

Original Article

Multimodal analgesia protocol for pain management after total knee arthroplasty: comparison of three different regional analgesic techniques

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Abstract

Objectives: To evaluate three different analgesic techniques, continuous epidural analgesia (EA), continuous intra-articular (IA) infusion analgesia and continuous femoral nerve block (FNB) in postoperative pain management, length of hospital stay (LOS), and time of patient mobilization after total knee arthroplasty (TKA). **Methods:** Seventy-two patients undergoing TKA were randomly allocated into three groups according to the analgesic technique used for postoperative pain management. Group EA patients received epidural analgesia (control group), group IA received intra-articular infusion and group FNB received femoral nerve block. **Results:** Upon analyzing the Numerical Rating Scale (NRS) scores at rest, at passive and active movement, up to 3 days postoperatively, we observed no statistically significant differences at any time point among the three groups. Similarly, no association among these analgesic techniques (EA, IA, FNB) was revealed regarding LOS. However, significant differences emerged concerning the time of mobilization. Patients who received IA achieved earlier mobilization compared to FNB and EA. **Conclusions:** Both IA and FNB generate similar analgesic effect with EA for postoperative pain management after TKA. However, IA appears to be significantly more effective in early mobilization compared to EA and FNB. Finally, no clinically important differences could be detected regarding LOS among the techniques studied.

Keywords: Epidural, Femoral Nerve Block, Intra-Articular Infusion, Postoperative Analgesia, Total Knee Arthroplasty

Introduction

Acute pain management after surgery is a major concern for both TKA candidates and clinicians, since it is closely associated with patient satisfaction, postoperative recovery and overall outcomes. Among the patients that undergo TKA, approximately 60% are reported to experience severe postoperative pain and 30% moderate pain¹. However, achieving optimal pain relief after TKA has proven to be

a great challenge for the anesthesiologists, and an area of intense research and debate, where several strategies have been proposed over the past decades. At present, multimodal analgesia is the recommended modality not only for the management of acute postoperative pain after TKA but also for the prevention of acute postoperative pain's progression to chronic postsurgical².

Several studies suggest that epidural analgesia (EA) remains the mainstay technique compared to parenteral opioids for postoperative pain control after TKA, resulting in better patient satisfaction and analgesia in the early postoperative period³⁻⁵. Regarding postoperative nausea-vomiting (PONV) and sedation in association to EA, a meta-analysis³ reported lower incidence of both PONV and sedation, but higher rates of pruritus, urinary retention and motor block. Especially for the elderly population Koh et al.⁶ revealed higher incidence of PONV and hypotension. The quality of EA with local anesthetic is improved when opioids⁷, or other adjuncts (e.g. clonidine) are added as the

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combination of these agents provides superior pain relief than either alone, resulting in decreased opioid consumption, without demonstrating a significant increase of side effects⁸.

Femoral nerve block (FNB) is a regional analgesic technique where either one (femoral nerve) or three (femoral, lateral femoral cutaneous and obturator nerves) of the major nerves supplying the lower extremities are blocked, inhibiting pain perception⁹. This promising technique is considered as the gold standard for postoperative analgesia following TKA surgery, providing numerous benefits compared to neuraxial block (e.g. reduced opioid consumption), similar postoperative analgesic efficacy but with minimal adverse effects and less neuraxial complications¹⁰. As a disadvantage, FNB is associated with quadriceps muscle weakness, resulting in delayed ambulation and increased risk of falling postoperatively¹¹.

Local infiltration analgesia (LIA) is a relatively simple, surgeon-administered technique of peri- or intra-articular infiltration of local anesthetics by catheter around or into the joint, respectively, which may provide effective postoperative pain relief. This comparatively new loco-regional anesthesia method has been successfully used in pain management after TKA, as it seems to be equivalent to neuraxial analgesia techniques as well as peripheral nerve blocks¹². LIA is considered as an alternative analgesic regimen to epidural anesthesia with equivalent efficacy in postsurgical pain, increased range of motion, less nausea, reduced LOS and no significant differences in the incidence of wound infection¹³. Compared to FNB and EA, LIA is shown to be either as effective or in some cases superior in providing improved analgesia with less opioid consumption in the early postoperative period after TKA and without impairment of quadriceps muscle function, which is the main drawback of FNB^{14,15}. Therefore, the analgesic potential, functional benefit, and safety profile of LIA versus EA and FNB remains controversial.

Materials and methods

Study design

This is a randomized, controlled, prospective study, approved by the Scientific Board of the University Hospital of Patras. Patients scheduled for TKA at the Department of Orthopedic Surgery, University Hospital of Patras were recruited. Participants were fully informed about the study and the related analgesic techniques. All patients gave written informed consent for their data to be included in this study. All surgeries were performed by the same orthopedic-surgical team with the same surgical technique. This study adhered to the tenets of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All procedures performed in this study were in accordance with the ethical standards of the institutional Ethical Committee of University Hospital of Patras in Greece. Ethics approval was granted by the Institutional Ethical Committee (# 81/15.04.16). Clinical Trials Number (NCT04344990).

Study population and selection criteria

Seventy-two patients, treated for knee osteoarthritis with unilateral TKA between January 2016 and October 2019, were included in the study. Selection criteria were the following:

Inclusion criteria

- Patients ≥ 55 years old scheduled for unilateral TKA to treat knee osteoarthritis (OA)
- Written informed consent to participate in the trial

Exclusion criteria

- American Society of Anesthesiologists (ASA) physical status $>III$
- Contraindication to subarachnoid anesthesia
- Hypersensitivity/allergy to study drugs

Data collection

For all patients included in the study the following data were collected:

- Demographic (gender, age, BMI) and clinical characteristics (ASA classification, allergies, smoking status)
- Comorbidities: cardiovascular, respiratory, endocrine, and other concomitant diseases (gastrointestinal, urogenital, psychiatric, musculoskeletal, oral hygiene)
- Pain intensity assessment in terms of numeric rating scale scores (NRS)
- Timing of patient mobilization (standing, in-room or out-of-room mobilization)
- Duration of postoperative hospital stay
- Postoperative adverse events: respiratory (atelectasis, infections) and cardiovascular (hypotension, arrhythmias, thrombosis, pulmonary embolism) complications, surgery-related adverse events (fat embolism, wound impairment/infection), sleep disorders or any other self-reported or significant adverse events.

Participants enrolment

Depending on the analgesic technique used for the postoperative pain management patients, using the online software <http://www.randomization.com>, were randomly allocated into 3 study groups as follows:

Group EA (control group): Patients in group EA (n=24) received postoperatively continuous epidural analgesia (EA) with a constant infusion of 0.2% ropivacaine and 150 mcg clonidine at a total volume of 150 ml (1 mcg/ml), at a rate of 2 ml/h by catheter.

Group IA: Patients in group IA (n=24) received postoperatively continuous intra-articular (IA) infusion of 0.2% ropivacaine and 150 mcg clonidine at a total volume of 150 ml (1 mcg/ml), by catheter, as an analgesic method, at a rate of 2 ml/h as well. The catheter tip was placed in the joint intra-articularly, at the end of surgery under aseptic conditions.

Group FNB: Patients in group FNB (n=24) received postoperative analgesia continuously through a femoral

Table 1. Patients demographics and clinical data.

	Total sample (Mean \pm SD) n = 72	Group EA - Control group (Mean \pm SD) n = 24	Group IA (Mean \pm SD) n = 24	Group FNB (Mean \pm SD) n = 24	P value
Age (years)	72.29 \pm 6.51	73.88 \pm 6.39	71.54 \pm 7.05	71.46 \pm 6.02	0.349
BMI (kg.m ⁻²)	30.07 \pm 4.81	29.66 \pm 4.53	31.22 \pm 5.93	29.31 \pm 3.68	0.347
Gender (men/women)	16/56	8/16	5/19	3/21	0.257
ASA Classification (ASA-2/ASA-3)	26/46	10/14	7/17	9/15	0.748
Cardiovascular diseases	57 (79.2%)	20 (83.3%)	17 (70.8%)	20 (83.3%)	0.618
Pulmonary diseases	13 (18.1%)	7 (29.2%)	5 (20.8%)	1 (4.2%)	0.065
Endocrine diseases	28 (38.9%)	9 (12.5%)	11 (45.8%)	8 (33.3%)	0.755
Other concomitant diseases	52 (72.2%)	19 (79.2%)	16 (66.7%)	17 (70.8%)	0.717
Smoking	14 (19.4%)	6 (25%)	4 (16.7%)	4 (16.7%)	0.809
Allergies	4 (5.6%)	1 (4.2%)	3 (12.5%)	0 (0%)	0.314

BMI: Body Mass Index; ASA: American Society of Anesthesiologists Classification; SD: Standard Deviation; EA: epidural analgesia; IA: intra-articular analgesia; FNB: femoral nerve block; n: number.

nerve block (FNB) catheter with a constant infusion of 0.2% ropivacaine and 150 mcg clonidine at a total volume of 150 ml (1 mcg/ml), at the same rate of 2 ml/h.

All patients received pre-emptive multimodal analgesia treatment one hour before surgery (time of incision), consisting of the following agents:

- 40 mg parecoxib (IV)
- 1 gr paracetamol (IV)
- 150 mg of pregabalin (PO)
- 8 mg of dexamethasone (IV)
- 50 mg ranitidine (IV)

All patients underwent surgery under subarachnoid anesthesia with 0.75% (7,5 mg/ml) ropivacaine (dose range 2-3 ml, depending on age and height) provided by the same anesthesiologist for every patient.

Epidural and femoral nerve block catheters were placed preoperatively, before the administration of subarachnoid anesthesia while the intra-articular catheter was placed at the end of surgery.

Patients in all groups received a constant infusion of 0.2% ropivacaine and 150 mcg clonidine at a total volume of 150 ml (1 mcg/ml), by catheter, with a flow rate of 2 ml/h, for a maximum of 48 hours. The analgesia catheter was connected to a "patient controlled analgesia" (PCA) pump, which was activated after surgery and removed 48 hours later. The PCA pump was set to deliver a 0.5 ml dose with a 15-minute lockout interval. Finally, all patients after surgery also received a regimen of parecoxib, paracetamol, pregabalin and ranitidine for the first three postoperative days, following a titration scheme.

Study assessments

Routine preoperative assessment included physical examination and taking of medical history.

The primary outcome of the present study was the assessment of pain intensity using the self-reported numerical rating scale measure (NRS), an eleven-point numerical scale (0=no pain; 10=worst pain). Assessments for postoperative pain were performed, at rest and on movement (active and passive), at the following time intervals: 0h, 2h, 4h, 6h, 12h, 24h, 36h, 48h, 60h and 72h after surgery. Additionally, secondary outcome measures included the examination of the association of the analgesic technique used for postoperative pain management with LOS and the timing of patient mobilization (standing, walking in room, walking out of room).

Statistics and data analysis

G-Power software was used to calculate the statistical power. With data: a) sample size equal to 72, b) number of categories equal to 3, c) number of repeated measurements equal to 10, d) correlation among repeated measurements equal to 0.5, e) nonsphericity correction ϵ (epsilon) equal to 1, and f) type I error equal to 0.05, the statistical power of the RM-ANOVA was estimated at 99.97 %.

Statistical analysis was performed with SPSS statistical software v25.0. Statistical significance was set at $p < 0.05$. Continuous data (e.g. age, BMI) is presented as mean \pm standard error (SD). Categorical data is presented as frequencies. The normality of the quantitative parameters was studied with the Shapiro-Wilk tests. The Repeated Measures ANOVA (RM-ANOVA) method was used with the univariate approach to determine differences in mean scores of the outcomes (NRS- at rest, NRS-passive movement, NRS-active movement) at different time reference points. The assumption of sphericity was checked with use of the Mauchly's test. In cases of violations of the sphericity assumption, Greenhouse-Geisser Epsilon correction was applied. For nonparametric data (hospital stay, mobilization),

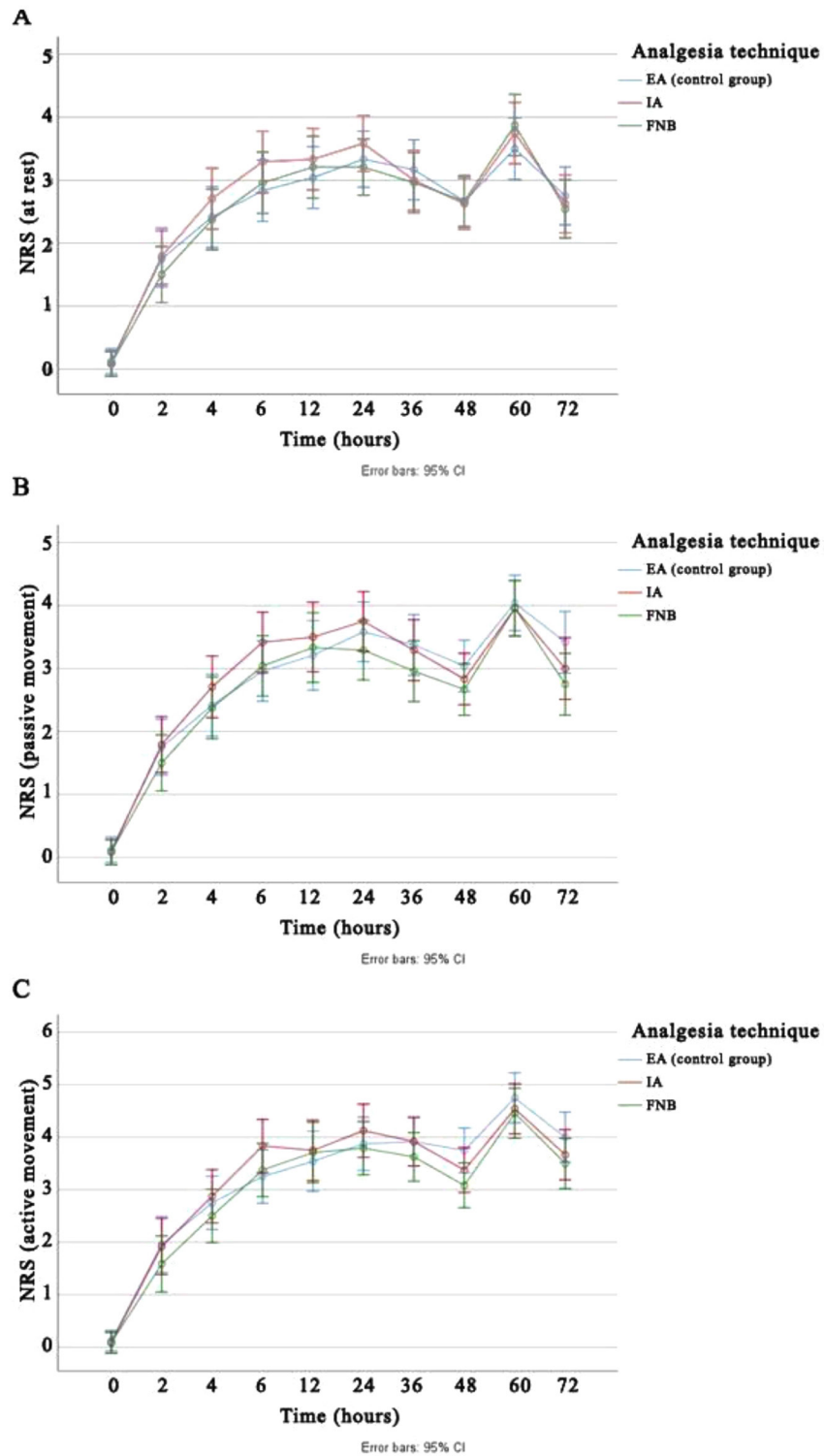


Figure 1. Numeric Rating Scores among study participants at rest (A) and upon passive (B) or active (C) movement are presented for the day of surgery (0 hours) until postoperative 72 hours. EA: Epidural Analgesia; IA: Intra-articular Infusion; FNB: Femoral Nerve Block.

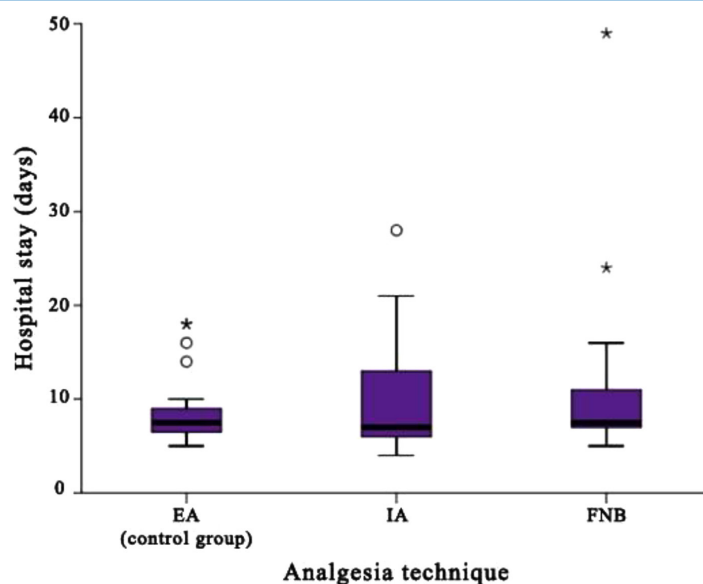


Figure 2. Effect of three different analgesic techniques (EA, IA, FNB) in LOS after TKA. EA: Epidural Analgesia; IA: Intra-articular Infusion; FNB: Femoral Nerve Block.

Kruskal-Wallis test was used to analyze the significant differences among and between the groups.

Results

After recruitment, 16 men (22.2%) and 56 women (77.8%), with a mean age of 72.3 years (range, 65.8-78.8 years), BMI of 30.1 kg.m⁻² (range, 25.3-34.9 kg.m⁻²) and physical status ASA II-III participated and completed the study. In the following table (Table 1), patients' demographics and relevant clinical data are presented, providing information on differences among the three groups.

Pain

NRS scores at rest (Figure 1A) and at passive (Figure 1B) or active (Figure 1C) movement did not show any statistically significant differences ($p > 0.05$) at any time among the three groups (EA, IA, FNB). In all groups, regardless of the analgesic technique used, pain values were gradually increased during the first 24 hours, decreased on postoperative day 2 and then slightly increased (48-60 hours) to fall afterwards on postoperative day 3 (Figure 1).

LOS

Neither IA (median=7, Q₂₅=6, Q₇₅=13 days) or FNB (median=7.5, Q₂₅=7, Q₇₅=11 days) resulted in reduced hospital stay comparing to EA (median=7.5, Q₂₅=6.5, Q₇₅=9 days). Kruskal-Wallis test showed no statistically significant differences between all the three studied groups regarding the length of hospital stay.

Mobilization

Upon analyzing the grade of mobilization outcomes, Kruskal-Wallis analysis revealed statistically significant differences among the three groups (Figure 3). Group IA patients achieved earlier mobilization and reached full standing as early as 24.9±3.8 (median=24, Q₂₅=22.5, Q₇₅=27) hours postoperative (Figure 3A), compared to group FNB and group EA patients, who were able to stand up at 26.7±4.4 (median=25, Q₂₅=24, Q₇₅=29) and 30.2±4.9 (median=30, Q₂₅=26, Q₇₅=22.5) hours respectively. Similarly, patients in the EA and FNB groups demonstrated statistically significant delayed ambulation (walking in/out of the room) compared to the IA group (walking in room: 35.8±5.8 (median=35, Q₂₅=31, Q₇₅=40) and 31.2±6.0 (median=30, Q₂₅=27.5, Q₇₅=34) hours vs. 29.1±5.2 (median=28, Q₂₅=26, Q₇₅=32) hours; walking out of room: 41.1±6.0 (median=41, Q₂₅=36, Q₇₅=44.5) and 36.4±8.3 (median=34, Q₂₅=30, Q₇₅=43) hours vs. 33.8±6.5 (median=32, Q₂₅=30, Q₇₅=38) hours (Figure 3B and Figure 3C). Consequently, our findings revealed a gradual increase after surgery of the level of mobilization in all groups. Whereas, patients receiving IA demonstrated earlier postoperative mobility in all cases (standing, walking in/out of room).

Adverse effects/Complications

All the catheter tips were cultured after having been removed under aseptic conditions. A total number of 3 patients out of 72 had positive catheter cultures, 1 in the EA group and 2 in the FNB group. Only one patient (FNB) had clinical signs and symptoms of infection which progressed

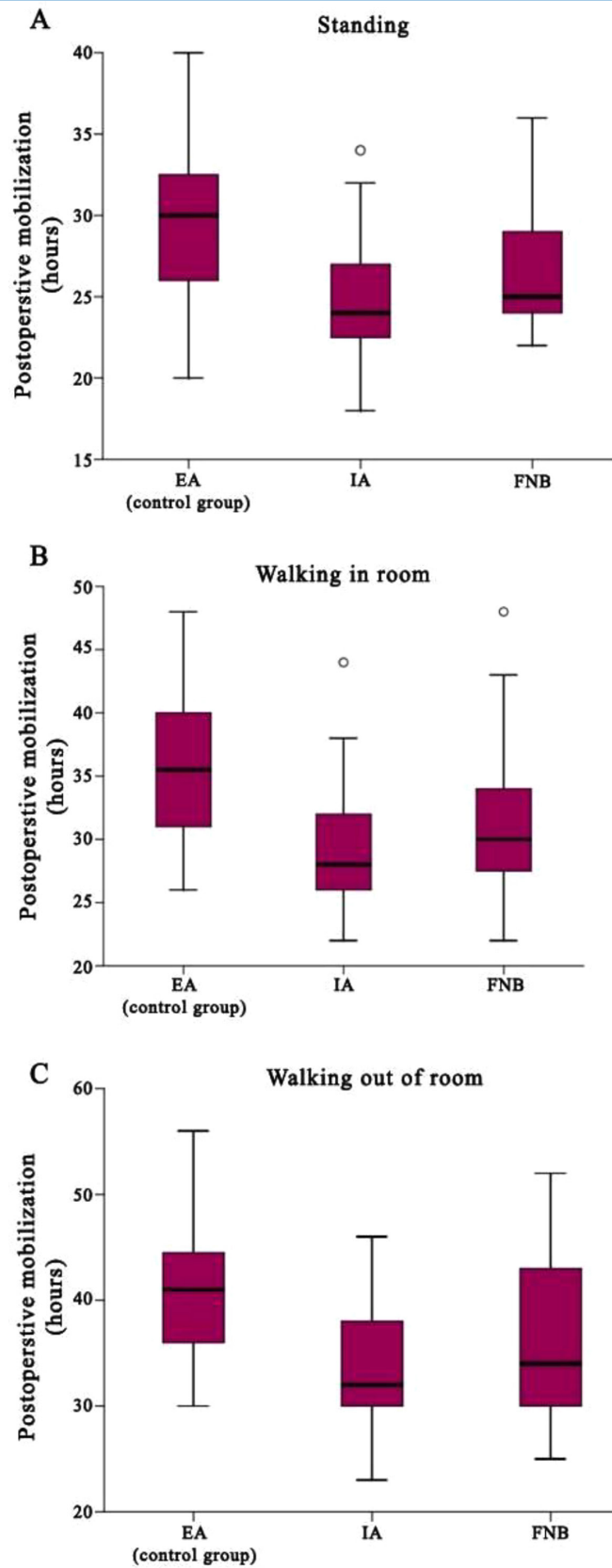


Figure 3. Effect of three different analgesic techniques (EA, IA, FNB) in postoperative mobilization (standing, walking in/out of room) after TKA. EA: Epidural Analgesia; IA: Intra-articular Infusion; FNB: Femoral Nerve Block.

Table 2. Adverse effects/complications distribution per group.

	Group EA (Control group) n=24	Group IA n=24	Group FNB n=24	Total n=72
Dizziness	2	0	0	2
Headache	0	0	1	1
Bradycardia	0	0	1	1
Hypotension	1	0	0	1
Insomnia	3	2	1	6
Motor blockade	0	0	1	1
Nausea	1	1	0	2
Numbness	1	0	1	2
Paresthesia	0	0	1	1
Diplopia	0	0	1	1
Infection	1	0	2	3
Total	9	3	9	p<0.001

EA: epidural analgesia; IA: intra-articular analgesia; FNB: femoral nerve block.

to bacteremia and sepsis, leading to prolonged hospital stay, while no patient with LIA had positive catheter cultures. Other complications were severe hypotension in 1 patient in the EA group, which demanded the administration of intravenous vasopressors for the first 12 hours post-operatively, and diplopia (up to 24 hours), mentioned by a patient in the FNB group. The distribution of adverse effects and complications per group are presented in Table 2. Patients in the IA group demonstrated remarkably less adverse effects and complications compared to group EA and FNB.

Discussion

Recently, there has been growing interest in achieving optimal pain relief and minimization of opioid consumption and adverse effects following TKA, due to their critical role in patient satisfaction, postoperative rehabilitation and overall surgical outcomes. There are multiple analgesic protocols available for postoperative pain control, each with its own limitations and drawbacks. Thus, the present study is an attempt to evaluate the effect of three regional anesthesia techniques (EA, IA and FNB) in terms of postoperative pain management, mobilization and LOS, after TKA. The results of our comparative study indicate that patients who underwent TKA achieved comparable levels of postoperative analgesia regardless of the applied analgesic technique at rest and upon passive/or active movement for a 72-hour time period after the surgery.

All patients in this study were scheduled for TKA, performed by the same team of Orthopedic Surgeons and Anesthesiologists. This practice reduces the risk of different surgical or anesthesiologic approaches to certain issues, such as the placement of the intra-articular catheter. Additionally, the convenience sampling method which was followed in our study, as the University Hospital of Patras is

the biggest hospital in our prefecture treating the majority of patients with osteoarthritis, increases the representativity of the sample, thus strengthens our study's results.

On the other hand, the most important limitations of the study include the unavailability of an adjusted postoperative physiotherapy plan, although every patient received the same physiotherapy protocol and current discharge criteria depending on some extent to social factors. Although, our study demonstrates significant differences in mobilization among the three methods, outcomes regarding LOS didn't result in reduced stay. The fact that the physiotherapy treatment plan wasn't individualized and patients' discharge criteria were mostly based on social factors (rural areas, lack of family support), limit our study's strength concerning LOS, since none of the patients was included in a fast-track surgery program. Finally, despite the ostensibly small sample size of our study, we believe that the present sample is sufficient to validate our results, as the statistical power has been estimated at 99.97%, suggesting that multimodal anesthesia along with different regional blocks can offer very satisfactory postoperative analgesia.

Regarding pain management, all three methods (EA, IA and FNB) displayed similar quality of pain relief, in agreement with previous studies. A meta-analysis by Li et al.¹³, concluded that LIA (continuous or single-shot) has equivalent efficacy to continuous EA for pain management with rest (at 12 and 24h postoperatively) and movement (at 24, 48, and 72 h postoperatively). While, VAS scores with rest at 48 and 72h indicated a reduction with the LIA method¹³. Other researchers have shown that LIA may even be associated with superior analgesic effects to continuous EA in pain relief¹⁶.

The findings of another meta-analysis by Hu et al.¹⁴ indicated that LIA versus regional blockade provided better pain control at rest in the immediate postoperative period, preserved quadriceps function and consumed significantly

less morphine. However, there were no significant differences in terms of NRS pain score at motion. Regarding the analgesia effect between FNB and EA, several studies suggest that FNB is comparable or even superior to EA and is associated with less side-effects and other neuraxial complications^{10,17}.

As for the LOS after TKA, decreasing inpatient stay is closely related to improved patient outcomes along with reduced hospital costs. There are several pre-operative and post-operative predictors of increased hospital LOS, such as patient-related factors and procedure or structural-related factors¹⁸. Moreover, improved analgesia methods and perioperative care are key elements in the philosophy of enhanced recovery after surgery for knee arthroplasty, resulting in earlier mobilization, functional rehabilitation and reduced LOS (1-3 days)¹⁹.

Therefore, in the present study we evaluated the effect of the three analgesic techniques (EA, IA, FNB) in LOS after TKA. Interestingly, no statistically significant differences arose from the comparison of the above techniques in LOS. Several researchers have found no significant difference in the time to fulfillment of discharge criteria between the LIA group and placebo/or other analgesic technique group, suggesting that it is not related to the applied analgesic technique²⁰. However, Li et al.¹³ has shown that LIA (continuous or single-shot) is positively associated with the reduction of nausea and LOS compared to EA. This finding is in consistency to prior studies where LIA compared to the saline group resulted in shorter time to home readiness, as well as lower postoperative pain intensity (at rest and on movement) and morphine consumption following TKA²¹.

The current study also assessed the efficacy of IA, FNB and EA with respect to the grade of mobilization after TKA and revealed significant differences among the three analgesic methods. Patients who received IA achieved earlier mobilization (full standing, walking in/out of room) compared to FNB and EA. Our results seem to be consistent with previous studies claiming that patients receiving local analgesia achieve earlier ambulation and shorter LOS. Moreover, Kasture and Saraf²² have shown that although the analgesic efficacy of continuous EA and LIA after TKA is comparable, patients receiving IA were able to stand/walk sooner. In addition, Reinhardt et al.²³ comparing the analgesic efficacy and functional recovery between continuous IA and continuous EA plus a single-injection FNB after TKA indicated similar pain control, but patients in the EA plus FNB group achieved delayed ambulation and were prone to knee buckling. In the same manner, researchers have shown that local and intraarticular infiltration compared to continuous EA significantly reduces opioid consumption and LOS, while improving mobilization after knee or hip arthroplasty²⁴.

However, Fowler et al.¹⁰ in a meta-analysis, that included six clinical studies, evaluated mobilization or rehabilitation in relation to the applied analgesia technique and reported that in most cases the outcomes between the EA and PNB groups of patients were generally similar. Likewise, Berninger et al.¹² reported no significant differences, at any time reference

point, in the degree of mobilization among EA, LIA and FNB after unicompartmental knee arthroplasty. Recently, Gandhi et al.²⁵ also observed that continuous FNB is as effective as continuous EA in terms of analgesia, rehabilitation and patient's satisfaction after TKA.

In conclusion, the findings from our study suggest that IA could be recommended as the preferred analgesic technique for TKA, since it facilitates comparative pain relief to EA and FNB, along with early functional recovery and shorter timing of mobilization (standing, walking in/out of room). In addition, IA is considered as an economical and technically easier to perform analgesia option, with less adverse effects and complications.

Acknowledgements - Authors' contributions

All authors contributed to the study conception and design and in particular: Conception and design of the study: G. Karpetas, F. Fligou, P. Megas, E. Panagiotopoulos. Generation, collection and integrity of the data: G. Karpetas, M. Spyraiki, S. Giakoumakis, E. Panagiotopoulos. Assembly, analysis and/or interpretation of the data: G. Karpetas, M. Spyraiki, G. Voyagis. Drafting and revising the manuscript: G. Karpetas, M. Spyraiki, G. Voyagis, E. Panagiotopoulos

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