postoperatively (33.3%) and 12h postoperatively (20%). Hypotension episodes, recorded 12 h after the operation in the CNB group, were more likely associated to the sympathetic blockade than to lack of insulin resistance.

Our study showed similar results with other authors, confirming the slight reduction in thyroid hormones and TSH

in the early postoperative period (up to 24 h) without significance among the groups³³.

Impaired glucose metabolism after hip replacement is strongly associated with wound infection, cardiac events and thromboembolic complications³⁴. Even mild changes in serum glucose concentrations perioperatively have been found to influence postoperative complications significantly, especially in elderly population³⁵⁻³⁷. Therefore, the appropriate choice of anesthetic technique, could have positive effects on glucoregulation and, consequently, number of complications, by reduction of stress response. According to recommendations of American Diabetes Association from 2015, values 7.8–10 mmol/L are considered as hyperglycemia. If values rise above 10 mmol/L, anti-hyperglycemic treatment is needed, because higher blood glucose values are connected with the higher number of postoperative complications³⁸. Lattermann et al.⁹ investigated the differences in intraoperative and postoperative plasma glucose concentrations in patients scheduled for hip replacement after combined spinal-epidural (CSE) or general anesthesia. Postoperative analgesia was maintained in the CSE group via the epidural catheter. General anesthesia was followed by intravenous PCA with opioids. Plasma glucose concentrations were significantly lower in the CSE group intraoperatively and immediately postoperatively ($p < 0.05$). On the first postoperative day, values were similar in both groups. Recent study of Gottschalk et al.³⁹ confirmed that the blood glucose levels were significantly lower immediately after surgery and 1 hour after surgery in non-diabetic patients following hip replacement, when spinal anesthesia was performed in comparison to general anesthesia ($p < 0.05$).

The present study showed that groups where regional anesthesia was performed and postoperative analgesia was maintained via peripheral or epidural catheter, had superior glycemic control. Ceasing regional anesthesia postoperatively, as it was in the SAM group, resulted in sharp rise in glucose levels, 12 h after the operation. These values were even higher in comparison to the GAM group. Furthermore, our study also confirmed results of Lattermann et al.³⁹ on the first postoperative day (24 h postoperatively). According to our findings, there were not significant differences in the blood glucose levels, 24 h after the operation, among the studied groups.

Study of Carli⁴⁰ showed that the treatment of postoperative pain was closely connected to stress induced hormonal release and represented an important factor in postoperative glucose metabolism and the insulin resistance. The present study confirmed that both the blood glucose levels and insulin levels were significantly lower in groups where anesthesia was maintained continuously in the postoperative period via epidural or peripheral catheter (the CNB and PNB group).

The scientific evidence, which confirmed influence of an anesthesia technique on inflammatory response after hip arthroplasty, has been inconclusive. Larsson et al.⁴¹ found out significant rise in the CRP levels after elective orthopedic surgery (hip and knee arthroplasty and microdiscectomy) without influence of an anesthetic technique among other

possible causes such as - bleeding, transfusion and operation time. On the other hand, Bagry et al.⁴² showed that the CRP and leukocyte count were lower if continuous peripheral nerve block was performed after knee arthroplasty in comparison to postoperative PCA with morphine ($p < 0.05$).

Chloropoulou et al.⁴³ showed that epidural anesthesia followed by epidural analgesia produced less inflammatory response in comparison to spinal anesthesia followed by intravenous morphine analgesia in the patients with total knee arthroplasty. The blood samples were collected preoperatively, immediately after the operation and 24 h postoperatively. They concluded that some novel markers, especially leukocyte activation molecules CD11b and CD62l showed more sensitivity in comparison with CRP and interleukins. Present study is in line with the findings of Larsson et al.⁴¹, showing continuous

rise in the CRP levels in all groups, independent of a type of intraoperative anesthesia or postoperative analgesia.

Conclusion

Administration of postoperative analgesia using continuous lumbar plexus block following hip arthroplasty reduces significantly stress response in comparison to postoperative PCA analgesia with morphine and has comparable effects on hormone release to epidural analgesia. Spinal anesthesia provides the best decrease of surgical stress response in comparison with the other types of intraoperative analgesia. In the postoperative period, after recovery from spinal anesthesia, the stress response cannot be attenuated successfully using patient controlled analgesia with morphine.

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