

## ORIGINAL RESEARCH

## ORTHOPEDIC ANESTHESIA

# Comparison of the effects of epidural analgesia and local infiltrative analgesia methods on pain control and stress response in patients undergoing total knee arthroplasty

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## ABSTRACT

**Background:** We compared the effects of epidural analgesia (EA) and local infiltrative analgesia (LIA) on pain control and stress response in the postoperative period in patients who underwent total knee arthroplasty.

**Methodology:** The patients were divided into two groups as those who were administered EA (Group EA; n = 25) and those who were administered LIA (Group LIA; n = 26). Pain at rest and during movement at the incision site was evaluated in both groups with NRS. In order to evaluate the stress response; cortisol, insulin, ACTH and glucose levels in serum were measured.

**Results:** All 51 patients included in the study were female, with a mean age of  $63.4 \pm 7.16$  y and a body mass index of  $32.4 \pm 4.77$  kg/m<sup>2</sup>. There was no difference between the two groups in terms of NRS values, whether at rest or in moving. There was no statistically significant difference between the two groups in terms of serum cortisol, insulin, ACTH, and glucose levels.

**Conclusion:** It was determined that both EA and LIA are similar effect in pain control at rest and movement, and both methods are effective in controlling the postoperative stress response in patients undergoing total knee arthroplasty.

**Abbreviations:** ACTH-Adrenocorticotrophic hormone; EA-epidural analgesia; LIA-local infiltrative analgesia; NRS-numeric rating scale; TKA-Total knee arthroplasty

**Key words:** arthroplasty, epidural analgesia, local anesthesia, pain, stress response

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## 1. INTRODUCTION

One of the most common orthopedic surgeries that results in severe postoperative pain is total knee arthroplasty (TKA). It has been noted that 60% of TKA patients experience severe pain after surgery, while 30% experience moderate discomfort.<sup>1,2</sup> During the early stages of recovery, it is critical to manage postoperative

pain adequately.<sup>3</sup> A variety of treatment modalities are being employed, including intrathecal morphine administration, epidural block, femoral nerve block, interfascial plane block, intra-articular and periarticular medication infiltration.<sup>4</sup> The main disadvantage of the aforementioned analgesia techniques is that they either provide analgesia but with a motor block, or fail to

provide adequate analgesia despite the absence of a motor block. Therefore, a combination of analgesic techniques called multimodal analgesia has become more common now-a-days. Non-opioid analgesia techniques are especially important in aging populations when comorbidities are considered.<sup>5</sup>

Local infiltration analgesia (LIA) method is included in multimodal analgesia in the treatment of postoperative pain and was defined by Kerr and Kohan in 2008.<sup>6</sup> In the recent years, there has been an increasing interest in the use of LI, containing various components, as a modality in postoperative pain control. The advantage of LIA is that it provides pain control without interfering with lower extremity motor power, thus allowing early ambulation of the patients. The infiltrative mixture is administered via a catheter to the superficial and deep soft tissues around the wound site during surgery and after surgery, typically for 48 h.<sup>6,7</sup>

LIA is applied in many types of surgery via continuous infusion, intermittent bolus, or patient-controlled analgesia, which is administered as an infusion to the wound site.<sup>5</sup> Although it is well known that epidural analgesia (EA) is more effective in the treatment of pain than other methods, some researchers argue that the benefit of EA should be balanced against its side effects, which include nausea, pruritus, hypotension, urinary retention, poor muscle control, delayed mobilization, and anticoagulant-induced spinal hematoma.<sup>8</sup>

By stimulating the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis with nerve terminals in the tissue damage area, surgical trauma triggers a stress reaction. As a result, catabolic hormones like catecholamines and pituitary hormones are secreted more than anabolic hormones like insulin and testosterone.<sup>9,10</sup> The resultant stress reaction is known to last throughout the postoperative period. In the postoperative period, the unregulated stress reaction

induces hemodynamic and metabolic immunological problems.<sup>11,12</sup> EA is known for its place in the treatment of pain after TKA and its suppressive effect on the stress response.

We aimed to compare the effects of EA and LIA on postoperative pain at rest and on movement of the patients with the Numeric Rating Scale (NRS) and the analgesic requirement (tramadol consumption). Secondary aim was to evaluate the post-operative stress response in patients and the presence of postoperative side effects

## 2. METHODOLOGY

### 2.2. Study design

This prospective randomized study was conducted at Samsun Education and Research Hospital, Samsun,

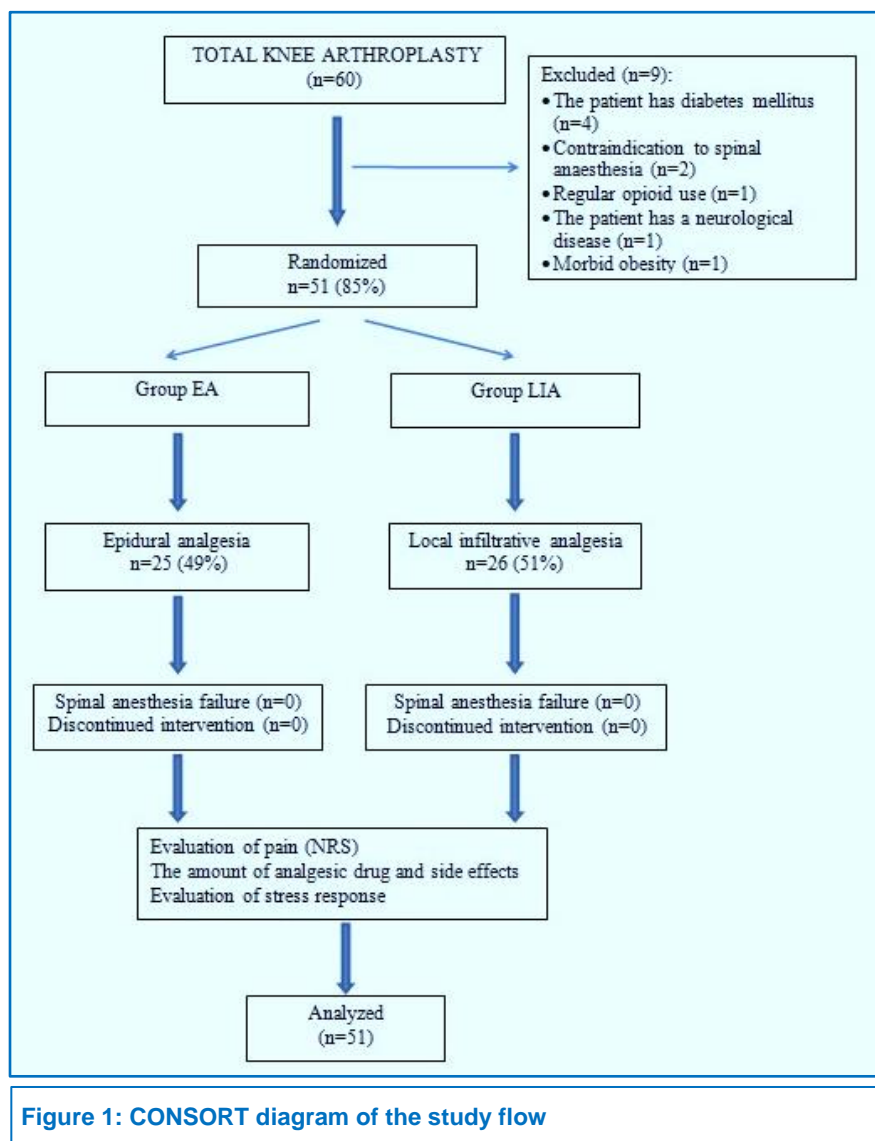


Figure 1: CONSORT diagram of the study flow

Turkey, after approval by the University Clinical Research Ethics Committee (No. KAEK 16/34) the study and it was registered in the Clinicaltrials.gov (No. NCT05344079). The study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients who were included in this study. CONSORT diagram of the study is shown in Figure 1.

## 2.2. Study population

Patients undergoing TKA under spinal anesthesia (SA), aged between 18–80 y with the ASA physical status I–III were included in our study. It is a known fact that the gender differences do exist in males and females regarding the stress response and pain perception.<sup>13</sup> Therefore, only female patients undergoing unilateral TKA were included in the study. All surgeries were performed before 11 am to ensure that the measurements of endocrine parameters matched the diurnal rhythm.

Exclusion criteria were as follows; patients who will undergo an extra surgical procedure or who will undergo bilateral TKA, those with local anesthetic sensitivity, morbidly obese, those with additional pathology that may constitute a contraindication to the application of regional anesthesia, those who did not give voluntary consent, had a history of anticoagulant use, had a history of cerebrovascular disease, those who received steroid therapy for any disease, who were diabetic and had a homeostasis assessment score (HOMA) above 2. For better standardization of data, surgical procedures lasting < 30 min or > 90 min were also excluded from the study.

## 2.3. Setting

A total of 51 ASA I-III patients scheduled for TKA were randomly divided into two groups; Group EA to receive EA (n = 25) and Group LIA administered LIA (n = 26). Since EA is the gold standard technique in patients undergoing knee surgery, the control group was not included in the study and the study was designed as two groups. Patients were assigned a random identification number before surgery and all data was collected using this identification number. Group assignments were determined using simple randomization using the sealed envelope technique. The anesthesiologist performing the simple randomization also performed the anesthesia but did not play role in the collection of postoperative data or its analysis.

The patients were transferred to the operating room, and routine ECG, non-invasive blood pressure, and peripheral oxygen saturation were monitored. Infusion of 10 mL/kg fluid was started to the patients. All patients received the same anesthesia and analgesia protocol. All patients were received antibiotic prophylaxis, according to the hospital protocol. The patients were kept

normothermic throughout the operation by using a heating pad. Heart rate, systolic blood pressure, mean arterial blood pressure, and peripheral oxygen saturation were recorded at 10-min intervals. A similar surgical technique was performed by the same surgeon in both groups.

**2.3.1. Group EA:** The epidural space was identified using the loss of resistance method with an 18-G Touhy needle (Egemen Combifix™ Standard Spinal Epidural Combined Set; Braun®, Turkey) at the L4–L5 or L5–S1 space. After the free cerebrospinal fluid flow was observed by passing the spinal needle through the epidural needle, spinal anesthesia was maintained with 10–15 mg hyperbaric bupivacaine (Bustesin 0.5% Spinal Heavy; VEM Pharmaceuticals Industry and Trade Ltd., Turkey). The epidural catheter was fixed at 5 cm in the epidural space, the adapter was inserted and fixed. Whether the catheter is in place or not was checked by 2 mL/40 mg lidocaine (Aritmal, Osel Pharmaceuticals Industry and Trade Ltd., Turkey) and 1/2000000 adrenaline test dose. No medication was administered to the patients through the epidural catheter during the surgery. At the end of the surgery, when the Bromage score was 2 in the recovery room, 0.9% NaCl 60 mL + 0.5% bupivacaine 60 mL (Bustesin 0.5%, VEM Pharmaceuticals Industry and Trade Ltd., Turkey) was inserted into the epidural catheter to provide continuous infusion at a rate of 5 mL/hour, and the participants were followed in the postanesthetic care unit for 24 h.

**2.3.2. Group LIA:** In this group, SA was maintained with 10–15 mg of hyperbaric bupivacaine after free cerebrospinal fluid flow was observed by entering the subarachnoid space with a 22 G spinal needle (Egemen Quincke Sharpened Spinal Anesthesia Needle, Turkey) at the L4–L5 or L5–S1 vertebral space. At the end of the operation a 20-G infiltrative analgesia catheter (ON-Q® catheter; I-Flow; Lake Forest, CA) was placed by the surgeon longitudinally just above the knee capsule. Then, the catheter was connected to an elastomeric pump (ON-Q® Pain Buster, Kimberly-Clark Health Care Company) that provides 5 mL/h infusion prepared with 60 mL of saline + 60 mL of 0.5% bupivacaine. The local anesthetic prepared to be administered through the catheter, was started when the patient was taken to the recovery room after the surgical procedure and the Bromage score fell below 2.

## 2.4. Standard analgesia protocol

The standard analgesia protocol was inj. paracetamol 4x1 gr iv. (Parol 10 mg/ml flk.; Atabay Kimya San ve Tic. A.Ş., Turkey), and inj. tenoxicam 2x20 mg iv. (Oksamen–L 20 mg flk.; Mustafa Nevzat Pharmaceuticals Industry and Trade Ltd., Turkey)

administered following the completion of the surgery, as a routine pain management regimen. If the NRS value was 4 and above, tramadol hydrochloride 50 mg iv. (Contromal; Abdi İbrahim Pharmaceuticals Industry and Trade Ltd., Turkey) was administered. In case of severe nausea and vomiting, ondansetron 8 mg iv. (Zofran 8 mg amp; GlaxoSmithKline, England) was administered to the patients.

## 2.5. Follow-up assessments

Motor blockade was assessed based on a Bromage scale<sup>14</sup> (as 0: no paralysis, the patient can move his foot and knee fully; 1: the patient only moves his knee and foot, cannot raise his leg straight; 2: the patient cannot move the knee, only the ankle; 3: unable to move any part of the lower limbs). When the Bromage scale fell below 2 in the postoperative recovery room, local anesthetic infusion was started in both groups. At the end of the postoperative 24th hour, the epidural catheter and infiltrative analgesia catheters were removed.

Intensity of knee pain was measured with the Numeric Rating Scale (NRS) both at rest and movement (passive flexion of the knee joint at the surgery site) at 4, 6, 12, and 24 h after surgery.

## 2.6. Outcome measures

The primary outcome of the study was to determine the pain with the NRS at 4, 6, 12 and 24 h postoperatively; the analgesic requirement (tramadol consumption) and presence of postoperative side effects. Side effects were evaluated as nausea (0 = absent, 1 = mild, 2 = severe), and vomiting (0 = absent, 1 = mild, 2 = severe). Secondary outcome was the evaluation of the postoperative stress response, by analyzing cortisol, insulin, ACTH and glucose levels in the serum, just before surgery, in the preoperative period, at 1, 4 and 24 h.

In addition, hospital length of stay (LOS) was recorded. Patients were discharged when they met the discharge

criteria; NRS < 3, and NRS with movement < 4, being able to provide personal hygiene, climbing stairs, not having a problem with wound healing, no complications related to clinical and radiological recovery, no deep vein thrombosis development, to ensure adequate hemoglobin level and to flex the knee joint at least 90 degrees.

## 2.7. Statistical Analysis

Using data obtained from previous similar studies and with an alpha of 0.05 and power of 90%, sample size was calculated as a minimum of 25 participants per group. Considering possible drop-outs, we decided to include at least 30 patients per group. The Shapiro-Wilks test was used to determine the adequacy of the parameters for normal distribution when analyzing the study data. Student t-test was used for the two-group comparisons of the normally distributed quantitative parameters, and the Mann Whitney-U test was used for the two-group comparisons of the quantitative parameters without normal distribution. Within-group comparisons of normally distributed parameters were made using analysis of variance with repetitive measurements, and the Bonferroni test was used to find the period that caused the difference. The Friedman test was used for the comparison of repeated observations that were not normally distributed, and the all pairwise test was used for pairwise comparisons. IBM SPSS Statistics 23 program (Chicago, IL, USA) was used for statistical analysis while evaluating the findings obtained in the study. P < 0.05 was considered statistically significant.

## 3. RESULTS

All 51 patients included in the study were women, and all had been operated on for osteoarthritis of the knee joint. The demographic characteristics of patients are given in Table 1. There was statistically no difference

**Table 1: Demographic characteristics of patients**

Variable	Group EA (n = 25)	Group LIA (n = 26)	P
Age (y)	63.52 ± 7.53 (50-78)	63.31 ± 6.94 (53-75)	0.917
Body Mass Index (Kg/m <sup>2</sup> )	31.63 ± 5.68 (22-46)	33.06 ± 3.68 (27-40)	0.290
Operation time (min)	59.80 ± 8.23 (45-70)	56.73 ± 7.99 (45-70)	0.196
Length of stay (days)	3.72 ± 0.45 (3-5)	3.63 ± 0.52 (3-5)	0.386
<b>ASA</b>			
▪ I	2 (8.0)	6 (23.1)	0.137
▪ II	21 (84.0)	15 (57.7)	
▪ III	2 (8.0)	5 (19.2)	

*Data presented as mean ± SD (Range) and n (%)*

**Table 2: Comparative heart rate values (beat/min)**

Time from the baseline (min)	Group EA	Group LIA	P <sup>1</sup>
5	76.4 ± 9.87	73 ± 10.18	0.124
10	75.9 ± 11.69	72.3 ± 10.31	0.247
15	72.4 ± 12.68	71.5 ± 10.54	0.765
20	71.7 ± 12.11	70.6 ± 10.95	0.734
25	71.8 ± 10.33	70.9 ± 9.99	0.748
30	71.7 ± 10.78	71.7 ± 9.65	0.997
35	71.2 ± 9.98	71.3 ± 9.84	0.989
40	70.9 ± 9.94	70.1 ± 9.08	0.753
45	71.8 ± 9.47	70.9 ± 8.5	0.706
50	72.3 ± 8.2	71.2 ± 8.43	0.643
55	72.7 ± 8.2	71.04 ± 8.34	0.482
60	72.3 ± 7.74	71.5 ± 8.16	0.728
<b>P<sup>2</sup></b>	0.065	0.083	

<sup>1</sup>Mann Whitney U test; <sup>2</sup>Friedman analysis of variance; Data presented as Mean ± standard deviation

**Table 3: Comparison of the groups in terms of mean arterial pressure values**

Time from the baseline (min)	Group EA	Group LIA	P <sup>1</sup>
5	93.9 ± 9.84	94.6 ± 8.12	0.845
10	91.4 ± 10.72	91.7 ± 9.11	0.906
15	91.6 ± 6.86	91.5 ± 7.33	0.975
20	91.4 ± 7.92	91.7 ± 7.22	0.891
25	90.1 ± 7.95	91.4 ± 6.72	0.530
30	90.3 ± 7.93	91.6 ± 6.64	0.529
35	91.9 ± 5.79	91.8 ± 6.07	0.984
40	90.4 ± 6.78	93 ± 5.81	0.141
45	91.9 ± 7.2	92.8 ± 6.46	0.660
50	92.3 ± 7.67	93.4 ± 6.13	0.586
55	91.3 ± 6.86	93.9 ± 6.33	0.165
60	91.9 ± 7.05	93.3 ± 6.61	0.472
<b>P<sup>2</sup></b>	0.431	0.073	

<sup>1</sup>Mann Whitney U test; <sup>2</sup>Friedman analysis of variance; Data presented as Mean ± standard deviation

between the groups regarding mean age and BMI and ASA status of the patients.

The mean operation time was equivalent with no difference between the groups (P = 0.196). There was no difference between the groups regarding the mean length of stay.

No statistically significant difference was found in the study between the groups in terms of heart rate (HR) values. In both groups, there was no statistically significant difference in terms of HR levels between the times within the group. (Table 2).

There was no significant difference between the groups in terms of mean arterial blood pressure values. Likewise, there was no statistically significant difference between within-group times (Table 3).

Postoperative pain assessment was performed with NRS, and there was no difference between the two groups in terms of NRS values at various time points, whether at rest or in moving (Table 4).

The use of tramadol as an additional analgesic in the postoperative period was lower in Group EA compared to Group LIA; 66 ± 45 mg vs. 76 ± 40.5 mg and the difference was statistically not significant (P = 0.345).

Regarding drug-related side effects, it was observed that there was a statistically significant difference. While mild nausea was observed in 16 (64%) patients and severe nausea was observed in 2 (8%) patients in group EA, mild nausea was observed in only 10 patients (38.5%) in group LIA (P = 0.022). Vomiting was observed in 6 (24%) patients in Group EA, but not in Group LIA (P = 0.01) (Table 5).

When serum cortisol levels were analysed, there was no statistical difference between the two groups, despite the fact that postoperative values were higher in group LIA. When the in-group times were compared in both groups, there was a statistically significant difference between serum cortisol levels (P < 0.001). As a result of the pairwise comparisons made to determine from which period the significance originated; measured at all other times serum cortisol level was observed to be higher than the level measured in the preoperative period (Figure 2A).

Despite the fact that serum ACTH and glucose levels were lower in group LIA than in group EA, there was no statistically significant difference between the two groups. There was no statistical difference between the



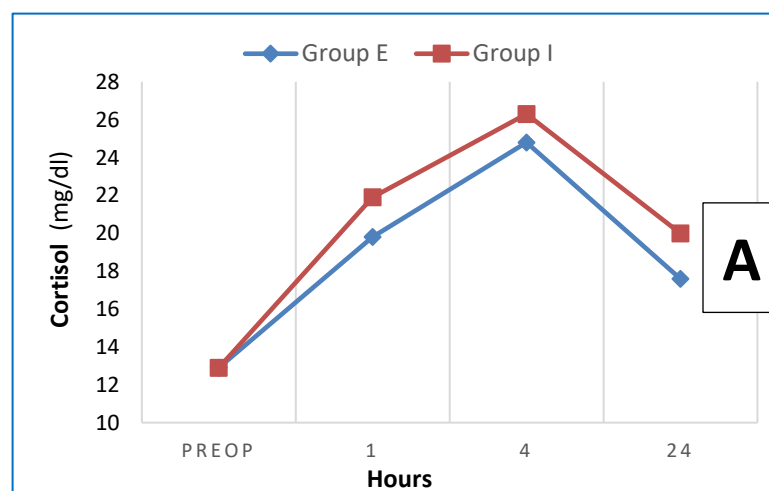
**Table 4: Comparison of the groups in terms of resting and moving NRS values.**

Postoperative Time (hour)	Group EA [median (Q1-Q3)]	Group LIA [median (Q1-Q3)]	P-value
<b>At Rest</b>			
4	3 (3-4)	4 (2-5)	0.781
6	3 (3-4)	4 (3-4)	0.992
12	2 (2-3)	3 (2-4)	0.204
24	2 (1-2)	2 (1-2)	0.635
<b>At Movement</b>			
4	4 (4-7)	5 (4-8)	0.280
6	4 (4-6)	6 (5-7)	0.126
12	4 (3-5)	5 (4-6)	0.182
24	2 (2-3)	2 (2-5)	0.684

*Q1: percentile 25, Q3: percentile 75; P value was obtained from Mann Whitney U test*

**Table 5: Comparison of groups in terms of tramadol-related side effects [n(%)]**

Side Effect	Group EA (n=25)	Group LIA (n=26)	p
Nausea	Mild	16 (64.0)	0.022
	Severe	2 (8.0)	
	None	7 (28.0)	
Vomiting	Mild	6 (24.0)	0.010
	None	19 (76.0)	



**Figure 2: Comparison of the groups in terms of A; Serum cortisol, B; Serum insulin, C; Serum ACTH, and D; Serum glucose values**

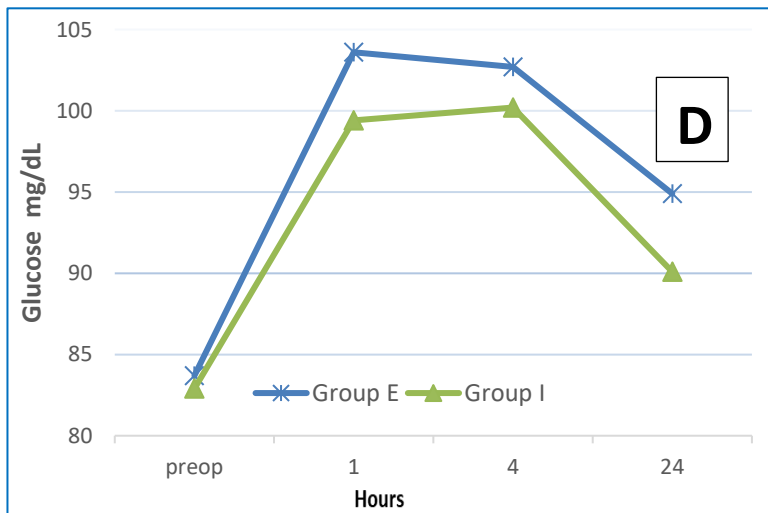
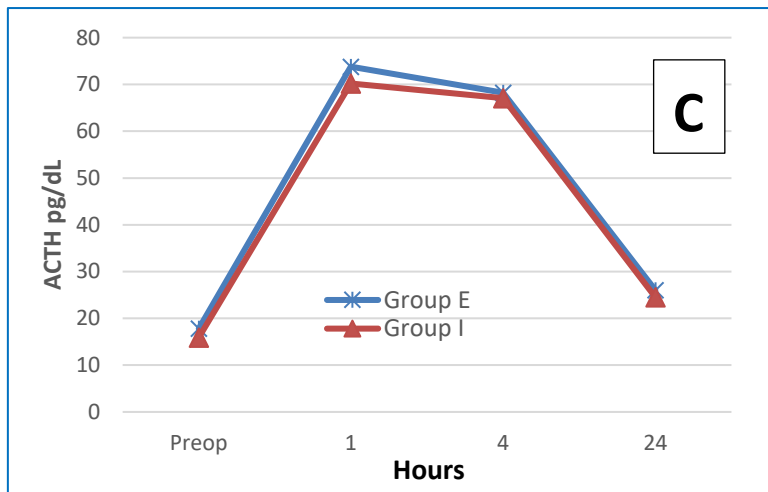
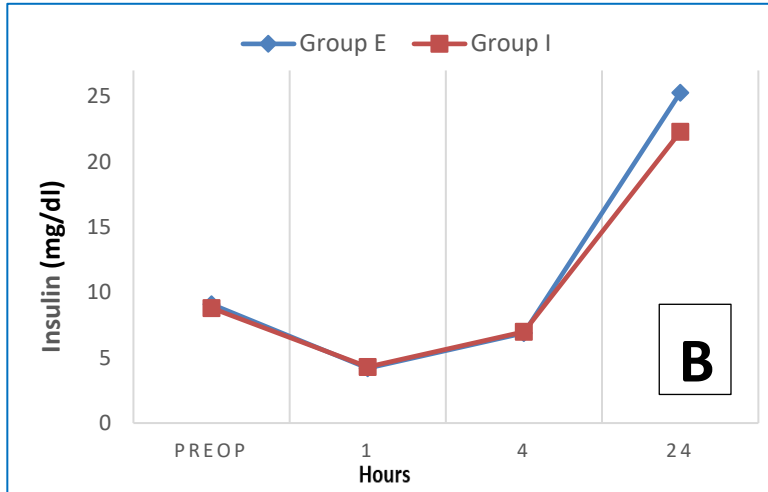
groups in terms of serum insulin values. Serum insulin, ACTH, and glucose levels were compared in patients in both groups and statistically significant difference was found between the levels ( $P < 0.001$ ). As a result of the pairwise comparisons made to determine from which period this difference originated; preoperatively measured values were observed to be significantly lower than the level measured at the 24th hour (Figure 2 B, C, D).

## 4. DISCUSSION

During this study, an infusion of 0.25% bupivacaine was administered @5 ml/h to both of the groups, and no adjuvant drug was added to the solution given to the patients in the LIA group. In the post-operative period, the same standard pain treatment was applied to the patients in both groups.

There are very different applications for LIA with different drug combinations, volumes and different adjuvant additions.<sup>4,5,7</sup> Having a methodology similar to our study, Fusco et al. reported that they achieved successful pain control in patients who underwent total hip surgery and applied continuous wound infiltration of levobupivacaine through a multi-lumen catheter for postoperative pain.<sup>15</sup> They discovered that the patient satisfaction was higher and that they performed better during rehabilitation. In patients undergoing total hip surgery, the authors suggested using continuous wound infusion for the first 72 h to help with analgesia. They concluded that the study group given local anesthetic was successful in the treatment of pain. In our study, a control group was not formed and the Group EA was accepted as the control group, because epidural analgesia is considered the gold standard method in this type of surgery.

Tsukada et al. compared postoperative epidural analgesia with intraoperative periarticular injection in patients undergoing knee arthroplasty under spinal anesthesia.<sup>16</sup> They observed that the patients who received periarticular injection had less pain at rest after the postoperative 72 h compared to the epidural patients, and VAS scores were similar with



**Figure 2: Comparison of the groups in terms of A; Serum cortisol, B; Serum insulin, C; Serum ACTH, and D; Serum glucose values**

movement. As a result, they reported that for treating postoperative pain in patients undergoing TKA periarticular injection can be preferred to epidural analgesia. Although this study provides useful information for clinicians in the choice of postoperative analgesic therapy, we think that an objective comparison cannot be made due to the different protocols of pain medication administered in both the epidural analgesia group and the periarticular injection group.

When we look at the recent literature, we come across many meta-analyses about LIA.<sup>4,17-19</sup> In one of them, Li et al. compared LIA with EA and found that LIA had an equivalent efficacy in relieving pain in the early and late period compared to EA in patients who underwent TKA.<sup>17</sup> The authors also stated that LIA is superior to EA in terms of the risk of nausea and vomiting, and that the hospital stay is shorter than in patients who receive epidural analgesia. Yan et al. evaluated nine randomized controlled studies in which they compared the efficacy and safety of LIA and EA and they found that LIA provided better early and late pain control than epidural analgesia in patients who underwent TKA.<sup>18</sup> In addition, they reported that LIA was not superior to EA in terms of pain relief after hip surgery, while LIA was superior to EA in the late postoperative period in patients who underwent TKA. Again, in a meta-analysis, Liu et al. reported that the VAS scores of the patients who underwent TKA were lower at the 48th and 72nd h postoperatively at rest and at 48 h during movement in the LIA group, and that the VAS scores of both groups were similar at 24 h.<sup>19</sup>

Paladini et al. have investigated the safety and effect of continuous wound infiltration in the treatment of postoperative pain, in different surgical fields and as a result of their meta-analysis, in which they scanned 95 articles, 17 of which were in lower extremity operations, it was seen that continuous wound infiltration was successful in different surgical fields.<sup>20</sup> In conclusion, it was emphasized that continuous wound infiltration is a simple

method and has the minimum risk of complications that can be applied in various types of surgery, and it has been reported that it can be included in multimodal treatment.

Considering the results of our study; there was no statistical difference between the LIA and EA groups in terms of NRS values at rest and on movement; and the need for additional doses of analgesics required in the postoperative period. The rate of nausea and vomiting was significantly higher in the EA group. No complications such as urinary retention or abdominal distension were observed in the patients.

It has been shown in many studies that the stress response is better suppressed with epidural analgesia.<sup>17,21</sup> Studies examining the effects of LIA technique on stress response are especially in abdominal surgery cases, and we see that studies on lower extremity surgery are very limited. Barr et al., in their study in which they performed laparoscopic colorectal surgery, examined serum insulin, cortisol, interleukin 6, and epinephrine levels in the preoperative 3rd, 6th, 12th, 24th hours, and postoperative period.<sup>22</sup> They found lower epinephrine and higher insulin levels at the postoperative 3rd and 6th hours in the EA group. They argued that this situation is due to the fact that the sympathetic block caused by epidural analgesia reduces the stress response and thus, a decrease in plasma catecholamine levels.

Cinar et al. used LIA as an analgesic in their study, found that postoperative cortisol and prolactin levels were significantly increased compared to preoperative levels.<sup>23</sup> They reported that this increase was less in patients who underwent LIA than in patients who did not, and that postoperative pain was also less. The authors believed that the main reason for the increase in postoperative stress hormone levels could not be pain alone, however, the application of levobupivacaine to the wound site before and after the incision was effective in reducing postoperative pain and analgesic consumption.

The amount of both preoperative and postoperative concentrations of cortisol, one of the major mediators of the stress response, depends on the degree of surgical trauma.<sup>24</sup> In our study, there was a significant increase in serum cortisol values at 1st and 4th hours compared to the preoperative period in both groups, but there was no difference between the groups. It was observed that serum cortisol values approached their normal values at 24th postoperative hour. Again, in both groups, we observed that the serum ACTH levels increased at 1st postoperative hour, remained high at 4th hour, and decreased compared to these two values at 24th hour postoperatively, but were higher than the preoperative values. Considering the increase in serum cortisol and ACTH levels in our study, the fact that the increase did not exceed twice the preoperative value shows that EA

and LIA are successful in suppressing the stress response due to surgery.<sup>25</sup>

Through glycogenolysis and gluconeogenesis, increased catecholamine levels in the postoperative phase promote an increase in blood glucose levels. The release of insulin in the blood increases as blood glucose levels rise, however this mechanism may not function properly during trauma, resulting in insulin deficiency. Studies have shown that insulin sensitivity due to surgical trauma can decrease up to 50%.<sup>9</sup> In our study, it was observed that the increase in intraoperative insulin level was prevented in both groups, but it was found that insulin resistance may occur after 24 h. When the serum glucose values were examined, although there was a slight increase in the values, there were no increases that required intervention, and no significant difference was observed between the groups. The effects of both analgesic techniques used in our study on blood glucose values were found to be similar.

## 5. LIMITATIONS

First; in our study power analysis results were calculated based on NRS values. Complications, nausea, vomiting, etc. values should also be taken into account when calculating the power analysis. Secondly, the patients were not evaluated in terms of motor block and muscle weakness. NRS values were evaluated at rest and with passive movement. This is because; in our hospital, active movement of the joint is not requested by the surgical team in the first 24 h and mobilization of the patient is not allowed in the first 24 h. Third; NRS values in the postoperative period were not evaluated by the primary anesthesiologist involved in the study. Since the catheters have different locations, they are seen by the person being evaluated, which prevents the evaluator from being blinded.

## 6. CONCLUSION

It was determined that local infiltrative analgesia and epidural analgesia used in knee arthroplasty operations, have similar effect in pain control at rest and movement, and both methods are effective in controlling the postoperative stress response in patients undergoing total knee arthroplasty.

## 7. Data availability

The numerical data generated in this study is available with the authors, and can be seen on a reasonable request.

## 8. Acknowledgements

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## 9. Conflict of interest

The authors have no potential conflict of interest to disclose.

## 10. Funding

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## 11. Authors' contribution

Both authors took equal part in concept, conduction of the study work and manuscript editing. Both authors have approved the final draft for publishing

## 12. REFERENCES

- Berninger MT, Friederichs J, Leidinger W, Augat P, Bühren V, Fulghum C, et al. Effect of local infiltration analgesia, peripheral nerve blocks, general and spinal anesthesia on early functional recovery and pain control in total knee arthroplasty. *BMC Musculoskelet Disord.* 2018;19(1):232. [PubMed] DOI: [10.1186/s12891-018-2154-z](https://doi.org/10.1186/s12891-018-2154-z)
- Seo SS, Kim OG, Seo JH, Kim DH, Kim YG, Park BY. Comparison of the effect of continuous femoral nerve block and adductor canal block after primary total knee arthroplasty. *Clin Orthop Surg.* 2017;9(3):303-9. [PubMed] DOI: [10.4055/cios.2017.9.3.303](https://doi.org/10.4055/cios.2017.9.3.303)
- Tulgar S, Selvi O, Senturk O, Serifsoy TE, Sanel S, Meydaneri S. Evaluation of analgesic regimens in total knee arthroplasty, retrospective study. *North Clin Istanbul.* 2017;4(2):124-30. [PubMed] DOI: [10.14744/nci.2017.88598](https://doi.org/10.14744/nci.2017.88598)
- Peng XQ, Fei ZG, Sun CG, Zhou QJ. Efficacy and safety of local infiltration analgesia for pain management in total knee and hip arthroplasty: A meta-analysis of randomized controlled trial. *Medicine (Baltimore).* 2020;99(22):e20640. [PubMed] DOI: [10.1097/MD.00000000000020640](https://doi.org/10.1097/MD.00000000000020640)
- Surange PN, Venkata Rama Mohan BC. Comparative evaluation of continuous lumbar paravertebral versus continuous epidural block for post-operative pain relief in hip surgeries. *Anesth Pain Med.* 2012;1(3):178-83. [PubMed] DOI: [10.5812/kowsar.22287523.3348](https://doi.org/10.5812/kowsar.22287523.3348)
- Kerr DR, Kohan L. Local infiltration analgesia: a technique for the control of acute postoperative pain following knee and hip surgery: a case study of 325 patients. *Acta Orthop.* 2008;79(2):174-83. [PubMed] DOI: [10.1080/17453670710014950](https://doi.org/10.1080/17453670710014950)
- Rewari V, Ramachandran R. Continuous wound infiltration of local anaesthetics for acute postoperative pain-A revisit. *Indian J Anaesth.* 2019;63(6):425-7. [PubMed] DOI: [10.4103/ija.IJA\\_425\\_19](https://doi.org/10.4103/ija.IJA_425_19)
- Maheshwari AV, Blum YC, Shekhar L, Ranawat AS, Ranawat CS. Multimodal pain management after total hip and knee arthroplasty at the Ranawat Orthopaedic Center. *Clin Orthop Relat Res.* 2009;467(6):1418-23. [PubMed] DOI: [10.1007/s11999-009-0728-7](https://doi.org/10.1007/s11999-009-0728-7)
- Gibbison B, Angelini GD, Lightman SL. Dynamic output and control of the hypothalamic-pituitary-adrenal axis in critical illness and major surgery. *Br J Anaesth.* 2013;111(3):347-60. [PubMed] DOI: [10.1093/bja/aet077](https://doi.org/10.1093/bja/aet077)
- Desborough JP. The stress response to trauma and surgery. *Br J Anaesth.* 2000;85(1):109-17. [PubMed] DOI: [10.1093/bja/85.1.109](https://doi.org/10.1093/bja/85.1.109)
- Burton D, Nicholson G, Hall G. Endocrine and metabolic response to surgery. *Cont Edu Anaesthe Crit Care Pain.* 2004;4(5):144-7. DOI: [10.1093/bjaceaccp/mkh040](https://doi.org/10.1093/bjaceaccp/mkh040)
- Şimşek T, Şimşek HU, Cantürk NZ. Response to trauma and metabolic changes: posttraumatic metabolism. *Ulus Cerrahi Derg.* 2014;30(3):153-9. [PubMed] DOI: [10.5152/UCD.2014.2653](https://doi.org/10.5152/UCD.2014.2653)
- Rosen S, Ham B, Mogil JS. Sex differences in neuroimmunity and pain. *J Neurosci Res.* 2017;95(1-2):500-8. [PubMed] DOI: [10.1002/jnr.23831](https://doi.org/10.1002/jnr.23831)
- Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. *Acta Anaesthesiol Scand.* 1965;16:55-69. [PubMed] DOI: [10.1111/j.1399-6576.1965.tb00523.x](https://doi.org/10.1111/j.1399-6576.1965.tb00523.x)
- Fusco P, Cofini V, Petrucci E, Scimia P, Fiorenzi M, Paladini G, et al. Continuous wound infusion and local infiltration analgesia for postoperative pain and rehabilitation after total hip arthroplasty. *Minerva Anestesiol.* 2018;84(5):556-64. [PubMed] DOI: [10.23736/S0375-9393.17.12110-3](https://doi.org/10.23736/S0375-9393.17.12110-3)
- Tsukada S, Wakui M, Hoshino A. Postoperative epidural analgesia compared with intraoperative periarticular injection for pain control following total knee arthroplasty under spinal anesthesia: a randomized controlled trial. *J Bone Joint Surg Am.* 2014;96(17):1433-8. [PubMed] DOI: [10.2106/JBJS.M.01098](https://doi.org/10.2106/JBJS.M.01098)
- Li C, Qu J, Pan S, Qu Y. Local infiltration anesthesia versus epidural analgesia for postoperative pain control in total knee arthroplasty: a systematic review and meta-analysis. *J Orthop Surg Res.* 2018;13(1):112. [PubMed] DOI: [10.1186/s13018-018-0770-9](https://doi.org/10.1186/s13018-018-0770-9)
- Yan H, Cang J, Xue Z, Lu J, Wang H. Comparison of local infiltration and epidural analgesia for postoperative pain control in total knee arthroplasty and total hip arthroplasty: A systematic review and meta-analysis. *Bosn J Basic Med Sci.* 2016;16(4):239-46. [PubMed] DOI: [10.17305/bjbm.2016.1072](https://doi.org/10.17305/bjbm.2016.1072)
- Liu X, Zhang H, Zhang H, Guo M, Gao Y, Du C. Local infiltration vs epidural analgesia for postoperative pain control after total knee or hip arthroplasty: A meta-analysis of randomized controlled trials. *Medicine (Baltimore).* 2020;99(44):e22674. [PubMed] DOI: [10.1097/MD.00000000000022674](https://doi.org/10.1097/MD.00000000000022674)
- Paladini G, Di Carlo S, Musella G, Petrucci E, Scimia P, Ambrosoli A, et al. Continuous wound infiltration of local anesthetics in postoperative pain management: safety, efficacy and current perspectives. *J Pain Res.* 2020;13:285-94. [PubMed] DOI: [10.2147/JPR.S211234](https://doi.org/10.2147/JPR.S211234)
- Adams HA, Saatweber P, Schmitz CS, Hecker H. Postoperative pain management in orthopaedic patients: no differences in pain score, but improved stress control by epidural anaesthesia. *Eur J Anaesthesiol.* 2002;19(9):658-65. [PubMed] DOI: [10.1017/s0265021502001084](https://doi.org/10.1017/s0265021502001084)

22. Barr J, Boulind C, Foster JD, Ewings P, Reid J, Jenkins JT, et al. Impact of analgesic modality on stress response following laparoscopic colorectal surgery: a post-hoc analysis of a randomised controlled trial. *Tech Coloproctol.* 2015;19(4):231-9. [PubMed] DOI: [10.1007/s10151-015-1270-0](https://doi.org/10.1007/s10151-015-1270-0)
23. Cnar SO, Kum U, Cevizci N, Kayaoglu S, Oba S. Effects of levobupivacaine infiltration on postoperative analgesia and stress response in children following inguinal hernia repair. *Eur J Anaesthesiol.* 2009;26(5):430-4. [PubMed] DOI: [10.1097/EJA.0b013e32832974fc](https://doi.org/10.1097/EJA.0b013e32832974fc)
24. Sato H, Carvalho G, Sato T, Lattermann R, Matsukawa T, Schrickler T. The association of preoperative glycemic control, intraoperative insulin sensitivity, and outcomes after cardiac surgery. *J Clin Endocrinol Metab.* 2010;95(9):4338-44. [PubMed] DOI: [10.1210/jc.2010-0135](https://doi.org/10.1210/jc.2010-0135)
25. Özgünay Ş, Kazak Z, Erdi H, Demiralp S, Ökten F. The patient-controlled analgesia technique in abdominothoracic esophagectomy procedures and its effects on the surgical stress response. *Türkiye Klinikleri J Anest Reanim.* 2006;4(2):58-67. [FreeFullText]