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Comparison of the Effect of Intra-Articular, Periarticular, and Combined Injection of Analgesic on Pain Following Total Knee Arthroplasty

A Double-Blinded Randomized Clinical Trial

Seyed Mohammad Javad Mortazavi, MD, Farzad Vosoughi, MD, Mirsaeed Yekaninejad, MD, Ehsan Ghadimi, MD, Mohammad Hasan Kaseb, MD, Mohammad Ayati Firoozabadi, MD, Ehsan Fallah, MD, Hesam Toofan, MD, and Seyed Khalil Pestehei, MD

Investigation performed at the Tehran University of Medical Sciences, Tehran, Iran

Background: The aim of this study was to compare the efficacy of 3 methods of intraoperative analgesic cocktail injection during total knee arthroplasty (TKA)—intra-articular (IA), periarticular (PA), and combined intra-articular and periarticular (IA+PA)—on controlling early postoperative pain.

Methods: This was a prospective double-blinded parallel randomized clinical trial. A total of 153 patients scheduled for TKA were allocated to IA, PA, or IA+PA (51 patients each) by block randomization. The primary outcome was morphine consumption. Secondary outcomes were visual analogue scale (VAS) pain, knee flexion, straight leg raising, Knee Society Score (KSS), and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

Results: The morphine consumption was lowest in the PA group (median = 0, interquartile range [IQR] = 5) and highest in the IA group (median = 10, IQR = 5). The PA group had significantly lower VAS pain at rest than either IA (mean difference = −0.70; 95% confidence interval [CI] = −0.93 to −0.46; $p < 0.001$) or PA+IA (mean difference = −0.41; 95% CI = −0.65 to −0.18; $p < 0.001$). The PA group had also lower VAS pain during activity compared with IA (mean difference = −0.63; 95% CI = −0.85 to −0.40; $p < 0.001$) and IA+PA (mean difference = −0.38; 95% CI = −0.61 to −0.16; $p < 0.001$). The PA group had significantly greater active knee flexion compared with IA (mean difference = 9.68°; 95% CI = 5.50° to 13.86°; $p < 0.001$) and IA+PA (mean difference = 5.13°; 95% CI = 0.95° to 9.31°; $p = 0.010$). Passive knee flexion was greater for PA than IA (mean difference = 7.85°; 95% CI = 4.25° to 11.44°; $p < 0.001$). Other outcome variables were not significantly different among the 3 groups. The only complications were wound drainage (1 each in the IA and IA+PA groups) and deep venous thrombosis (1 in the IA group).

Conclusions: PA was associated with less early postoperative pain and greater active knee flexion compared with the other 2 analgesic methods.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

Intraoperative intra-articular and periarticular analgesic injections (i.e., local infiltration analgesia [LIA]) have been demonstrated to be an effective and safe method for controlling pain after total knee arthroplasty (TKA) in multiple systematic reviews and meta-analyses[1-3].

Despite the literature support for LIA use, the best location for injection of the analgesic cocktail (intra-articular [IA] versus periarticular [PA] versus combined intra-articular and periarticular [IA+PA]) is still a matter of debate[4,5]. To our knowledge, no clinical trial simultaneously comparing IA+PA with both IA and PA has previously been published. As the highest pain receptor density has been discovered to be in the periarticular tissues (including the infrapatellar fat pad, collateral ligaments, and joint capsule)[6], the PA and IA+PA methods may theoretically be better able to address the wide distribution of pain receptors around the knee joint. On the other hand, the IA method is

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJSOA/A421).

A **data-sharing statement** is provided with the online version of the article (http://links.lww.com/JBJSOA/A422).

simpler (involving a single site of injection) and potentially safer (as no analgesic cocktail is injected near the peroneal nerve).

The aim of this study was therefore to compare the PA, IA, and IA+PA methods of analgesic cocktail injection in terms of postoperative pain control and functional recovery following TKA. As the IA method does not address the pain receptors in the infrapatellar fat pad and collateral ligaments directly, our hypothesis was that the IA method would be associated with greater postoperative pain (on a visual analogue scale [VAS]) and morphine consumption and poorer functional recovery (as measured by knee flexion and the Knee Society Score [KSS] and WOMAC [Western Ontario and McMaster Universities Osteoarthritis Index]).

Materials and Methods

This prospective double-blinded parallel clinical trial was performed from June 2021 to March 2022 on patients with advanced knee osteoarthritis who were referred to our center. It followed the CONSORT (Consolidated Standards of Reporting Trials) guidelines[7,8] and was registered at www.irct.ir (registration number IRCT20210613051559N1). The study was approved by the institutional review board (IR.TUMS.IKHC.REC.1399.434), and written informed consent was obtained from all participants.

Study Population

Patients scheduled for TKA who were 18 to 80 years old, had a body weight of 50 to 120 kg, and had the ability to read and write our native language and complete the informed consent form were potentially eligible for the study. Patients with drug dependence, allergy to any of our drug protocols, psychiatric issues, inflammatory arthritis, cardiac illness, or a renal or liver comorbidity were excluded. Of 160 patients with knee osteoarthritis, 7 were excluded (2 had rheumatoid arthritis and 5 did not wish to participate in the study).

Recruitment and Randomization of Participants

Block randomization was performed using www.randomisation.com. The randomization allocations were placed in sealed opaque envelopes. For each patient scheduled for TKA, 1 of the investigators (F.V.) opened the patient's envelope and became aware of the patient's allocation. During the surgery, after bone cut preparation and before inserting the components, the surgeon's circulating nurse called that investigator to ask the patient's allocation, then informed the surgeon of that. The postoperative outcome assessor (E.G.), patients, nurses, and physiotherapists were blinded to the allocation status.

Interventions

The interventions in the study differed only with respect to the site of the intraoperative analgesic cocktail injection. The surgery was performed under spinal analgesia with 10 to 15 mL of bupivacaine in all included patients. The preoperative preemptive analgesia, postoperative drugs, and rehabilitation were the same among the participants.

Based on a study by Busch et. al.[9], 400 mg of ropivacaine, 5 mg of morphine, 0.6 mL of 1:1,000 epinephrine, and 30 mg of ketorolac were diluted with sterile normal saline solution to create 100 mL of analgesic cocktail. In the IA group, all of the cocktail was injected through the joint space after suturing of the knee capsule. In the PA group, after bone cut preparation and before inserting the component, 30 mL of the cocktail was injected into the posterior capsule; 10 mL, into the medial collateral ligament; and 10 mL, into the lateral collateral ligament. While the cement was curing, another 20 mL was injected into the quadriceps and medial and lateral retinacular tissue. The remaining 30 mL of the cocktail was injected into the infrapatellar fat pad and subcutaneous tissue. In the IA+PA group, 30 mL of the cocktail was injected into the posterior capsule and lateral and medial collateral ligaments after bone cut preparation but before component insertion. While the cement was curing, another 10 mL was injected into the quadriceps, patellar tendon, and medial and lateral retinacular tissue. Also, 10 mL was injected into the infrapatellar fat pad and subcutaneous tissue. Finally, after watertight capsular closure, the remaining 50 mL was injected into the knee joint space.

Preoperative and Postoperative Medications

All patients received 400 mg of celecoxib, 1,000 mg of acetaminophen, and 75 mg of pregabalin 1 hour before the surgery as preemptive analgesia. After the surgery, patients were prescribed 200 mg of celecoxib twice daily, 75 mg of pregabalin daily, and 500 mg of acetaminophen every 4 hours. In case of intolerable pain (VAS score of >8), 5 mg of intravenous (IV) morphine sulfate was injected as rescue analgesia. Aspirin (325 mg twice a day for 4 weeks) was used for routine prophylaxis against venous thromboembolism (VTE). However, for those with additional VTE risk factors (e.g., patients with a history of VTE, with thrombophilia, on chronic anticoagulation, or with active cancer), 40 mg of enoxaparin was used for chemoprophylaxis.

Surgery

Surgery was performed in all patients by the same surgeon (S.M.J.M.) through a medial parapatellar approach without use of a drainage catheter. A posterior-stabilized knee prosthesis (NexGen; Zimmer Biomet) and a pneumatic tourniquet were used in all procedures.

Outcome Measures

The primary outcome of the study was the postoperative morphine consumption. The total amount of morphine (in mg) injected into each patient within the first 48 hours following surgery was documented.

In addition, secondary outcomes were evaluated. Preoperative pain, assessed with a VAS (from 0 for no pain to 10 for the most severe pain ever felt), was measured after admitting the patient to the hospital but before starting the preemptive analgesia protocol. Postoperative VAS pain was documented at 3, 6, 24, and 48 hours, 2 weeks, 1 month, and 2 months after the TKA. Three other patient-reported outcome measures, the KSS knee subscore, KSS function subscore, and WOMAC, were assessed at 2 weeks, 1 month, and 2 months after the surgery. The

maximum tolerable active and passive knee flexion and ability to perform straight leg raises (SLRs) were measured at 3, 6, 24, and 48 hours postoperatively.

Sample Size

A sample size calculation[10] indicated that at least 32 patients would be needed in each group to detect a difference in morphine consumption of at least 2 mg with a power of 95% and type-I error of 5%, assuming that the standard deviation of the morphine consumption in each group would be 2 mg as in a previous study[11].

Statistical Analysis

The chi-square test was used to compare preoperative categorical variables (gender, side of the affected knee) among the 3 analgesia groups, and 1-way analysis of variance (ANOVA) was used to compare preoperative quantitative variables. The Kruskal-Wallis test was used to compare postoperative total morphine consumption among the groups, as that did not have a normal distribution. Repeated-measures ANOVA was used to compare all other postoperative quantitative variables; when the result was significant, the Sidak test was used to perform pairwise comparisons between groups.

The Benjamini-Hochberg false-discovery-rate correction was performed to adjust the p value for multiple comparisons[12], using R (R Foundation for Statistical Computing). All other analyses were performed using SPSS software for Windows (version 25; IBM). All analyses were 2-sided, and significance was set at $p < 0.05$.

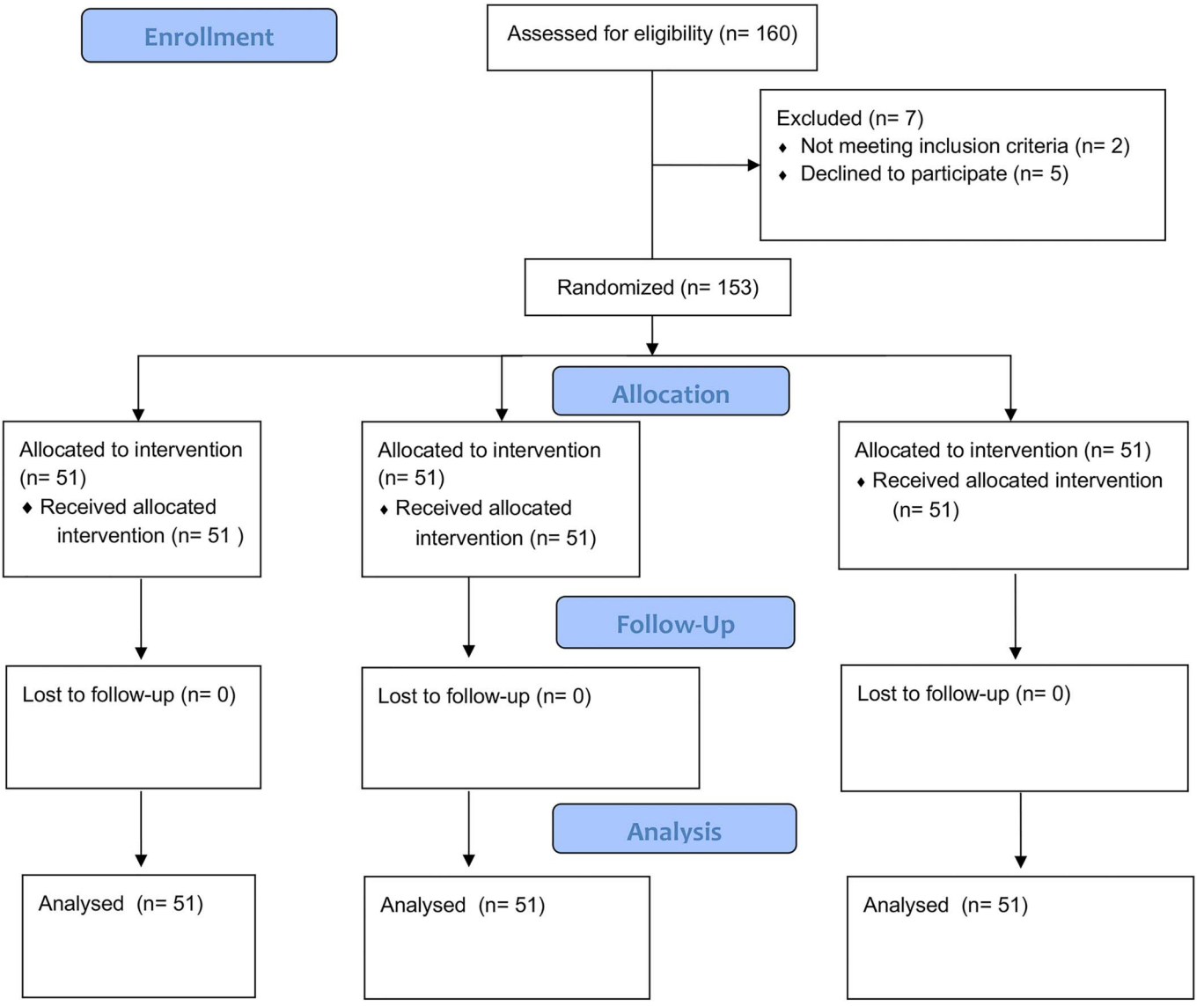

Fig. 1

CONSORT diagram showing patient flow through the study.

TABLE I Preoperative Variables*

	IA	PA	IA+PA	P Value
Age† *(yr)*	63.12 (9.18)	65.53 (5.67)	65.35 (5.96)	NS
Male to female ratio	0.24	0.16	0.08	NS
Weight† *(kg)*	76.94 (11.26)	75.90 (11.33)	79.33 (12.71)	NS
Height† *(cm)*	159.86 (8.39)	160.64 (8.88)	161.80 (7.31)	NS
BMI† *(kg/m^2)*	30.19 (4.41)	29.51 (4.48)	30.31 (4.58)	NS
Side of the affected knee, left/right	21/30	25/26	30/21	NS
Varus angle† *(°)*	12.20 (8.69)	11.82 (9.77)	13.90 (7.32)	NS
Active flexion† *(°)*	112.98 (28.81)	120.49 (23.91)	117.27 (17.05)	NS
Active extension† *(°)*	7.16 (11.54)	6.47 (9.71)	4.31 (8.31)	NS
Passive flexion† *(°)*	117.65 (26.18)	125.61 (22.69)	121.27 (16.37)	NS
Passive extension† *(°)*	4.84 (8.67)	4.63 (7.83)	9.31 (35.21)	NS
VAS pain†	8.52 (0.58)	8.56 (0.94)	8.25 (0.75)	NS
WOMAC†	39.08 (10.58)	39.60 (13.66)	36.84 (11.02)	NS
KSS knee subscore†	41.90 (14.91)	39.60 (15.46)	41.20 (16.14)	NS
KSS function subscore†	45.47 (17.23)	47.34 (18.59)	51.57 (10.61)	NS
Tourniquet time† *(min)*	75.65 (11.99)	71.47 (16.16)	70.73 (6.15)	NS

*IA = intra-articular, PA = periarticular, PA+IA = combined intra-articular and periarticular, NS = not significant, BMI = body mass index, VAS = visual analogue scale, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, KSS = Knee Society Score. †The values are given as the mean and standard deviation.

Source of Funding
This study had no source of funding.

Results

A total of 153 cases were included in the study (Fig. 1). There were no significant differences in preoperative variables among the groups (Table I).

Primary Outcome

Morphine consumption was significantly lower in the PA group (median = 0, interquartile range [IQR] = 5) compared with the IA group (median = 10, IQR = 5) and IA+PA group (median = 5, IQR = 0) ($p < 0.001$). The IA+PA group had lower morphine consumption than the IA group ($p < 0.001$).

Secondary Outcomes

Overall, the PA group had significantly lower VAS pain at rest than the IA (mean difference = –0.70; 95% confidence interval [CI] = −0.93 to −0.46; $p < 0.001$) and PA+IA groups (mean difference = −0.41; 95% CI = −0.65 to −0.18; $p < 0.001$). The PA group also had lower VAS pain during activity compared with the IA (mean difference = −0.63; 95% CI = −0.85 to −0.40; $p < 0.001$) and IA+PA groups (mean difference = −0.38; 95% CI = −0.61 to −0.16; $p < 0.001$). VAS pain (at rest and during activity) was significantly lower in the PA group than in the IA and IA+PA groups at 6, 24, and 48 hours postoperatively ($p < 0.05$) (Table II).

The PA group had significantly greater postoperative active knee flexion compared with the IA (mean difference = 9.68°; 95% CI = 5.50° to 13.86°; $p < 0.001$) and IA+PA groups (mean difference = 5.13°; 95% CI = 0.95° to 9.31°; $p = 0.010$). Passive knee flexion was also greater in the PA group than in the other 2 groups, although this benefit was only significant compared with the IA group (mean difference = 7.85°; 95% CI = 4.25° to 11.44°; $p < 0.001$). The PA group had significantly greater passive and active flexion compared with the IA group at 6 and 24 hours after surgery ($p < 0.05$) (Table II).

The earliest time at which any of the patients were able to perform SLRs was 6 hours. At that time, 12%, 16%, and 4% of participants were able to raise their leg straight out in the PA, IA+PA, and IA groups, respectively ($p = 0.14$). At 24 hours, 67%, 49%, and 59% of the patients in the PA, IA+PA, and IA groups could perform SLRs, respectively ($p = 0.19$) At 48 hours, all patients except 1 in the IA group could perform SLRs ($p = 0.60$).

The mean hospital length of stay did not differ significantly among the 3 groups: a mean (and standard deviation) of 2.90 ± 0.85 days for IA, 3.02 ± 0.47 days for PA, and 3.10 ± 0.41 days for IA+PA ($p = 0.267$). There were no significant differences in postoperative patient-reported outcome measures (KSS knee subscore, KSS function subscore, WOMAC) among the 3 groups at 2 weeks, 1 month, or 2 months after the surgery (Figs. 2, 3, and 4; see also Appendix).

Complications

The only postoperative complications were 1 case of wound drainage and 1 case of deep venous thrombosis in the IA group and 1 case of wound drainage in the IA+PA group. The patient

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TABLE II Pairwise Comparisons of Outcome Variables*

Variable	PA Compared with IA		PA Compared with IA+PA		IA+PA Compared with IA	
	Mean Diff. (95% CI)	Adjusted P Value†	Mean Diff. (95% CI)	Adjusted P Value†	Mean Diff. (95% CI)	Adjusted P Value†
Pain at rest 3 hr postop.	0.41 (−0.37 to 1.19)	0.566	0.41 (−0.37 to 1.19)	0.660	0 (−0.78 to 0.78)	1.000
Pain at rest 6 hr postop.	−2.29 (−3.09 to −1.50)	0.002	−1.31 (−2.11 to −0.52)	0.003	−0.98 (−1.77 to −0.19)	0.747
Pain at rest 24 hr postop.	−1.63 (−2.49 to −0.77)	0.002	−1.69 (−2.55 to −0.83)	0.003	0.059 (−0.78 to 0.90)	1
Pain at rest 48 hr postop.	−1.72 (−2.42 to −1.03)	0.002	−1.22 (−1.91 to −0.52)	0.003	−0.51 (−1.20 to 0.18)	0.496
Pain during activity 3 hr postop.	0.51 (−0.1 to 1.12)	0.156	0.49 (−0.12 to 1.10)	0.242	0.02 (−0.59 to 0.63)	1
Pain during activity 6 hr postop.	−2.27 (−3.08 to −1.47)	0.002	−1.43 (−2.24 to −0.62)	0.003	−0.84 (−1.65 to −0.04)	0.148
Pain during activity 24 hr postop.	−1.35 (−2.20 to −0.51)	0.002	−1.55 (−2.39 to 0.70)	0.003	0.2 (−0.65 to 1.04)	1
Pain during activity 48 hr postop.	−1.37 (−2.13 to −0.62)	0.002	−0.94 (−1.70 to −0.18)	0.024	−0.43 (−1.19 to 0.32)	0.775
Active flexion 3 hr postop. *(°)*	4.71 (−4.73 to 14.14)	0.580	8.23 (−1.20 to 17.67)	0.212	−3.53 (−12.96 to 5.90)	1
Passive flexion 3 hr postop. *(°)*	3.43 (−3.94 to 10.80)	0.600	−2.06 (−9.43 to 5.31)	0.934	5.49 (−1.88 to 12.86)	0.496
Active flexion 6 hr postop. *(°)*	17.16 (7.25 to 27.06)	0.002	5.39 (−4.52 to 15.30)	0.660	11.76 (1.86 to 21.67)	0.075
Passive flexion 6 hr postop.	14.31 (5.50 to 23.12)	0.002	3.82 (−4.99 to 12.63)	0.802	10.49 (1.68 to 19.30)	0.075
Active flexion 24 hr postop. *(°)*	12.94 (3.59 to 22.29)	0.005	7.65 (−1.70 to 17.00)	0.242	5.29 (−4.06 to 14.65)	0.775
Passive flexion 24 hr postop. *(°)*	8.82 (1.30 to 16.34)	0.026	7.06 (−0.46 to 14.58)	0.167	1.76 (−5.75 to 9.28)	1
Active flexion 48 hr postop. *(°)*	6.08 (−0.31 to 12.47)	0.097	1.18 (−5.21 to 7.56)	0.960	4.90 (−1.48 to 11.29)	0.496
Passive flexion 48 hr postop. *(°)*	4.70 (−0.66 to 10.08)	0.139	1.96 (−3.41 to 7.33)	0.870	2.74 (−2.62 to 8.11)	0.838

*PA = periarticular, IA = intra-articular, IA+PA = combined intra-articular and periarticular, and CI = confidence interval. †P values were adjusted using the Benjamini-Hochberg method to control the false-discovery rate.

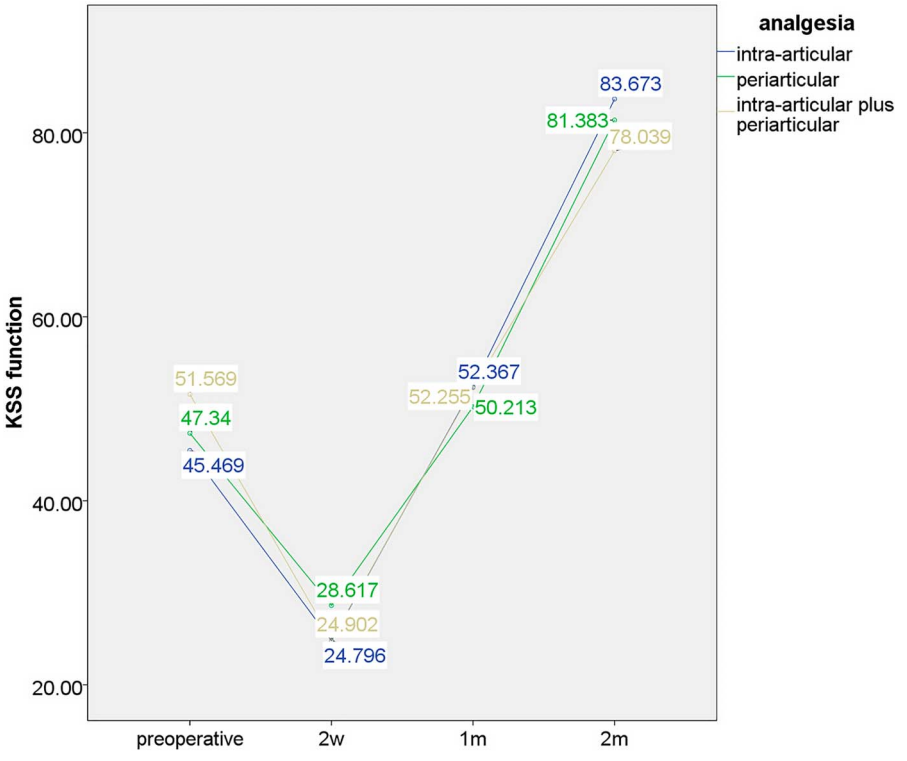

Fig. 2

Mean KSS function subscore within each analgesia group before and after surgery. The groups did not differ significantly at any time point.

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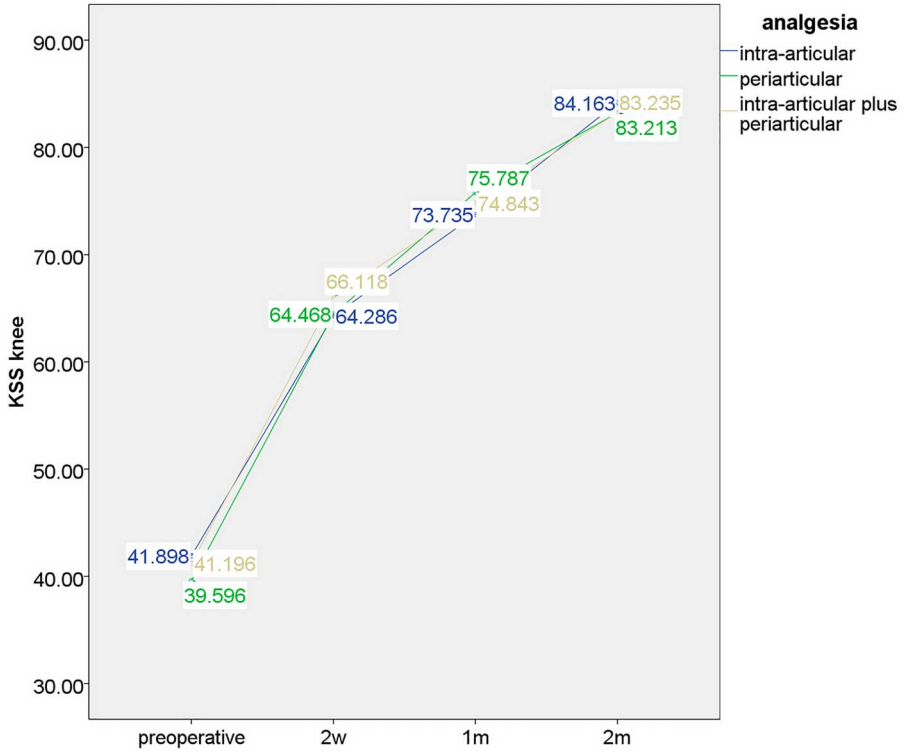

Fig. 3

Mean KSS knee subscore within each analgesia group before and after surgery. The groups did not differ significantly at any time point.

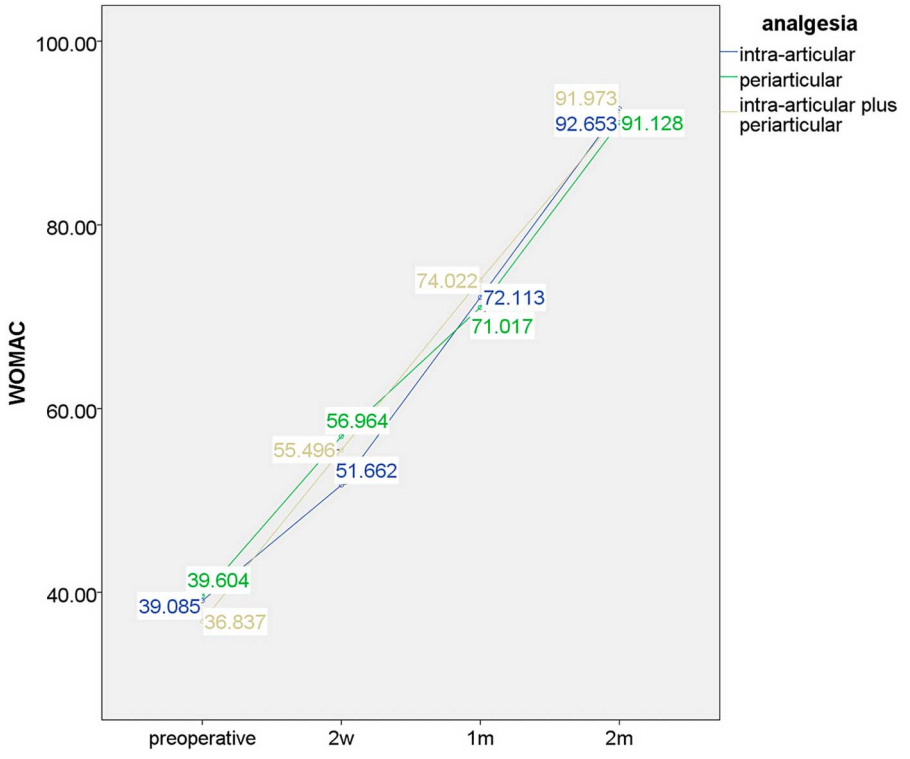

Fig. 4

Mean WOMAC score within each analgesia group before and after surgery. The groups did not differ significantly at any time point.

with venous thrombosis was managed with a therapeutic IV dose of heparin (a 5,000-unit bolus, then 1,300 units per hour) and recovered uneventfully. The 2 patients with wound drainage were both managed with a change in the chemoprophylaxis regimen, wound dressing changes, and immobilization, and the drainage resolved within a week.

Discussion

The most important finding of this study was the overall superior effect of the PA method compared with IA and IA+PA in controlling early postoperative pain. The PA injection was associated with the lowest morphine consumption during hospitalization, and the IA injection was associated with the highest morphine consumption. Overall, the PA group also had significantly greater postoperative active knee flexion than the IA and IA+PA groups. To our knowledge, this is the first clinical trial simultaneously comparing the PA, IA, and IA+PA methods using a similar cocktail composition.

The greatest pain score difference among the 3 analgesic groups was usually at 6 hours after surgery, when the effect of the spinal analgesia had ended but the local analgesic effect of the applied cocktail was still in place. After that, the pain difference among the 3 groups decreased with the passage of time and metabolism of the drugs in the cocktail.

Overall, the PA method was associated with lower morphine consumption and greater postoperative active knee flexion compared with the IA and IA+PA methods. This is in accordance with 2 other studies indicating greater knee flexion and a trend toward lower morphine consumption in the PA group compared with IA[11,13]. The superior analgesic effect of PA is intuitive, as this method does not address the pain receptors in the infrapatellar fat pad or collateral ligaments directly.

Another study also indicated a superior effect of intraoperative PA injection (100 mg) plus incisional injection (10 mg) of bupivacaine compared with either placebo or only PA injection (100 mg) within the first 4 hours following TKA. However, a larger total analgesic cocktail was used in the PA+IA group compared with the PA group in that study, resulting in uncertainty whether the better analgesia in the PA+IA group was due to the larger analgesic dose or different injection method[14].

Contrary to our findings, Jain et al. found the mean pain score, the maximal pain score, and the mean morphine consumption to be similar between the IA and PA injection methods[15]. This discordance may be due to the volume of the cocktail used. Jain et al. used 30 mL of 0.25% bupivacaine, 1;200,000 epinephrine, and 10 mg of morphine for both the PA and IA injections. The smaller volume of cocktail solution used in their study may have limited the amount of analgesic cocktail that could be administered per unit area of the entire exposed periarticular tissue. Most studies supporting the superiority of the PA method used a total volume of >60 mL for the PA injection[9,16,17].

There are a handful of articles disclosing a slight risk of transient peroneal nerve palsy (all of which resolved spontaneously within 48 hours after the surgery) with use of the PA method, with incidences of 0.9%[16], 1.3%[18], and 6.6%[19]. However, in accordance with many other studies of PA[9,20-23] and IA+PA[24-27] methods, we did not have any case of peroneal nerve palsy in either the IA+PA or the PA analgesic group. Avoiding injection near the fibular head may eliminate the potential risk of transient peroneal nerve palsy.

This work has potential limitations. All of our patients underwent TKA because of degenerative knee joint disease. This may limit the generalizability of our results. There was a potential increased risk of complications, including peroneal nerve palsy, with the IA+PA injection compared with IA or PA. Therefore, the same total analgesic dosage was used in the IA+PA, PA, and IA groups to limit this possibility. As the aim of the study was solely to compare the analgesic effect among different injection locations, using a similar analgesic dosage in the 3 groups would also exclude the possible bias resulting from different dosages when comparing pain among the groups. Finally, the difference in morphine consumption might depend not only on the method of analgesia, but also on some other preoperative variables including the patient's weight, height, and recent smoking. However, in this study, the differences in weight, height, and body mass index (BMI) among the IA, PA, and IA+PA groups were not significant (Table I). Also, in accordance with consensus, patients underwent surgery on the condition that they were either nonsmokers or had stopped smoking >1 month before surgery. Furthermore, any patient with inflammatory arthritis was excluded to eliminate any possible bias due to chronic analgesic and corticosteroid use in such patients.

In conclusion, PA was associated with less early postoperative pain and greater active knee flexion compared with the other 2 analgesic options. The better early postoperative pain control with the PA method may be especially relevant for fast-track arthroplasty settings.

Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJSOA/A423). ■

Seyed Mohammad Javad Mortazavi, MD[1]
Farzad Vosoughi, MD[1]
Mirsaeed Yekaninejad, MD[2]
Ehsan Ghadimi, MD[1]
Mohammad Hasan Kaseb, MD[1]
Mohammad Ayati Firoozabadi, MD[1]
Ehsan Fallah, MD[1]
Hesam Toofan, MD[1]
Seyed Khalil Pestehei, MD[3]

[1]Joint Reconstruction Research Center, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran

[2]Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

[3]Department of Anesthesiology, Imam Khomeini Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Email for corresponding author: smjmort@yahoo.com

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