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ORIGINAL RESEARCH

# Lumbar epidural analgesia and sciatic and femoral peripheral nerve blocks attenuate the stress-induced response in patients during the early postoperative period following total knee replacement

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## Abstract

Invasive surgical procedures cause immune system downregulation by inducing a profound proinflammatory response. Establishing the most effective type of postoperative analgesia is crucial to maintain the equilibrium of the immune system. The purpose of this research was to evaluate the influence of epidural analgesia, peripheral nerve blockade as well as systemic analgesia on stress response in patients during the early postoperative period following total knee replacement. In total, 60 patients undergoing total knee replacement were allocated into three groups (n = 20, per group) in this prospective randomized study. Group 1, Group 2 and Group 3 received epidural analgesia, sciatic and femoral peripheral nerve blocks and systemic analgesia, respectively. Intensity of pain was measured at rest and upon movement. Blood samples were collected at baseline (T0), immediately before (T1) and after (T2) surgery, and 24 (T3) and 72 (T4) h postoperatively. The absolute number of leukocytes, concentrations of catecholamine, cortisol and C-reactive protein were determined. Patients in Group 1 and Group 2 exhibited lower pain scores than Group 3. Concentrations of cortisol and norepinephrine, but not epinephrine, were significantly lower in Group 1 and Group 2 at T2 than in Group 3. Significantly lower interleukin-1$\beta$ concentrations were observed in Group 1 and Group 2 at T3 and T4 than in Group 3. Interleukin-6 concentrations were minor in Group 1 and Group 2 at T2 than in Group 3. Lumbar epidural analgesia and sciatic and femoral peripheral nerve blocks are effective analgesic techniques that reduce the acute inflammatory stress response in patients during the early postoperative period following total knee replacement.

## Keywords

Analgesia; Cytokines; Hormones; Pain; Stress response; Total knee replacement

## 1. Introduction

Total knee replacement (TKR) is a common orthopedic surgical procedure performed for the treatment of degenerative osteoarthritis of the knee [1]. Following TKR, patients may experience significant postoperative pain, which, in concomitance with tissue damage, induces strong inflammation and neuroendocrine activation [2]. Postoperative inflammation serves to defend the host and initiate tissue repair. Injured cells produce proinflammatory cytokines, bradykinins and prostaglandins, which stimulate nociceptors and cause pain. To counteract these events, leukocytes are attracted to the injured tissue by chemokines and release analgesic agents, which bind to nociceptors and produce an analgesic effect. The balance between analgesic and hyperalgesic agents determines pain intensity [3–5]. Locally produced interleukin (IL)-6 and IL-1 are released into the bloodstream, resulting in a systemic inflammatory response [6]. Higher production of IL-1, IL-6 and tumor necrosis factor-alpha (TNF-$\alpha$) has been associated with higher pain intensity sensation [7]. The pain intensity varies according to individual characteristics, such as age, genetic features and co-morbidity [8].

Pain is also a mediator of a complex activation of the neuroendocrine and immunologic axes, resulting in immunodepression of innate and adaptive immunity. The resulting activation of the hypothalamic-pituitary-adrenal axis and sympathetic nerve system increases plasma catecholamines, corticotropin-releasing hormone, adrenocorticotropin and cortisol [9]. Depending on the intensity and duration of the pain, variable increases in catecholamine and cortisol concentrations


  

are observed [10]. Catecholamine and cortisol induce inhibition of IL-12, interferon (IFN)-$\gamma$ and TNF-$\alpha$ production and stimulate the production of anti-inflammatory cytokines. This leads to the downregulation of the Th1 response, which is a protective response necessary for the body to heal. However, exaggerated stress-related immunodepression is harmful and can lead to postoperative complications in perioperative settings [10, 11]. The postoperative immunodepression caused by extensive surgical tissue trauma with affection of the adjacent nerves may be prolonged after TKR. Therefore, determining the effects of different types of postoperative pain management on humoral and cellular immunity is crucial to establish effective postoperative analgesia [11–13].

Thus, the purpose of this study was to compare the effect of epidural analgesia, peripheral blockade of the sciatic and femoral nerves, and systemic analgesia on the stress response in patients during the early postoperative period following TKR. We hypothesized that regional analgesia would lower stress mediator concentrations better than systemic analgesia and thus improve patient recovery.

## 2. Materials and methods

### 2.1 Patients

The study was conducted from June 2016 until January 2020. The study included 60 patients scheduled to undergo elective total knee replacement surgery to treat primary degenerative osteoarthritis at the Clinic for Orthopedics and Traumatology Lovran, Croatia, who were classified as American Society of Anesthesiologists (ASA) physical status I–III and were able to completely understand the study protocol. Exclusion criteria on patient selection are shown in Fig. 1. All patients eligible as per the inclusion criteria signed informed consent forms before participating in the study.

Sixty patients were randomly assigned, according to the postoperative analgesia management method that they received, to each of the three study groups using the Datlnf Ranolist computer program (Clinical trail, Datlnf GmbH®, Tubingen, Germany): Group 1 received epidural analgesia, Group 2 received peripheral nerve blocks (sciatic and femoral nerve blocks), and Group 3 received systemic analgesia. For all patients included in the study, the following data were collected: gender and age, duration of surgery and duration of anesthesia. A visual analogue scale (VAS) was used to assess the subjective perception of pain intensity for each patient before surgery (T1), after surgery (T2) and 24 (T3) and 72 hours (T4) after surgery at rest and upon movement. All patients included in the study underwent surgery by the same surgical team.

### 2.2 Anesthesia and postoperative analgesia

Lumbar spinal anesthesia with 15 mg of 0.5% bupivacaine (Marcaine® 0.5% Spinal; 20AA052, Astra Zeneca, France) that was administered intrathecally was performed for all patients.

To manage postoperative pain, patients in Group 1 received epidural analgesia consisting of a continuous infiltration of a mixture of 0.25% levobupivacaine (Chirocaine® 0.5%; 12TBA08, AbbVie S.r.l., Campoverde Di Aprilia, Italy) and 0.5 mcg/mL sufentanil (Sufentanil®; 208660, Renaudin, France), administered at a rate of 2–15 mL/h depending on the patient's VAS score. Continuous epidural analgesia was initiated immediately after the operation. After 24 h, intermittent epidural boluses of 10 mL 0.25% levobupivacaine (depending on the patient's VAS score) were applied every 4–6 h. The catheter was removed on postoperative day 3.

In Group 2, ultrasound-guided (Sonosite EDGE ultrasound system with the C60x/5–2MHz transducer$^{TM}$; SonoSite, Inc., Bothel, WA, SAD) sciatic and femoral nerve blocks were administered to each patient's operated leg immediately following surgery to manage postoperative pain. The blocks were performed using an ultrasound-guided "in plane" technique. Sciatic blockade (subgluteal approach) was assessed with 20 mL of 0.5% levobupivacaine. Femoral nerve block was assessed with 10 mL of 0.5% levobupivacaine near the nerve, and the femoral catheter (non-stimulating catheter system, Contiplex Tuohy; B. Braun Melsungen, Germany) was set up under the femoral nerve. Boluses of 10 mL of 0.25% levobupivacaine were administered every 4–6 h *via* the femoral catheter according to the patient's VAS score.

In the patients in Group 3 intravenous administration of acetaminophen (Paracetamol Kabi®; 14SD37, Fresenius Kabi, Friedberg, Germany) began immediately upon commencement of surgical wound closure. After the initial dose, patients received 1 g of acetaminophen every 6 h until the third postoperative day. Patients also received 200 mg of tramadol (Tramal®; 00641S, Grunenthal Gmbh, Aachen, Germany) and 2.5 g of metamizole sodium (Alkagin® Alkaloid-Int d.o.o., 301001, Ljubljana, Slovenia) every 10–12 h. All medications and procedures are standard and approved for the treatment of patients at the Clinic for Orthopedics and Traumatology Lovran, Croatia.

### 2.3 Determination of laboratory parameters

From each patient included in the study peripheral blood was sampled in heparin vacutainer blood collection tubes (Becton Dickinson$^{TM}$, Erembodegem, Belgium) at time points T1, T2, T3 and T4. Plasma was obtained by centrifugation at 200 g for 10 min and was stored at −80 °C until further analyses were conducted.

The absolute number of leukocytes was determined by an electronic counter (Technicom H-1 system$^{TM}$, New York, NY, USA). The C-reactive protein (CRP) concentration was determined using an automatic analyzer (biochemistry analyser, Olympus$^{TM}$; Tokyo, Japan).

Serum levels of TNF-$\alpha$, IL-6 and IL-1$\beta$ were measured using a high-sensitivity enzyme-linked immunosorbent assay (ELISA; Invitrogen ThermoFisher Scientific$^{TM}$, Carlsbad, CA, USA) in accordance with the manufacturer's instructions.

Serum cortisol concentrations were measured using a autjomatic analyser (Cobas e411 analyzer, Roche Diagnostic$^{TM}$, Mannheim, Germany) by an immunoassay.

To determine the urinary concentrations of creatinine and catecholamines (epinephrine and norepinephrine), spot urine samples were collected the day before surgery (T0) as baseline samples and immediately before (T1) and after (T2) surgery.

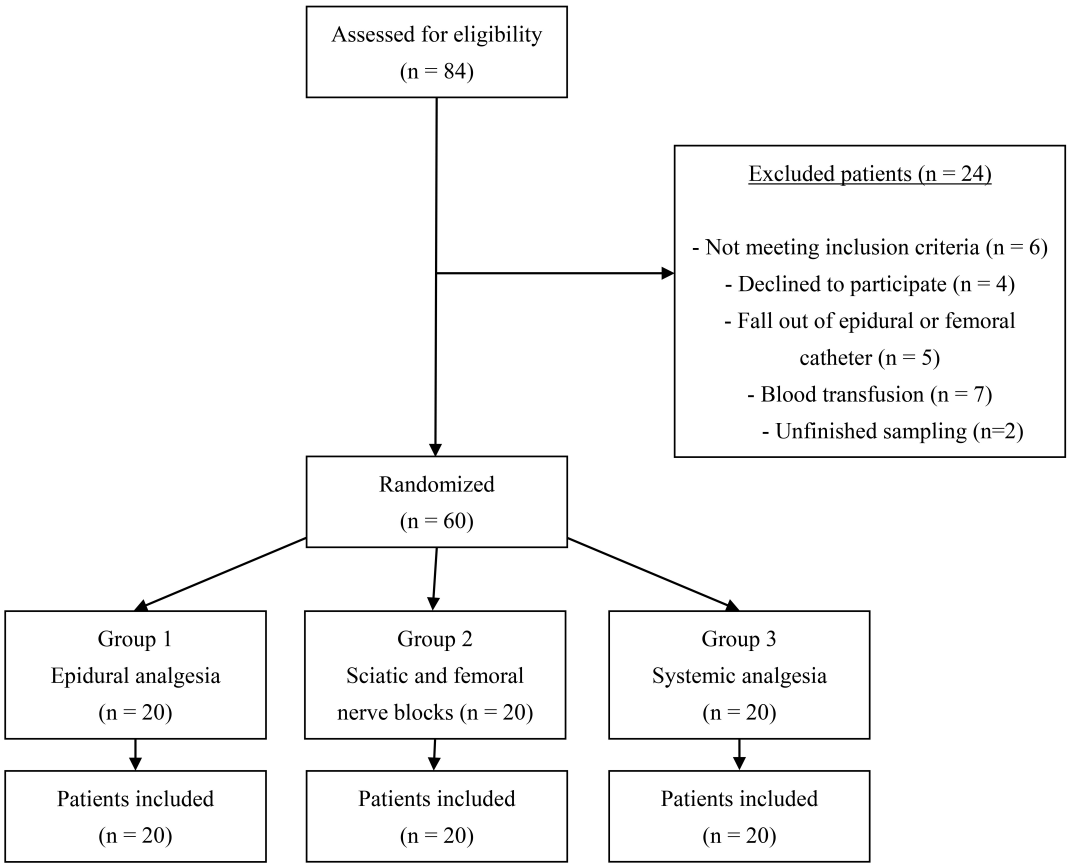


**FIGURE 1. Flow diagram of the study.**

The urinary creatinine concentration was determined using Jaffe's kinetic method (Cobas 6000 c501 module$^{TM}$; Roche Diagnostic, Mannheim, Germany). The urinary epinephrine and norepinephrine concentrations were measured by a high-performance liquid chromatography (HPLC) system (Shimadzu$^{TM}$, Osaka, Japan), with an electrochemical detector (ED 3000$^{TM}$; Recipe, Munich, Germany), as well as a solvent delivery pump, an autosampler, and an oven (LC-10AD$^{TM}$, SIL-10AD$^{TM}$ and CTO-10AC$^{TM}$, respectively; Shimadzu, Osaka, Japan). A commercial HPLC kit for urinary catecholamines Recipe$^{TM}$, Munich, 2000, Germany) was used for urine sample preparation (*i.e.*, solid-liquid extraction) prior to conducting chromatography. Isocratic chromatography was performed under the following conditions: flow rate, 1.0 mL/min; column temperature, 30 °C; injection volume, 20 $\mu$L; and injection interval, 20 min. The results are expressed as the epinephrine/creatinine and norepinephrine/creatinine ratios.

## 2.4 Statistical analysis

Data analysis software (Statistica 14$^{TM}$; TIBCO Software Inc, Palo Alto, CA, USA) was used for statistical analysis. The sample size was calculated according to our previous study [14]. The Kolmogorov-Smirnov test for normal distribution was performed. Since the data did not show normal distribution, non-parametric statistical analysis was performed. The Friedman test and *post-hoc* Wilcoxon rank sum test was used to compare time points within groups. The nonparametric Kruskal-Wallis test was used to analyze differences between groups. The Mann-Whitney U test was used as a *post hoc* test to determine which groups differed significantly. Bonferroni adjustment was used for multiple comparisons. The $p$ value $< 0.05$ was considered statistically significant. All data are presented as 25–75 percentile values.

# 3. Results

## 3.1 Demographic and surgical data

No significant differences among Group 1, Group 2 and Group 3 according to age, gender, duration of surgery and duration of anesthesia were observed (Table 1).

## 3.2 Comparison of VAS scores at rest and upon movement

The VAS scores of the patients in Groups 1, 2 and 3 recorded at rest (Fig. 2A) and upon movement (Fig. 2B) at time points T1, T2, T3 and T4 are presented in Fig. 2. When comparing VAS scores at rest (Fig. 2A) and upon movement (Fig. 2B) within each group, statistically significantly higher VAS scores were recorded in Group 3 at time points T2, T3 and T4 in comparison with time point T1, but not in Group 2 and Group 3.

When comparing VAS scores among the groups, statistically significantly higher scores were observed in Group 3 at time points T2, T3 and T4 in comparison with Group 1 and Group 2 at rest and upon movement.

**TABLE 1. Demographic and clinical parameters of patients in all groups.**

| | Group 1 (n = 20) | Group 2 (n = 20) | Group 3 (n = 20) | *p* value |
|---|---|---|---|---|
| Age (yr) | 68.5 (64.0–72.0) | 67.0 (62.0–70.0) | 70.5 (64.0–74.5) | 0.875 |
| Gender (M/F) | 9/11 | 10/10 | 11/9 | 0.786 |
| Duration of surgery (min) | 72.5 (65.0–88.5) | 67.5 (64.5–77.5) | 65.5 (60.0–73.0) | 0.125 |
| Duration of anaesthesia (min) | 316 (277.5–407.5) | 339 (299.0–369.5) | 318 (294.0–359.5) | 0.652 |

*Group 1 presents patients who received epidural analgesia, Group 2 presents patients who received sciatic and femoral nerve blocks, and Group 3 presents patients who received systemic analgesia. Data are shown as median (25th–75th percentile).*

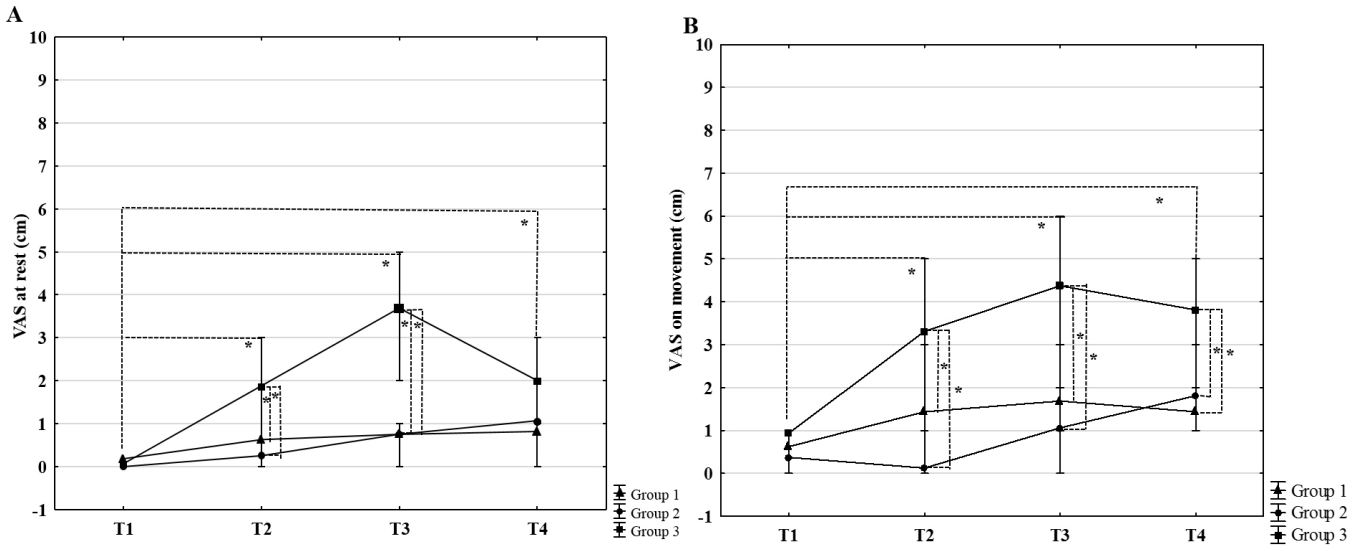


**FIGURE 2. Comparison of visual analogue scores (VAS).** VAS (A) at rest, (B) on movement at different time points in patients allocated to Group 1 (▲), Group 2 (●) and Group 3 (■) at time points T1 (before surgery), T2 (after surgery), T3 (24 h after surgery) and T4 (72 h after surgery). Data are presented as median (25th–75th percentile). Level of statistical significance: $^{*}p < 0.05$.

## 3.3 The influence of different types of postoperative analgesia on laboratory parameters

The absolute number of leukocytes is shown in Fig. 3A. The absolute number of leukocytes was higher at time point T2 when compared with T1 in Group 1 and in Group 3, but not in Group 2.

The CRP concentration values in Group 1, Group 2 and Group 3 were significantly higher at time points T3 and T4 in comparison with time points T1 and T2 (Fig. 3B). No significant difference was found in the CRP concentrations among groups.

Dynamic changes of cytokines IL-1$\beta$ (Fig. 4A), IL-6 (Fig. 4B) and TNF-$\alpha$ (Fig. 4C) in the plasma of the patients in Group 1, Group 2 and Group 3 at different time points are shown in Fig. 4.

Concentrations of IL-1$\beta$ in Group 3 were statistically significantly higher at time points T3 and T4 in comparison with time points T1 and T2, but not in Group 1 and Group 2 (Fig. 4A). Additionally, concentrations of IL-1$\beta$ were statistically significantly higher at time points T3 and T4 in Group 3 in comparison with Group 1 and Group 2 (Fig. 4A).

Serum IL-6 levels were statistically significantly increased in Group 1, Group 2 and Group 3 at time points T3 and T4 in comparison with time points T1 and T2 (Fig. 4B). At time points T2 and T3, statistically significantly higher concentrations of IL-6 were observed in Group 3 in comparison with Group 1 and Group 2 (Fig. 4B).

No statistically significant differences were found in the concentrations of TNF-$\alpha$ in all the groups at all the time points (Fig. 4C).

Dynamic changes of cortisol in plasma (Fig. 5A), epinephrine (Fig. 5B), and norepinephrine (Fig. 5C) in the urine of the patients in Groups 1, 2 and 3 at different time points are shown in Fig. 5.

The cortisol level at baseline (T0) was not significantly different within analyzed groups (Fig. 5A). In Group 1, Group

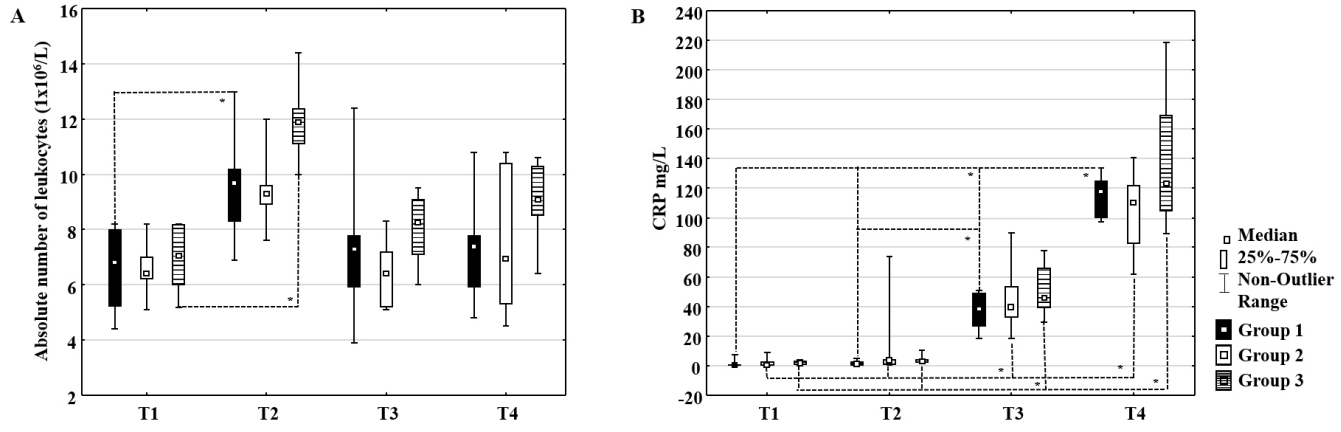


**FIGURE 3. Dynamic changes of the absolute number of leukocytes (Lkc) and concentration of C-reactive protein (CRP).** (A) Absolute number of Lkc, (B) concentration of CRP in peripheral venous blood in patients allocated to Group 1 (■), Group 2 (□) and Group 3 (=) at time points T1 (before surgery), T2 (after surgery), T3 (24 h after surgery) and T4 (72 h after surgery). Data are shown as median (▫), 25th–75th percentile (□), non-outlier range (I) and outliers (◦). Level of statistical significance: *$p < 0.05$.

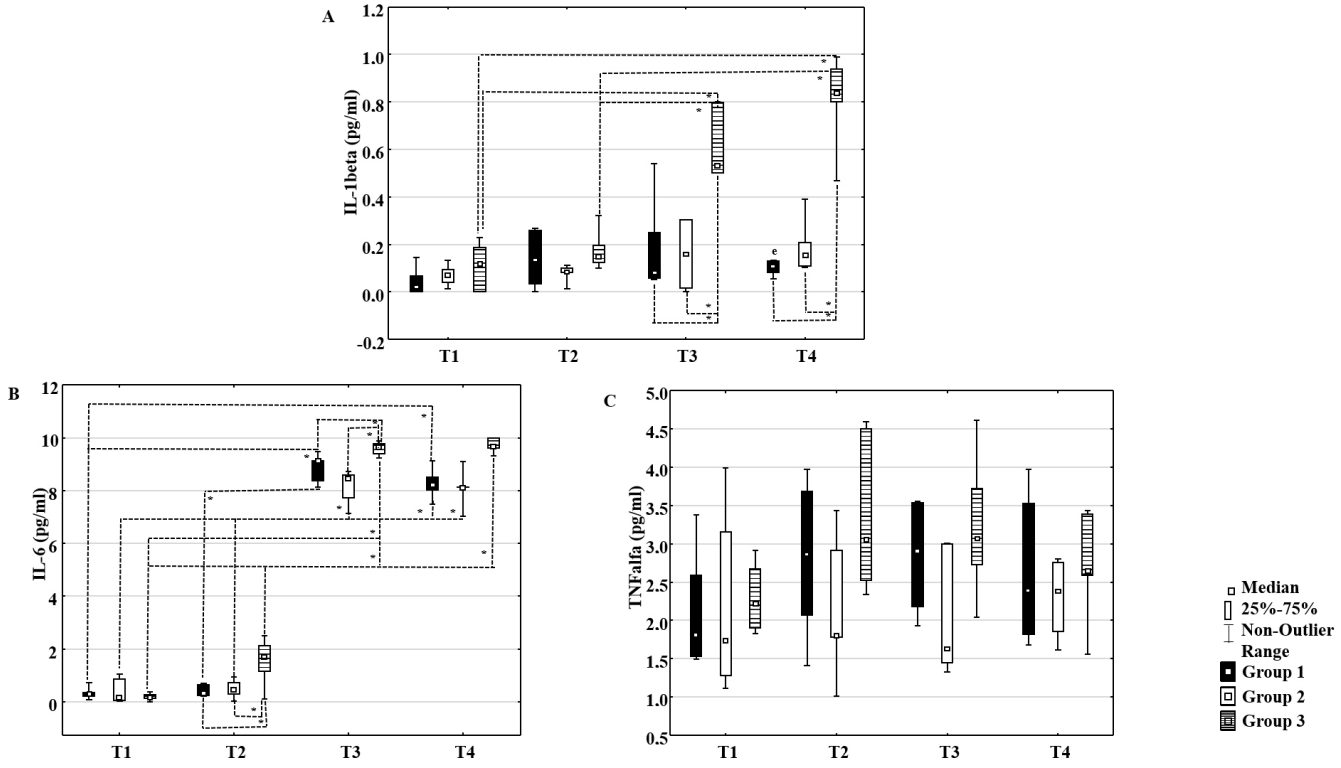


**FIGURE 4. Dynamic changes of IL-1$\beta$, IL-6 and TNF-$\alpha$ plasma concentrations.** (A) IL-1$\beta$, (B) IL-6 and (C) TNF-$\alpha$ plasma concentrations in patients allocated to Group 1 (■), Group 2 (□) and Group 3 (=) at time points T1 (before surgery), T2 (after surgery), T3 (24 h after surgery) and T4 (72 h after surgery). Data are shown as median (▫), 25th–75th percentile (□), non-outlier range (I), and outliers (◦). Level of statistical significance: *$p < 0.05$. IL: interleukin; TNF: tumor necrosis factor-alpha.

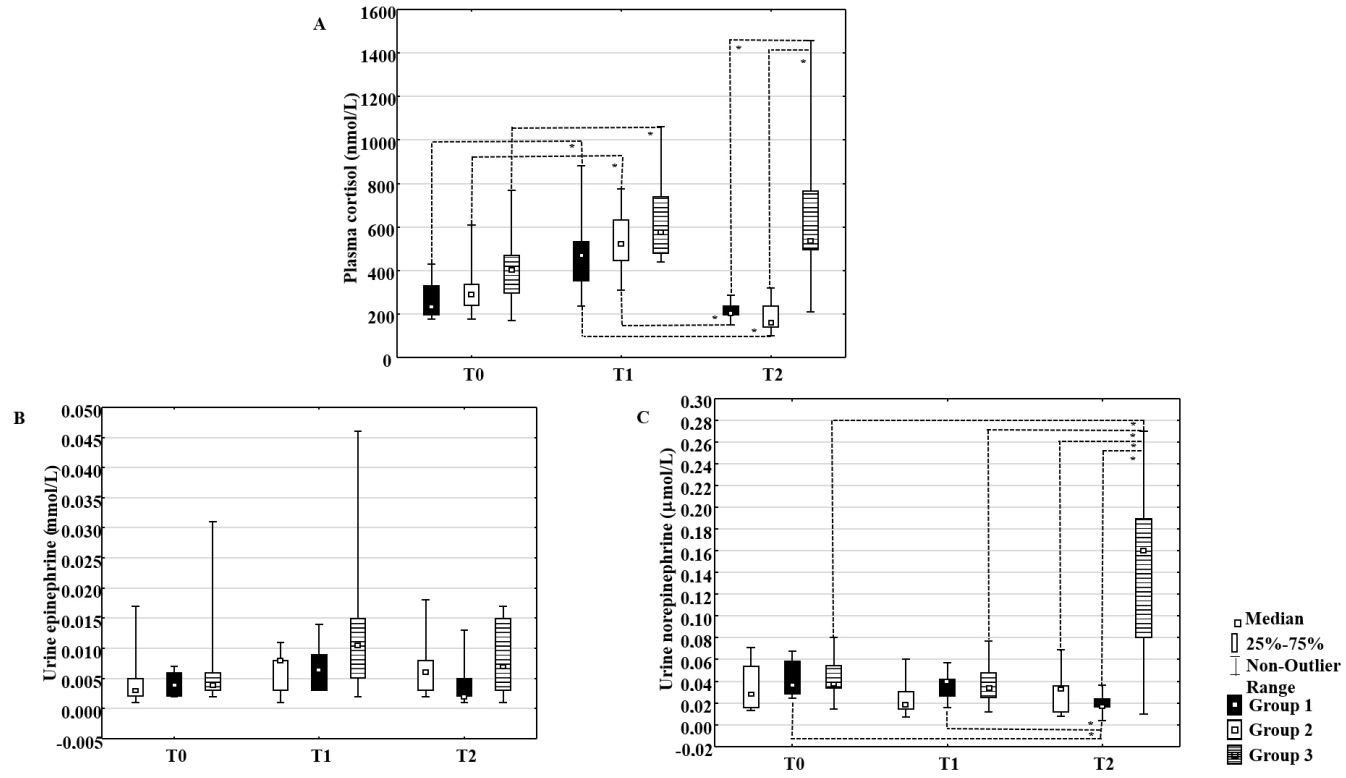


**FIGURE 5. Dynamic changes of neuroendocrine hormone levels.** (A) Plasma cortisol, (B) urine epinephrine, and (C) urine norepinephrine in Group 1 (■), Group 2 (□) and Group 3 (=) at time points T0 (baseline level at the day before surgery), T1 (before surgery) and T2 (after surgery). Data are presented as median (▫), 25th–75th percentile (□), non-outlier range (I) and outliers (◦). Level of statistical significance: $*p < 0.05$.

2 and Group 3, cortisol levels increased statistically before surgery (T1) in comparison with T0. In Group 1 and Group 2, plasma cortisol levels statistically significantly decreased after surgery (T2), but not in Group 3.

The urinary epinephrine levels did not differ within and between all the groups at investigated time points (Fig. 5B).

In Group 1, at time points T0, T1 and T2, there were no statistically significant differences in urinary norepinephrine levels. Significantly lower urine norepinephrine levels were found in Group 2 at time point T2 in comparison with time points T0 and T1. The urine norepinephrine levels after surgery (T2) increased statistically in Group 3 in comparison with Group 1 and Group 2 (Fig. 5C).

## 4. Discussion

The goal of this research was to determine parameters of the stress-induced response in patients during the early postoperative period following TKR and evaluate the effectiveness of lumbar epidural analgesia and sciatic and femoral peripheral nerve blocks in attenuating pain sensation. The results obtained with this study revealed that patients that received regional analgesia exhibited lower pain scores than patients who received intravenous analgesia. Additionally, our study revealed that concentrations of cortisol and norepinephrine, as well as IL-1$\beta$ and IL-6, were significantly lower in patients who received regional analgesia compared with patients who received intravenous analgesia. These findings suggest that regional methods of analgesia such as epidural analgesia and sciatic and femoral peripheral nerve blocks are effective analgesia techniques that reduce the acute inflammatory stress response in patients during the early postoperative period following TKR.

TKR is a major orthopedic surgery with high-intensity postoperative pain [15]. The tissue damage produced by the surgical procedure, in concomitance with the anesthesia and postoperative pain, leads to immunological and neuroendocrine alterations that induce immune system downregulation [16]. This observed immunodepression can result in delayed wound healing, cardiopulmonary complications, infections and chronic pain [12]. By analyzing the patients' intensity of experienced pain, we found that epidural analgesia and nerve blockade of the sciatic and femoral nerves offer better postoperative analgesia than systemic analgesia, both at rest and upon movement; therefore, these two types of postoperative analgesia are reliable analgesic treatments following TKR. These findings about subjective perception of pain are similar to previous studies [17–21].

To evaluate stress response, we measured cortisol and catecholamine levels, as well as inflammatory biomarker concentrations for IL-1$\beta$, IL-6 and TNF-$\alpha$. IL-1$\beta$, IL-6 and TNF-$\alpha$ have pro-nociceptive roles and are associated with painful conditions and hyperalgesia [22]. In this study, the measured cytokine values of IL-1$\beta$ and IL-6 clearly indicated that postoperative management of pain using lumbar epidural analgesia or peripheral nerve blockade reduced the patients'

early pro-inflammatory response to TKR surgery. IL-1$\beta$ levels increased in the patients that received systemic analgesia, but they did not increase at any observed time in the patients that received regional analgesia. IL-6 is known to be correlated with the extent of the surgery rather than the surgery's duration [23]. Kugisaki found higher concentrations of IL-6 in patients having had bilateral *vs.* unilateral TKR [23]. In the present study, lower levels of IL-6 observed 24 and 72 h after surgery in the epidural analgesia and peripheral nerve blockade groups in comparison with the systemic analgesia group indicate that the lower cytokine levels were due to better postoperative analgesia.

Changes in plasma TNF-$\alpha$ concentrations did not differ significantly between the groups. TNF-$\alpha$ is an acute phase cytokine that has a very short half-life (<20 min), which may be the reason why there was no significant difference in concentration of this cytokine among the three groups [24]. Kuchálik *et al.* [25] demonstrated that local infiltration analgesia after total hip replacement had an effect on the reduction in IL-6 concentration, but no change in TNF-$\alpha$ concentration. Furthermore, Zhang *et al.* [13] concluded that epidural anesthesia followed by epidural analgesia can reduce the inflammatory response after TKR, modulating the leucocyte activation molecules without influence on IL-1$\beta$, IL-6 or TNF-$\alpha$. In contrast, Martin *et al.* [17] found that combined sciatic and continuous femoral blocks did not have any effect on inflammatory response after TKR, but they did observe inhibited clinical inflammation.

In this study, we observed increasing CRP values in all groups, with the peak value occurring 72 h postoperatively. CRP values tend to be higher following systemic analgesia, but unexpectedly, a statistical difference was not observed compared with CRP values following regional analgesia [26].

A complex interaction between stress hormones and the immune system affects the secretion of glucocorticoids and catecholamines in the systemic circulation [10]. The decreased plasma cortisol and urinary norepinephrine levels observed in the present study suggest that epidural analgesia and peripheral nerve block suppress the surgical stress response in the early perioperative period. A possible explanation for the inhibition of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system after epidural analgesia could be the induced blockade of sympathetic pathways at the spinal level [11]. In peripheral nerve blockade, the findings could be explained by the sustained blockade of C-fibers of afferent and efferent nerves by the local anesthetics, resulting in blockade of sensitization, transmission and modulation of nociceptive impulses, thereby reducing neuroinflammation and attenuating the early inflammatory and stress responses during the first 24 hours [27, 28]. In addition, we cannot exclude the possibility that local anesthetics themselves may modulate the inflammatory response locally and systemically [26]. Since norepinephrine in plasma originates from the presynaptic sympathetic nerves and epinephrine from the adrenal medulla, the decreased levels of norepinephrine, but not epinephrine, observed 24 hours after surgery in the regional anesthesia groups can be explained by the inhibitory effect of local anesthetics on the sympathetic nervous system [28].

Complications such as delayed wound healing or infection did not occur in any of our patients. A limitation of the study is the small number of patients recruited in each group analyzed, which limits our conclusions. Another limitation of this study may be that patient satisfaction was not compared in terms of quality of analgesia. Further studies should clarify whether the results of this study can be translated into improved outcomes after TKR.

## 5. Conclusions

In conclusion, the present study demonstrates that maintaining an appropriate balance between the neuroendocrine and immune systems by treating postoperative pain with epidural analgesia or blockade of the sciatic and femoral nerves in patients after TKR can modulate surgical inflammatory and stress responses and thus improve patients' prognosis better than systemic analgesia. The proinflammatory cytokines IL-1$\beta$ and IL-6 as well as plasma cortisol and urinary norepinephrine are the most sensitive biomarkers to support our statement.

### ABBREVIATIONS

IL, interleukin; TKR, total knee replacement; TNF-$\alpha$, tumor necrosis factor-alpha; VAS, visual analogue scale.

### AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

### AUTHOR CONTRIBUTIONS

SVB, VS and MA—designed the research, wrote the manuscript and performed the research. KB, DL and NG—provided help and advice on the study protocol. DPK—analyzed the data. TB and LB—helped with the manuscript preparation. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the local ethics committee of the Clinic for Orthopedics and Traumatology Lovran, (IRB: 317/2015), Croatia, in accordance with the Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (2013) and registered in the ISRCTN registry under the number ID ISRCTN17389296.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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