**Choice of Anesthesia and Postoperative Analgesia and Surgical Stress Response Following Hip Arthroplasty**

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 can be initiated by the hip replacement surgery, consisted of hormonal, metabolic and inflammatory changes. 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 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 PCA analgesia with morphine. **Methods.** Prospective study included60 patients, scheduled for total hip arthroplasty. Patients were randomized into 4 groups: Group CNB (Central nerve block - epidural), group PNB (Peripheral nerve block - lumbar plexus block), SAM (Spinal anesthesia- PCA (Patient controlled anesthesia) morphine) and GAM (General anesthesia - PCA Morphine). Serum levels of cortisol, thyroid hormones (T3, T4) and TSH, insulin, glucose and CRP (C-reactive protein) were measured in all groups – preoperatively and 4h, 12h and 24h after surgery. **Results.** The study showed that average serum cortisol levels were significantly lower 4h 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 12h after the operation (F = 8.050; p < 0.01). The highest serum insulin levels were detected 4h postoperatively in the CNB and PNB group, while the lowest were in GAM group. (F = 5.811; p < 0.05) Twelve hours after the operation, the lowest values of insulin were measured in SAM group (F = 5.052; p < 0.05), while 24h postoperatively, the lowest values were found in 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, 4h after surgery, with the highest values recorded in the GAM group and the lowest in the SAM group. (F = 10.084; p < 0.01). On the other hand, 12h 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 12h and 24h after 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 analgesia 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 to other types of intraoperative analgesia.

**Key words:**

**hip arthroplasty; surgical stress response; cortisol level; insulin; lumbar plexus block; epidural analgesia;**

**Apstrakt**

**Uvod/ Cilj.** Zamena totalne proteze kuka može izazvati značajan sistemski odgovor na hirurški stres, koji uključuje hormonske, 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 pacijenata 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 odgovor na hirurški stres u poređenju sa drugim vrstama postoperativne analgezije – kontinuiranom epiduralnom analgezijom i intravenskom PKA (pacijent kontrolisanom analgezijom) morfinom. **Metode.** U prospektivnu studiju je bilo uključeno 60 pacijenata, predviđenih za aloartroplastiku kuka. Pacijenti 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 morfin) i OAM (opšta anestezija - PKA morfin). Serumske vrednosti kortizola, tiroidnih hormona (T3, T4) i TSH, kao i vrednosti insulina, serumske glukoze i CRP (C-reaktivnog proteina) su merene u svim grupama, 4h, 12h i 24h nakon operacije. **Rezultati.** Istraživanje je pokazalo dasu prosečne vrednosti serumskog kortizola bile značajno niže 4h 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 je bio značajno niži 12h posle operacije, (F = 8.050; p < 0.01). Najveći porast serumskog nivoa insulina je detektovan 4h postoperativno u CNB i PNB grupi, a najmanji u grupi OAM, (F = 5.811; p < 0.05). Dvanaest sati nakon operacije, najniže vrednosti insulina su izmerene u SAM grupi (F = 5.052; p < 0.05), dok su nakon 24h, njegove najniže vrednosti bile u SAM i GAM grupi, (F = 6.394; p < 0.05). Nivoi T3, T4 i TSH su bili blago sniženi u odnosu na preoperativne vrednosti, 4h, 12h i 24h nakon operacije. Vrednosti glikemije su se statistički značajno razlikovale među grupama, 4h posle operacije, a najviše vrednosti su zabeležene u OAM grupi, dok su najniže bile u grupi SAM, (F = 10.084; p < 0.01). Nasuprot tome, 12h nakon operacije, značajan porast u nivou glukoze u serumu je detektovan u SAM grupi, (F = 7.186; p < 0.01). Vrednosti CRP-a su primetno rasli 12h i 24h postoperativno, ali bez statistički značajne razlike između grupa. **Zaključak.** Primena kontinuiranog bloka lumbalnog pleksusa nakon aloartroplastike kuka, smanjuje značajno sistemski odgovor na stres u poređenju sa postoperativnom pacijent kontrolisanom analgezijom (PKA) morfinom i po hormonskom odgovoru se može 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:**

**aloartroplastika kuka, sistemski odgovor na hirurški stres, nivo kortizola; insulin; blok lumbalnog pleksusa; epiduralna analgezija**

**Introduction**

Significant surgical stress response can be initiated by the hip replacement surgery, consisted of hormonal, metabolic and inflammatory changes.1 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 Aδ nerve fibers. Afferent impulses are transmitted throughout spinal cord and reach reticular formation and limbic system. Impulses also travel to hypothalamus and cerebral cortex.2

Activation of the neuroendocrine and immune system includes stimulation of hypothalamo-pituitary-adrenal axis, resulting in secretion of “stress hormones”, predominantly ACTH, cortisol and catecholamines. Increase in cortisol level represents the key result of the excitation of hypothalamus and secretion of adrenocoticotropic hormone (ACTH). It has been known that serum concentration of cortisol is doubled two hours after the surgical incision, while maximum of cortisol level (around 35µg/dl) is reached eight hours after surgery.  Thereafter, serum concentration of cortisol starts to decline, reaching 22µg/dl, 24h postoperatively, and remains stable in the seven following days.3 Production of thyroid hormones, thyroxine (T3) and tri-iodothyronine (T4) is affected by cortisol and catecholamines. Concentrations of total and free T3 decrease few days after surgery, while TSH levels fall within the 2h 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 predomination 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 cateholamines. Furthermore, the rate of glucose utilization is impaired by reduced peripheral sensitivity to insulin.7,8,9,10

Level of C-reactive protein (CRP), an acute phase protein, is expected to rise following hip arthroplasty, reaching its maximum 24h postoperatively. It can be used as non-specific marker of inflammatory response in these patients.11

Influence of anesthesia on stress response to surgery has been well established in patients scheduled for major abdominal and cardiac surgery.12,13,14 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 hormones.1

On the contrary, regional techniques, such as spinal and epidural anesthesia cease the nocicepive signals from surgical wound, preventing their transfer to central nervous system. As the result, release of pituitary hormones is attenuated significantly. Blocking of efferent signals, caused by regional anesthesia is also an important factor of preventing hormonal release from target organs.2 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 surgery.15 Therefore, peripheral nerve blocks have gained the popularity, providing adequate analgesia with less side effects and complications.16, 17,18 Surgical stress response after peripheral nerve blocks, such as 3-in-1 block and lumbar plexus block, was not studied extensively in patients 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 epidural or peripheral catheter. In the early postoperative period, up to 24h 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 PCA (patient controlled analgesia) 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 diminution of surgical stress response and may reduce perioperative complications, such as myocardial infarction, stroke and organ dysfunction.21,22,23

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 PCA analgesia with morphine.

**Methods**

This prospective, randomized study was conducted in 60 patients (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 to age, gender, body mass index, type of implant prosthesis, duration of surgery and postoperativeblood loss in 24h.

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). Patients were randomized into 4 groups of 15 patients: Group CNB (Central nerve block - epidural), group PNB (Peripheral nerve block - lumbar plexus block), SAM (Spinal anesthesia- IV morphine) and GAM (General anesthesia - IV Morphine).

All patients received midazolam 0.03mg/kg intravenously, 20 minutes before planned surgery. Preoperatively, in the group CNB, epidural space was identified with normal saline, using 18G epidural needle. Thereafter, epidural catheter 20G (Braun, Meslungen, Germany) was inserted. Bolus of 3ml chirocaine 0.5% and fentanyl 50µg was administered via epidural catheter before anesthesia induction. Intraoperatively, boluses of 5ml chirocaine 0.5% were added on a regular basis, every 30 minutes. Anesthetic induction was performed using propofol 2mg/kg, fentanyl 100 µg and rocuronium 0.6 mg/kg. Following endotracheal intubation, anesthesia was maintained using sevoflurane 1-2% in a 50%/50%mixtureof oxygen and N2O. Postoperative analgesia was maintained via epidural catheter during the first 24h, by continuous infusion of a mixture - 0.1% chirocaine and fentanyl 2 µg/ml, 8-15ml/h.

In the group PNB, lumbar plexus was identified by nerve stimulator according to Capdevila’s approach,24 using 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. Peripheral catheter (Braun, Meslungen, Germany) was inserted into psoas compartment where lumbar plexus is situated. A total of 20ml levobupivacaine 0.25% was administered. Following catheter insertion, general anesthesia was performed in the same way as in the group CNB. Postoperative analgesia was maintained via peripheral catheter during the first 24h, by continuous infusion of 0.25 levobupivacaine, 5-10ml/h. Initial titration was performed postoperatively, using a 10 cm visual analog scale (VAS) scale and providing pain score lower than 3 cm.

In the group GAM, all patients received general anesthesia, using the same protocol as it was used for the patients from 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, patients included into SAM and GAM group were informed about postoperative pain management using patient controlled analgesia (PCA) devices. In the recovery room, patients from SAM and GAM groups received initial intravenous boluses of morphine hydrochloride (5mg doses at 5min intervals), titrated manually until their pain score was lower than 3 on a 10 cm visual analog scale (VAS). Thereafter, PCA analgesia was initiated. PCA pump (µSP 6000, Arcomed ga, Switzerland) was connected, delivering 1mg doses of morphine intravenously, with a 7min 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 2 h 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 subarachnodal space at L3-4 spinous level. Postoperative analgesia was administered intravenously, using 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, 4h, 12h and 24h after surgery. Electrochemiluminescence immunoassay was used to determine serum concentrations of cortisol, thyroid hormones (T3, T4) and TSH, insulin. To estimate blood glucose levels, glucose oxidase enzymatic method was used. CRP levels were determined by immunoturbidimetric assay. Non-invasive intermittent blood pressure monitoring was performed intraoperatively using measurements at five 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 χ2 test and Fisher’s exact test. The differences were considered to be significant if p < 0.05.

**Results:**

Data analysis showed that preoperative levels of serum cortisol did not differ significantly among the studied groups. Average value was within the normal range (around 18,0 µg/dl). (F = 2.011; p > 0.05). However, 4h after the operation, average values of serum cortisol rose significantly, especially in GAM group. (F = 19.867; p < 0.01) The lowest levels of cortisol, still in normal range, were observed in SAM group. Levels of serum cortisol in PNB group were nearby the levels in GAM group, whilst the values of cortisol in CNB group were similar to the values from SAM group.

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

Finally, 24h after surgery, serum cortisol levels return to preoperative values, except in GAM group and this difference is significant. (F = 3.894; p < 0.05) In CNB group, serum cortisol was even lower compared to preoperative values, but still within the normal range (7-28 μg/dL), (Table 1)

**Table 1**

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

|  |  |
| --- | --- |
| Group | Mean serum cortisol (µg/dL) ± SD‡  |
| Preoperatively | 4h | 12h | 24h | Average † |
| CNB | 18.70±1.14 | 22.34±2.21 | 19.17±1.90 | 14.89±1.26 | 18.77±1.23 |
| PNB | 19.97±1.51 | 29.94±1.95 | 21.51±1.43 | 19.10±1.51 | 22.63±1.60 |
| SAM | 15.83±1.02 | 15.59±0.99 | 33.39±2.25 | 18.94±1.41 | 20.93±1.67 |
| GAM | 19.09±1.26 | 33.66±1.82 | 27.14±2.77 | 22.03±1.65 | 25.48±1.92 |

†Average values of serum cortisol within the group; ‡Standard deviation; CNB - Central nerve block (epidural); PNB - Peripheral nerve block (lumbar plexus block); SAM - Spinal anesthesia + IV morphine; GAM - General anesthesia - IV Morphine;

Preoperative values of serum insulin, did not show any significant difference among studied groups and average value in each group was around 10 mlU/L, (F = 1.511; p > 0.05). After the operation, levels of serum insulin have been significantly changed. Four hours postoperatively, the highest serum insulin levels were detected in CNB and PNB group, while the lowest were in GAM group, (F = 5.811; p < 0.05). Twelve hours after the operation, average levels of serum insulin showed significant differences among the groups, (F = 5.052; p < 0.05). The highest values were also observed in CNB group, while the lowest one was found in SAM group. Serum insulin levels in PNB and GAM group were close to the levels in CNB group. Twenty four hours after surgery, there was a remarkable drop in serum insulin levels in all groups. CNB had still the highest values, while the lowest were found in SAM and GAM groups and this difference was statistically significant, (F = 6.394; p < 0.05); (Table 2).

**Table 2**

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

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

†Average values of serum insulin within the group; ‡Standard deviation; CNB - Central nerve block (epidural); PNB - Peripheral nerve block (lumbar plexus block); SAM - Spinal anesthesia + IV morphine; GAM - General anesthesia - IV Morphine;

T3, T4 and TSH levels showed slight reduction of their values 4h, 12h and 24h postoperatively without statistical significance.

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

**Table 3**

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

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

‡Standard deviation; CNB - Central nerve block (epidural); PNB - Peripheral nerve block (lumbar plexus block); SAM - Spinal anesthesia + IV morphine; GAM - General anesthesia - IV Morphine;

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

**Table 4**

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

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

‡Standard deviation; CNB - Central nerve block (epidural); PNB - Peripheral nerve block (lumbar plexus block); SAM - Spinal anesthesia + IV morphine; GAM - General anesthesia - IV Morphine;

Number of episodes of hypotension did not differ signifficantly among groups, 4h (χ2 = 3.057; p > 0.05), 12h (χ2 = 2.243; p > 0.05) and 24h after the operation (0% in all groups), (Table 5).

**Table 5**

 **Incidence of hypotension 4h and 12h after the hip replacement**

|  |
| --- |
| Number/percentage of patients with hypotensive episodes  |
| Group | 4h postop.\* | 12h postop.\* |
| 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%) |

\*postoperatively; CNB - Central nerve block (epidural); PNB - Peripheral nerve block (lumbar plexus block); SAM - Spinal anesthesia + IV morphine; GAM - General anesthesia - IV Morphine;

**Discussion**

Surgical stress response depends on type of surgery and can be modulated by anesthetic technique intraoperatively 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 in cortisol levels, but less than regional techniques.25 Postoperative epidural analgesia is found to be extremely efficacious in prevention of the increase in cortisol and catecholamine levels.26 Our study confirmed that immediately after the operation patients from CNB, PNB and SAM group, where regional anesthesia techniques were performed, had significantly lower cortisol levels when compared to GAM group. Especially in SAM group, as long as spinal anesthesia lasted (around 4-5h), cortisol levels were even lower than preoperatively. After recovering from spinal anesthesia, there was a sharp increase of the serum corisol levels. Values were even higher than cortisol values in GAM group, 12h after the operation, (Table 1). Only if postoperative analgesia is continued using regional anesthesia techniques, significant increase in cortisol levels was prevented (CNB and PNB group). Rodgers at al.27 in extensive meta-analyses 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 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 lack of properly designed prospective studies, which compared modern general and regional anesthesia for hip and knee arthroplasty, enabled setting of recommendations and anesthesia protocols for this type of surgery.

Donatelli28 and al. investigated insulin resistance in sixty patients underwent hip and knee arthroplasty under epidural anesthesia/postoperative analgesia or general anesthesia followed by intravenous PCA analgesia. 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. Authors did not found significant difference in insulin resistance in any group of patients who were not previously insulin resistant. We found significant differences in serum insulin levels among our studied groups 4h and 12h postoperatively, with the highest insulin concentration in CNB and PNB group, (Table 2). Despite the elevation of serum insulin concentrations, 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, (Table 3). According to our results, neuraxial block (epidural and spinal anesthesia) can influence positively insulin secretion, but does not affect insulin resistance, which was present in all studied groups.

Hyperglycemia induced by insulin resistance may influence surgical outcome after hip replacement significantly, leading to higher risk of wound infections, sepsis and organ failure.29,30,31 In spite of the large body of evidence that has confirmed negative effects of insulin resistance following surgery, Hahn et al.32 found out reduction in number of early side effects after hip replacement under spinal anesthesia in non-diabetic patients, estimated as insulin resistant preoperatively, using oral glucose tolerance test (OGTT). Therefore, episodes of nausea, vomiting and hypotensive events (systolic arterial pressure < 80 mmHg) were recorded. Patients with 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 patients with spinal and epidural anesthesia. The highest percentage of episodes of hypotension was recorded in CNB group, 4h postoperatively (33.3%) and 12h postoperatively (20%). Hypotension episodes, recorded 12h after the operation in the CNB group, were more likely associated to the sympathetic blockade than to lack of insulin resistance. Episodes of nausea have been recorded in SAM group only in 6.7% of patients 4h postoperatively. Twelve hours postoperatively, it was found in 46.7% of patients from SAM group.The incidence in other groups was lower, especially in the PNB group, where none of the patients had nausea, (Table 5). (χ2 = 9.712; p < 0.01) Possible explanation is – significantly increased consumption of morphine after recovering from spinal anesthesia and consequently, nausea as a side effect of narcotic analgesics.

Our study showed similar results with other authors, confirming the slight reduction in thyroid hormones and TSH in the early postoperative period (up to 24h) without significance among the groups.33

Impaired glucose metabolism after hip replacement is strongly associated with wound infection, cardiac events and thromboembolic complications.34 Even mild changes in serum glucose concentrations perioperatively have been found to influence postoperative complications significantly, especially in elderly population.35,36,37 Therefore, 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 higher number of postoperative complications.38 Lattermann R.39et al. 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 CSE group via epidural catheter. General anesthesia was followed by intravenous patient-controlled analgesia with opioids.  Plasma glucose concentrations were significantly lower in 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.40 confirmed that blood glucose levels were significantly lower immediately after surgery and one 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 SAM group, resulted in sharp rise in glucose levels, 12 h after the operation. These values were even higher in comparison to GAM group. Furthermore, our study also confirmed results of Lattermann R.39 et al. on the first postoperative day (24 h postoperatively). According to our findings, there were not significant differences in blood glucose levels, 24 h after the operation, among the studied groups, (Table 3).

Study of Carli F.41 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 insulin resistance. The present study confirmed that both 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 (CNB and PNB group), (Table 2, 3).

The scientific evidence, which confirmed influence of anesthesia technique on inflammatory response after hip arthroplasty, has been inconclusive. Larsson et al.42 found out significant rise in CRP levels after elective orthopedic surgery (hip and knee arthroplasty and microdiscectomy) without influence of anesthetic technique among other possible causes such as - bleeding, transfusion and operation time. On the other hand, Bagry43 et al. showed that C-reactive protein and leukocyte count were lower if continuous peripheral nerve block was performed after knee arthroplasty in comparison to postoperative patient-controlled analgesia with morphine (p< 0.05).

Chloropoulou et al.44 showed that epidural anesthesia followed by epidural analgesia produced less inflammatory response in comparison to spinal anesthesia followed by intravenous morphine analgesia in patients with total knee arthroplasty. Blood samples were collected preoperatively, immediately after the operation and 24 hours postoperatively. They concluded that some novel markers, especially leukocyte activation molecules CD11b and CD62l showed more sensitivity in comparison to CRP and interleukins. Present study has been in line with findings of Larsson et al.42, showing continuous rise in CRP levels in all groups, independent of type of intraoperative anesthesia or postoperative analgesia.

**Conclusions**

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 diminution of surgical stress response in comparison to other types of intraoperative analgesia. In the postoperative period, after recovery from spinal anesthesia, stress response cannot be attenuated successfully using patient controlled analgesia with morphine.

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