

CLINICAL STUDY

A multimodal opioid-sparing pain management following total knee replacement

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ABSTRACT

OBJECTIVE: The purpose of this study is to compare the pain scores, opioid consumption, and range of motion of the operated knee after total knee replacement (TKR) in the 10-day follow-up period between a traditional opioid-containing pain management protocol and a multimodal opioid-sparing treatment protocol. **METHODS:** This prospective, randomized, single-center study included 90 patients (24 men and 66 women; mean age 69.7±7.2 years) undergoing TKR for osteoarthritis between October 2019 and October 2020. Patients were randomized into 3 cohorts for comparison: traditional opioid-containing pain management protocol (n=30), multimodal opioid-sparing pain management protocol (n=30), and traditional opioid-containing pain management protocol with additional local infiltration analgesia (LIA). Changes in visual analog scale for pain (VAS), range of motion (ROM), and opioid consumption were compared between groups. **RESULTS:** A lower mean postoperative VAS score was observed in the opioid-sparing cohort, which was statistically significant at all time points compared with the traditional cohorts. Mean total morphine consumption was significantly lower in the opioid-sparing cohort (2.7±5.8 MMEs) compared to the traditional (14.0±14.8 MMEs) and traditional with LIA cohorts (8.3±9.5 MMEs; p<0.05). The mean degree of flexion of the operated knee of patients was significantly greater in patients in the opioid-sparing group than in the other groups on the postoperative day 3 (opioid-sparing: 87.0±11.2°; traditional: 74.1±11.6°; traditional with LIA: 84.7±8.9°; p<0.05), as well as on day 10 (opioid-sparing: 99.3±10.8°; traditional: 87.3±12.4°; traditional with LIA: 92.5±9.7°; p<0.05). The rate of adverse events after TKR did not differ between the groups. **CONCLUSION:** The results of this study suggest that a multimodal opioid-sparing pain protocol after TKR, which includes oral non-opioid medications and periarticular injection with bupivacaine, provides better pain relief and early functional gains with fewer rescue opioids compared to traditional opioid-based protocols (Tab. 4, Fig. 2, Ref. 22). Text in PDF www.elis.sk **KEY WORDS:** total knee replacement, postoperative pain, pain management, opioid-sparing.

Abbreviations: TKR – Total knee replacement, LIA – Local infiltration analgesia, MMEs – Morphine milligram equivalents, BMI – Body mass index, ASA – American Society of Anesthesiologists, VAS – Visual analogue scale of pain, ROM – Range of motion

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Introduction

Total knee replacement (TKR) is performed in patients with end-stage knee osteoarthritis to relieve pain, improve function and enhance the quality of life. TKR is associated with significant postoperative pain – 60 % of patients experience severe pain and 30 % experience moderate pain (1). Postoperative pain affects rehabilitation, patient satisfaction, and overall outcome after TKR.

Currently, there are many different approaches to relieve severe postoperative pain, such as pre-emptive analgesia, epidural anesthesia, peripheral nerve blocks, local infiltration analgesia (LIA), opioids and patient-controlled analgesia. Adequate analgesia should reduce pain, opioid consumption and consequently opioid-related side effects, improve early mobility, range of motion and patient satisfaction (2). Adequate analgesia is a prerequisite for enhanced recovery after surgery protocols (3). For this purpose, multimodal analgesia has been introduced in the last decade. Multimodal analgesia combines several types of medications that act on different targets of the pain pathways. However, the optimal protocol of multimodal analgesia needs further investigation (4).

The aim of this study is to determine an effective and safe analgesic protocol after TKR. Pain scores, opioid consumption, and range of motion of the operated knee were compared between a traditional opioid-containing pain management protocol and a multimodal opioid-sparing management protocol during the 10-day follow-up period after the TKR procedure. We hypothesized that a multimodal opioid-sparing protocol provides better pain relief and functional outcomes with fewer opiates.

Material and methods

This prospective, randomized, single-center study included 90 patients (24 men and 66 women; mean age 69.7 ± 7.2 years; range 52 to 80 years) who underwent unilateral total knee replacement at University Hospital of Louis Pasteur in Kosice for primary or secondary osteoarthritis between October 2019 and October 2020.

Inclusion criteria included patients aged 18 to 80 years, with body mass index between 18 and 40 kg/m² and an American Society of Anesthesiologists functional status of 1 to 3. Exclusion criteria included allergy to a drug administered in the study and chronic opioid use (daily use of opioids for more than 3 months before surgery).

Patients were randomized into 3 cohorts for comparison: (1) traditional opioid-containing pain management protocol (n=30), (2) multimodal opioid-sparing pain management protocol (n=30), and (3) traditional opioid-containing pain management protocol with additional LIA (n=30). Subjects were randomly assigned to 3 groups with equal sample sizes using online statistical computing programming (www.graphpad.com/quickcalcs) on the internet

(5). The diagram CONSORT, illustrating the enrolment of patients, is shown in Figure 1.

The study protocol was approved by the local ethics committee (12/Sep/2019), registration number: 2019/EK/9043). Written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Anesthetic and analgesic techniques

All TKRs were performed under spinal anesthesia with 3 ml of 0.5 % levobupivacaine. Local infiltration analgesia (consisting of 20 ml 0.5 % levobupivacaine and 60 ml isotonic sodium chloride solution) was injected into the deep soft tissue around the knee before implantation of the tibial and femoral components and then into the fat and subcutaneous tissue before skin closure. A pressure dressing was applied from the ankle to the thigh and an ice pack was placed around the surgical site.

The traditional opioid-containing pain management protocol included: Infusion with metamizole 2 g and tramadol 100 mg every 8 hours for 2 postoperative days followed by metamizole 1000 mg orally every 8 hours. Administration of the medications begins after surgery.

As part of the multimodal opioid-sparing pain protocol, patients received all medications orally: celecoxib 200 mg every 12 hours, paracetamol 1000 mg every 8 hours, pregabalin (Lyrica) 75 mg once daily before bedtime. The first administration of the drugs was the evening before surgery.

Patient-controlled analgesia was administered with opiates (Dolsin 100 mg, Nalpain 10 mg) as a rescue medication. The dose

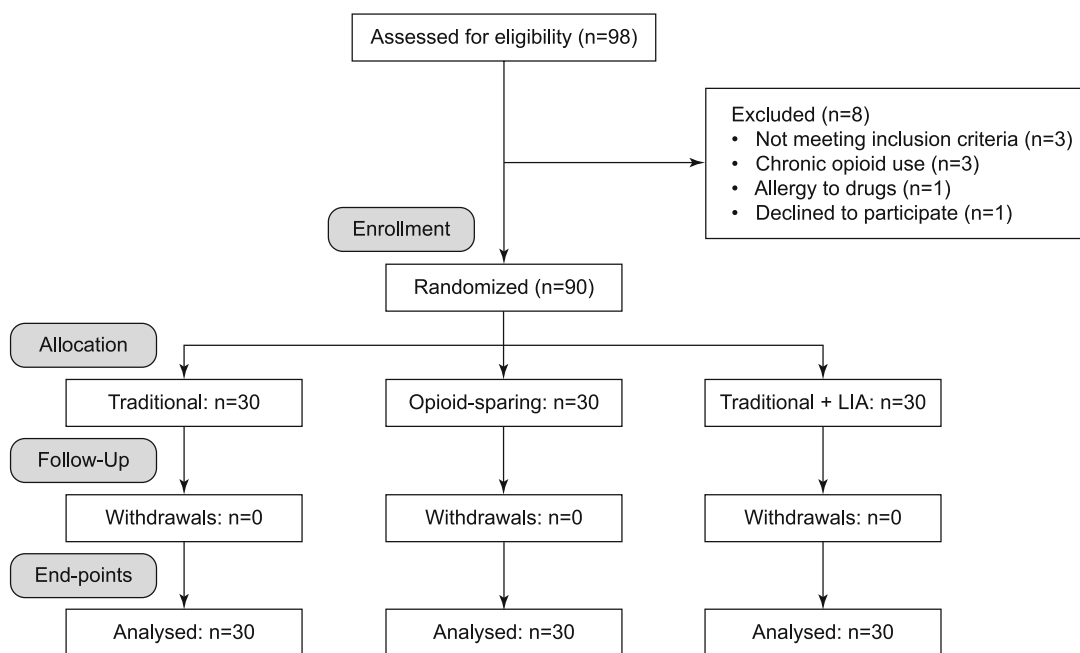


Fig. 1. Consolidated standards of reporting trials flow diagram describing the grouping and flow of patients in the study.

Tab. 1. Summary of demographic data.

Variable	Traditional	Opioid-sparing	Traditional+LIA	p
Patients	30	30	30	NS
Male/female ratio	7:23	8:22	9:21	NS
Mean age (years)	70.1 (±7.2)	69.7 (±6.5)	69.5 (±8.3)	NS
Mean BMI (kg/m ²)	31.7 (±5.2)	31.0 (±4.3)	30.3 (±4.4)	NS
ASA class (I/II/III)	0/15/15	2/14/14	1/14/15	NS
Mean preoperative hemoglobin level (mg/l)	13.3 (±0.9)	13.8 (±0.8)	13.2 (±0.9)	NS
Mean duration of operation (min.)	80 (±12.3)	82 (±11.6)	84.3 (±12.2)	NS

Traditional – group of patients with traditional opioid-containing pain management; Opioid-sparing – group of patients with multimodal opioid-sparing pain management protocol; Traditional + LIA – group of patients with traditional opioid-containing pain management with additional local infiltration analgesia; ASA – American Society of Anesthesiologists; NS – Not significant; ± – Standard deviation; p value was calculated using the Kruskal–Wallis test

of Dolsin and Nalpain was recorded and converted to the MMEs (morphine milligram equivalents (6)).

Surgical techniques

TKRs were performed by 5 experienced orthopedic surgeons who inserted a bicondylar cemented posterior cruciate-retaining total knee replacement using the medial parapatellar approach. A tourniquet was applied only during cementing.

Data collection

Baseline characteristics of each group were based on mean age, male-to-female ratio, body mass index (BMI), perioperative risk classification according to the American Society of Anesthesiologists (ASA), mean preoperative hemoglobin levels, and duration of surgery.

Outcome measures

The pain of the operated knee was assessed and measured each morning before the start of the rehabilitation program using the Visual Analog Scale for pain (VAS; 0=no pain, 10=worst pain imaginable; (7)). This parameter was measured at the following

time points: 8 hours after surgery (day 0), on the first 3 postoperative days (days 1–3) and on the tenth day (day 10) after surgery.

Total mean opiate consumption was recorded, which was standardized using morphine milligram equivalents (MMEs) for an observation period of 10 days after surgery.

The degree of flexion of the operated knee was recorded preoperatively and on the morning of the 3rd and 10th postoperative day. The patient was asked to actively move the operated knee joint, and the angle was measured with a goniometer.

In addition, all postoperative complications and adverse events (nausea, vomiting, urinary retention, arterial hypotension, systemic toxicity of drugs) were recorded.

Statistical analysis

Simple sorting scatters analysis was performed to test the hypothesis of equality of the mean values of each parameter. Normality of distribution for numerical variables was tested using the Shapiro-Wilk test. Accordingly, categorical variables are presented as means with standard deviation (±). Data for comparison between groups were tested using one-way test ANOVA if the data were normally distributed and Kruskal-Wallis test if they were not normally distributed. Statistical significance was defined with a significance level of $p < 0.05$. SigmaPlot version 12.5 (Systat Software, Inc., San Jose, CA, USA) was used for statistical analyzes.

Results

There were no statistically significant differences between groups in mean age, sex, body mass index, ASA, preoperative hemoglobin levels, or duration of surgery (Tab. 1).

Tab. 2. Visual analogue scale pain severity comparison.

	Traditional	Opioid-sparing	Traditional + LIA	p		
				Trad vs Opioid-sparing	Trad vs Trad+LIA	Opioid-sparing vs Trad + LIA
Preop pain	7.5 (±1.5)	7.3 (±1.4)	7.2 (±1.4)	NS	NS	NS
Postop Pain						
Day 0	7.8 (±1.7)	5.2 (±3.2)	7.7 (±2.4)	$p < 0.05$	NS	$p < 0.05$
Day 1	5.9 (±2.0)	3.2 (±1.8)	5.5 (±1.8)	$p < 0.05$	NS	$p < 0.05$
Day 2	4.5 (±1.7)	2.2 (±1.3)	4.3 (±1.7)	$p < 0.05$	NS	$p < 0.05$
Day 3	4.1 (±1.8)	1.7 (±1.4)	3.7 (±1.9)	$p < 0.05$	NS	$p < 0.05$
Day 10	3.1 (±1.5)	1.1 (±1.1)	2.9 (±1.5)	$p < 0.05$	NS	$p < 0.05$

NS – Not significant; ± – Standard deviation; p value was calculated using Kruskal–Wallis test

Tab. 3. Mean visual analogue scale pain severity, rate of patients with mild pain and total opioid consumption (period days 0–10).

	Traditional	Opioid-sparing	Traditional + LIA	p		
				Trad vs Opioid-sparing	Trad vs Trad + LIA	Opioid-sparing vs Trad + LIA
Mean Postop Pain Days 0-10	4.8 (±1.4)	2.5 (±1.3)	4.5 (±1.5)	$p < 0.05$	NS	$p < 0.05$
Rate of patients with mild pain (VAS ≤ 3)	23.3%	86.7%	46.7%	$p < 0.05$	NS	$p < 0.05$
Total morphine consumption (MMEs)	14.0 (±14.8)	2.7 (±5.8)	8.3 (±9.5)	$p < 0.05$	NS	$p < 0.05$

VAS – Visual analogue scale of pain; MMEs – morphine milligram equivalents; NS – Not significant; ± – Standard deviation; p value was calculated using Kruskal–Wallis test

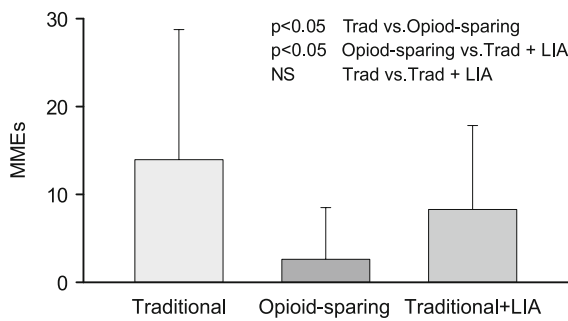


Fig. 2. Total rescue opiate consumption (MMEs – morphine milligrams equivalents; NS – Not significant; p-value was calculated using the Kruskal–Wallis test).

Pain scores

No statistically significant difference in mean preoperative VAS score was found between all 3 groups (p=0.84).

A lower mean postoperative VAS score was observed in the opioid-sparing cohort, which was statistically significant compared to the traditional cohorts at all time points (days 0–10). There was no significant difference in VAS score between the traditional and traditional with LIA groups. Pain scores are shown in Tables 2 and 3.

Approximately 87 % of patients in the opioid-sparing protocol had a mean of mild postoperative pain (mild pain=VAS 1 to 3), which was significantly more than in the traditional (23 %) and traditional with LIA cohorts (46 % patients; p<0.05).

Total morphine consumption

Mean total morphine consumption was significantly lower in the opioid-sparing cohort (2.7±5.8 MMEs) than in the traditional (14.0±14.8 MMEs) and traditional with LIA cohorts (8.3±9.5 MMEs; p<0.05) (Fig. 2 and Tab. 3). There was no significant difference in morphine-equivalent consumption between the traditional and traditional with LIA groups, although we noted lower morphine consumption in the traditional with LIA cohort.

The rescue narcotic analgesia was used in 6 (20 %) patients in the opioid-sparing protocol, whereas this was the case in 22 (73 %) patients in the traditional protocol and 17 (57 %) patients in the traditional with LIA protocol (p<0.05).

Functional outcomes

There were no differences in preoperative range of motion of the affected knee between the 3 groups (p=0.52).

Range of motion improved in all groups from day 3 to day 10. However, at postoperative testing, we found that the mean degree of flexion of the operated knee was significantly greater in patients in the opioid-sparing group than in the other groups on postoperative day 3 (opioid-sparing: 87.0±11.2°; traditional: 74.1±11.6°; traditional with LIA: 84.7±8.9°; p<0.05), as well as on day 10 (opioid-sparing: 99.3±10.8°; traditional: 87.3±12.4°; traditional with LIA: 92.5±9.7°; p<0.05). The measurement of functional outcome between groups after the TKR procedure can be seen in Table 4.

Complications

During the observation period, transient nausea, vomiting or a hypotensive event occurred in 2 (7 %) patients on the opioid-sparing protocol, 3 (10 %) patients on the traditional protocol and 4 (13 %) patients on the traditional with LIA protocol (p=0.69). No significant postoperative complications or symptoms indicative of local anesthetic or cyclooxygenase-2 inhibitor system toxicity were observed.

Discussion

Optimal analgesia after TKR is essential for reducing postoperative complications, and improving patient recovery and satisfaction (8). The inclusion of opioids in pain management protocols increases the risk of complications and adverse events, particularly pronounced in elderly osteoarthritic patients (9). This is the rationale for the introduction of multimodal, opioid-sparing pain protocols after TKR. The results of this prospective randomized study demonstrate that a multimodal opioid-sparing protocol after TKR can provide better postoperative pain control, greater range of motion of the operated knee, and reduce opioid consumption than a traditional opioid-containing protocol and a traditional opioid-containing protocol with LIA added.

In the present study, statistically significant lower postoperative pain score was observed in the opioid-sparing cohort compared with the traditional cohorts at each postoperative time point. Previous studies have reported equivalent pain control after TKR with both opioid-sparing and opioid-based pain management protocols (9, 10). This discrepancy could be due to differences in surgical procedures or pain management protocols. Multimodal analgesia includes preoperative, intraoperative, and postoperative analgesic regimens that target numerous pain pathways, and aim to maximize analgesic efficacy while minimizing adverse side effects. Multimodal analgesia was first introduced by Wall in 1988 (11). Currently, there are various protocols with different combinations

Tab. 4. Comparison of mean preoperative and postoperative range of motion of the affected knee.

	Traditional	Opioid-sparing	Traditional + LIA	p		
				Trad vs Opioid-sparing	Trad vs Trad + LIA	Opioid-sparing vs Trad + LIA
Preop ROM	94.2 (±16.1)	99.6 (±20.3)	97.7 (±16.3)	NS	NS	NS
Postop ROM						
Day 3	74.1 (±11.6)	87.0 (±11.2)	84.7 (±8.9)	p<0.05	p<0.05	NS
Day 10	87.3 (±12.4)	99.3 (±10.8)	92.5 (±9.7)	p<0.05	NS	NS

ROM – Range of the movement of operated knee; NS – Not significant; ± – Standard deviation; p value was calculated using Kruskal–Wallis test

of different types of drugs, their dosages and routes of administration, which have different results in terms of efficacy compared to other analgesic protocols. The pain protocol in our study consists of pre-emptive analgesia combined with spinal anesthesia and local infiltration analgesia. Pre-emptive analgesia is an anti-nociceptive intervention that starts before the surgical procedure, and usually combines paracetamol, cyclooxygenase-2 inhibitors, and pregabalin because of their synergistic analgesic effects (2). In our study, the same drugs were used, but only in oral dosage form. Local infiltration analgesia has emerged as an alternative postoperative analgesic regimen for femoral nerve blockade without affecting quadriceps muscle strength (12), adductor canal blockade with significantly better postoperative pain control (13) and epidural anesthesia with less frequent adverse effects, such as urinary retention, hypotension and motor blockade (14). Nevertheless, there is still no consensus on the optimal composition and infiltration technique of LIA. Usually, LIA cocktails consist of levobupivacaine or ropivacaine, ketorolac, morphine and adrenaline diluted with saline to a total volume of 80 to 150 ml (2). In our study, only levobupivacaine diluted in saline was used. Liposomal levobupivacaine, ropivacaine and ketorolac are not approved as drugs in our country. In our institute, adrenaline is excluded from LIA cocktails because of the lack of benefits and possible adverse effects of adrenaline in LIA mixtures according to TKR (15, 16).

The results of the study show that the opioid-sparing pain management protocol significantly reduces the consumption of opioids for breakthrough pain in the first 10 days after surgery. These results are consistent with those of Padila et al. and Post et al (9, 17). In the Peters et al. study, significantly lower narcotic consumption was found for the opioid-sparing cohort undergoing total hip arthroplasty, whereas consumption was similar in patients undergoing TKR (18).

We found that the multimodal opioid-sparing approach minimized overall opioid consumption, but the rate of adverse events after TKR did not differ between the two groups. No adverse event related to local anesthetic or cyclooxygenase-2 inhibitor toxicity was noted. While Peters et al (18) found similar results, Post et al (17) and Padila et al (9) reported a reduction in adverse effects in opioid-sparing cohorts, including nausea, vomiting, pruritus, constipation and dizziness, which can negatively affect patient well-being and early postoperative rehabilitation.

The rehabilitation program is an important component of postoperative recovery. Early mobilization after TKR may result in better functional outcomes and reduced morbidity (19). It follows that assessment of range of the motion is important to ensure early mobilization after TKR (20). There are many factors, such as preoperative ROM, soft tissue status, alignment of the knee, muscle strength of the knee, psychological condition, and surgical procedure, that affect the postoperative ROM (21, 22). These aspects were not investigated in this study. One of the most important factors influencing ROM is probably postoperative pain. This assumption can be confirmed by the results of this study. It was found that ROM of the subjects in the multimodal opioid-sparing cohort performed significantly better than the traditional cohorts due to better pain control at both measurement time points.

Limitation

This study has several limitations that may represent potential bias. The study was conducted at a single institution, but 5 different orthopedic surgeons were involved in the TKR. Although the surgeons underwent standardized training in the proper use of LIA, the method of LIA administration may vary, and the efficacy of the periarticular injections is highly dependent on technique. Another limitation is that patient-reported pain scores are subjective and individual characteristics affecting pain perception may vary among patients. Finally, this study was limited to inpatient pain management. No post-discharge pain analysis was performed.

The strength of this study is its prospective nature with randomization to equal comparison cohorts with similar demographic characteristics. In addition, to reduce bias in the analysis of total opioid use, we did not include patients with chronic preoperative opioid use.

In conclusion, the results of this study suggest that a multimodal opioid-sparing pain protocol after TKR that includes oral non-opioid medications and periarticular injection with bupivacaine, provides better pain relief and early functional improvement with a lower number of rescue opioids compared with traditional opioid-based protocols. Further investigation with high-quality, randomized clinical trials is needed to optimize pain management for patients undergoing total knee arthroplasty.

References

1. **Bonica JJ, Loeser JD, Chapman CR, Fordyce WE.** The management of pain. Philadelphia, PA: Lea and Febiger; 1990: 461–480.
2. **Li JW, Ma YS, Xiao LK.** Postoperative Pain Management in Total Knee Arthroplasty. *Orthop Surg* 2019; 11 (5): 755–761.
3. **den Hartog YM, Hannink G, van Dasselaaar NT, Mathijssen NM, Vehmeijer SB.** Which patient-specific and surgical characteristics influence postoperative pain after THA in a fast-track setting? *BMC Musculoskelet Disord* 2017; 18: 363.
4. **Moucha CS, Weiser MC, Levin EJ.** Current strategies in anesthesia and analgesia for total knee arthroplasty. *J Am Acad Orthop Surg* 2016; 24 (2): 60–73.
5. **Suresh K.** An overview of randomization techniques: An unbiased assessment of outcome in clinical research. *J Hum Reprod Sci* 2011; 4 (1): 8–11.
6. **Centers for Disease Control and Prevention (CDC).** Opioid oral morphine milligram equivalent (MME) conversion factors. 2017. <https://www.cdc.gov/drugoverdose/resources/data.html>. Accessed November 10, 2020.
7. **Boonstra AM, Schiphorst Preuper HR, Reneman M, Posthumus JB, Stewart RE.** Reliability and validity of the visual analogue scale for disability in patients with chronic musculoskeletal pain. *Int J Rehabil Res* 2008; 31 (2): 165–169.
8. **Parvizi J, Miller AG, Gandhi K.** Current concepts review multimodal pain management after total joint arthroplasty. *J Bone Joint Surg Am* 2011; 93 (11): 1075–1084.
9. **Padilla JA, Gabor JA, Schwarzkopf R, Davidovitch RI.** A Novel Opioid-Sparing Pain Management Protocol Following Total Hip Arthroplasty: Effects on Opioid Consumption, Pain Severity, and Patient-Reported Outcomes. *J Arthroplasty* 2019; 34 (11): 2669–2675.

- 10. Winther SB, Foss OA, Wik TS et al.** 1-year followup of 920 hip and knee arthroplasty patients after implementing fast-track. *Acta Orthop* 2015; 86 (1): 78–85
- 11. Wall PD.** The prevention of postoperative pain. *Pain* 1988; 33 (3): 289–290.
- 12. Zhang LK, Ma JX, Kuang MJ, Ma XL.** Comparison of periarticular local infiltration analgesia with femoral nerve block for total knee arthroplasty: a meta-analysis of randomized controlled trials. *J Arthroplasty* 2018; 33 (6): 1972–1978.
- 13. Sardana V, Burzynski JM, Scuderi GR.** Adductor canal block or local infiltrate analgesia for pain control after total knee arthroplasty? A systematic review and meta-analysis of randomized controlled trials. *J Arthroplasty* 2019; 34 (1): 183–189.
- 14. Kasture S, Saraf H.** Epidural versus intra-articular infusion analgesia following total knee replacement. *J Orthop Surg* 2015; 23 (3): 287–289.
- 15. Schotanus MGM, Bemelmans YFL, van der Kuy PHM, Jansen J, Kort NP.** No advantage of adrenaline in the local infiltration analgesia mixture during total knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc* 2017; 25 (9): 2778–2783.
- 16. Altay N, Sarıkaya B, Karahan MA, Büyükfırat E, Binici O, Ertürk C, Altay MA.** Comparison of efficacy between combined periarticular and incisional injections versus periarticular injection alone of bupivacaine for pain control after total knee arthroplasty: A prospective randomized controlled trial. *Acta Orthop Traumatol Turc* 2020; 54 (4): 402–407.
- 17. Post ZD, Restrepo C, Kahl LK, van de Leur T, Purtill JJ, Hozack WJ.** A prospective evaluation of 2 different pain management protocols for total hip arthroplasty. *J Arthroplasty* 2010; 25 (3): 410–415.
- 18. Peters CL, Shirley B, Erickson J.** The effect of a new multimodal perioperative anesthetic regimen on postoperative pain, side effects, rehabilitation, and length of hospital stay after total joint arthroplasty. *J Arthroplasty* 2006; 21 (6 Suppl 2): 132–138.
- 19. Chua MJ, Hart AJ, Mittal R, Harris IA, Xuan W, Naylor JM.** Early mobilisation after total hip or knee arthroplasty: A multicentre prospective observational study. *PLoS One* 2017; 12 (6): e0179820.
- 20. Vavro M, Ziakova E, Gazdikova K, Farkasova D.** Does standard post-operative rehabilitation have its place after total knee replacement? *Bratisl Med J* 2016; 117 (10): 605–608.
- 21. Lubis AMT, Rawung RBV, Tantri AR.** Preemptive Analgesia in Total Knee Arthroplasty: Comparing the Effects of Single Dose Combining Celecoxib with Pregabalin and Repetition Dose Combining Celecoxib with Pregabalin: Double-Blind Controlled Clinical Trial. *Pain Res Treat* 2018; 7: 3807217.
- 22. Jakobsen TL, Christensen M, Christensen SS, Olsen M, Bandholm T.** Reliability of knee joint range of motion and circumference measurements after total knee arthroplasty: does tester experience matter? *Physiother Res Int* 2010; 15: 126–134.

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