Randomized Controlled Trial

The Use of Combination Paracetamol and Ibuprofen in Postoperative Pain after Total Knee Arthroplasty, a Randomized Controlled Trial

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Background: Adequate pain management has an important role in supporting early ambulation after total knee arthroplasty (TKA). Multimodal analgesia is one of the modalities of overcoming postoperative pain. The use of a combination of paracetamol and ibuprofen is expected to reduce the total morphine requirement after TKA.

Objectives: The use of a combination of paracetamol and ibuprofen to reduce morphine requirement after TKA, to provide adequate pain management and early ambulation.

Study Design: Patients scheduled for total knee arthroplasty who met the requirements for inclusion criteria were consented and randomized using randomizer.org in a 1:1:1 ratio to receive either combination paracetamol iv and ibuprofen iv (Group II), paracetamol iv only (Group II), or ibuprofen iv only (III).

Setting: Thirty-six patients aged 63-68 years who underwent TKA were included in this study.

Methods: All patients were divided into 3 groups. Group I received paracetamol 1 g and ibuprofen 800 mg, group II received 1 g paracetamol iv and 100 mL normal saline, group III received 800 mg ibuprofen iv and 100 mL normal saline, 10 minutes before the end of surgery and every 6 hours up to 24 hours. Total morphine consumption, pain score (resting, walking, knee flexion), and 2 minute-length walking tests were measured in hour 24 postoperative. Data were analyzed with SPSS 16.0.

Results: Median of total morphine consumption between 3 groups respectively was 7.5 (3.0-36.0) mg vs 15.0 (4.5-28.5) mg vs 9.0 (0.0-24.0) mg with no difference ($P = 0.391$). Mean of pain score at walking phase respectively was 4.8 ± 0.5 vs 7.3 ± 1.2 vs 5.6 ± 0.5 (hour 24, $P < 0.01$). Medians of 2-Minute Walking Test respectively were 6.0 (2-16) meters vs 0.0 (0-4) meters vs 0.0 (0-4) meters (hour 24, $P < 0.01$).

Limitations: The total morphine requirement measured in this study illustrates the consumption of morphine in resting phase.

Conclusion: The combination of paracetamol and ibuprofen is better in reducing the total morphine requirement after TKA when compared with the administration of paracetamol injection alone or ibuprofen injection alone. Combination paracetamol injection and ibuprofen injection also provides adequate pain management in order to help early ambulation.

Key words: Multimodal analgesia, paracetamol, ibuprofen, TKA, morphine consumption, pain score

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The number of patients requiring total knee arthroplasty (TKA) increases as the population ages (1). Postoperative pain that arises immediately after the TKA can be very severe and difficult to overcome (2,3). Despite the success of TKA to reduce daily pain and improve the quality of life of patients suffering from osteoarthritis, postoperative pain that arises immediately will increase the risk of complications, including delay in normal functioning, delay in rehabilitation programs, increase in pain threshold levels persistence, and extended hospital stay (3). Effective pain management will increase satisfaction, increase initial mobilization and physiotherapy, resulting in a reduction in heart-lung complications, increased recovery time, improved quality of life, and decreased risk of developing chronic pain syndrome (4,5).

In general, management of postoperative pain in a TKA depends on the use of oral opioids, patient-controlled analgesia, or epidural analgesia (6). These modalities of pain provide very strong analgesic effects but also cause severe side effects (7). In order to increase the effectiveness of postoperative pain management, several management concepts have been developed, including preemptive analgesia, preventive analgesia, and multimodal analgesia. Multimodal analgesia consists of administering 2 or more types of drugs that work with different mechanisms to provide analgesic effects. The main aim of multimodal analgesia is to improve pain management while reducing the need for opioids and also to reduce the side effects that occur due to opioid use (7). The concept of multimodal analgesia refers to the theory that drugs with different analgesic mechanisms may have a synergistic effect in preventing or treating acute pain when administered combined (8). Analgesia modalities that are currently available for postoperative pain management include opioids, local anesthetic techniques, paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase (COX)-2-specific inhibitors, as well as analgesic adjuncts such as steroids, NMDA antagonists, α-2 agonists, and anticonvulsants (9).

Paracetamol and NSAIDs are 2 drugs commonly used as postoperative non-opioid analgesia. Both drugs have been shown to show analgesic effects when given separately, but evidence of the effects of analgesia when given in combination is limited (10,11). In this study, we tested the hypothesis that paracetamol and ibuprofen, when intravenously given in combination, would reduce morphine requirements after total knee arthroplasty, provide adequate pain management and early ambulation.

Methods

Study Design

Patients scheduled for total knee arthroplasty who met the requirements for inclusion criteria (primary OA, age 60-75 years, body mass index 20-30 kg/m^2, and knee varus under 20°) and did not meet any exclusion criteria (impaired cardiac, liver, and/or renal function, patient with history of substance abuse or chronic pain, and patients known to be hypersensitive to any of the components of ibuprofen iv or paracetamol) were consented and randomized using randomizer.org in a 1:1:1 ratio to receive either combination paracetamol iv and ibuprofen iv (Group 1), paracetamol iv only (Group 2), or ibuprofen iv only (Group 3) (Table 1).

Patients in group 1 received a combination of 1000 mg paracetamol iv and 800 mg ibuprofen iv at the end of the surgery, followed by 1000 mg paracetamol iv and 800 mg ibuprofen iv every 6 hours up to 24 hours. Patients in group 2 received 1000 mg paracetamol iv at the end of surgery followed by 1000 mg paracetamol iv every 6 hours up to 24 hours. Patients in group 3 received 800 mg ibuprofen iv at the end of surgery followed by 800 mg ibuprofen every 6 hours up to 24 hours. All patients had spinal regional anesthesia using 15-20 mg bupivacaine 5%; the procedure was done by an anesthesiologist. Two orthopedic surgeons competent in arthroplasty completed the TKA, and the average length of the surgical procedure was approximately 90 minutes. Data collected for every patient was recorded in the patient's medical chart as part of their standard medical care. Patient enrollment, data collection, and analysis were completed within one year. This study was approved by the ethical committee at the Faculty of Medicine institution, number 1115/UN2.F1/ETIK/2018 and registered on Clinicaltrial.gov NCT04414995.

Analysis and Methods

Sample size calculations were completed using the 2 means equation in the Power and Sample Size Calculation program (12). Mean and standard deviation of pain score at rest (12 - 24 hours) from a previously completed study were used to calculate the sample size (13). The mean difference between the study and control group was 2.49, and the detectable difference for pain was set at 2.8. Two-tailed hypothesis testing con-

cluded that each group needed 12 patients to achieve a power of 80%, with an error rate of 5%, and therefore a total of 36 patients were scheduled for enrollment in this study.

The effectiveness combination of ibuprofen and paracetamol compared to ibuprofen alone and paracetamol alone was demonstrated by measuring opioid requirements delivered by patient-controlled analgesia morphine for 24 hours (primary endpoint). Secondary endpoints include patients' self-assessment of pain intensity using a numeric rating scale pain score (at rest, while walking, and at full knee flexion), early ambulation using 2-minute walking test (2MWT) at hour 24 postoperative (Table 2). The study investigators prepared and maintained adequate and accurate case report forms (CRF) of the study data obtained from the medical charts. Blinded data were then entered and analyzed in a password-protected computer database.

Statistical Analysis

Data entry and analysis were performed with SPSS Version 20.0 (IBM Corporation, Armonk, NY). Demographic and patient characteristics were obtained for all enrolled patients. Mean and standard deviation (SD) were obtained for age and body mass index. The number of observations was obtained for gender. The data were analyzed using the Anova One Way test. *P* values and 95% confidence interval (CI) were obtained to report any statistically significant differences. Comparison between groups and opioid requirements at hours 24 were made with Kruskal Wallis test. Median (minimum-maximum) *P* values were reported. Comparisons between groups and pain scores (at rest, walking, and full knee flexion) were made with the Anova One Way test. Mean (SD), 95% CI, *P* values, and post hoc Bonferoni test were reported. Comparisons between groups and 2MWT were made with the Kruskal Wallis test. Median (minimum-maximum), *P* values, and post hoc Mann Whitney test were reported. Statistical significance was set at 0.05.

Results

The study was completed over the course of 8 months at 2 major university public hospitals. A total of 36 patients were enrolled, and 12 patients were randomized into each treatment group; all patients completed all acceptable study procedures and were included in the analysis.

Demographic and patient characteristics of the study population are presented in Table 1. There was no significant difference observed between groups in terms of age and body mass index; 30 were female patients with the age range of 63-67 years. The body mass index of individuals included in the study was dominant in individuals with excess body weight.

Statistically, this study showed no significant difference in the median total morphine consumption between the 3 study groups (Table 3). However, when compared with the median of each group, this study showed that the median total morphine consumption was lowest in Group I (median 7.5 mg). There was no adverse event related to opioid recorded.

A statistically significant difference was seen in the comparison of 2MWT tests in the 3 study groups. Clinically, it appears that the 2MWT test in the group given combination paracetamol-ibuprofen shows better results compared to the group that was given paracetamol only or ibuprofen only.

Discussion

Management of postoperative pain using multimodal analgesia aims to prevent delays in the recovery period and accelerate early ambulation. Multimodal analgesia involves the use of a combination of drugs that work synergistically through different mechanisms of action to prevent and manage pain (8). The main goal of multimodal analgesia is to improve pain management while reducing the need for opioids and reduce the side effects that occur due to the use of high-dose opioid (7).

This study shows that the administration of mul-

Table 1. *Patient characteristic of study population.*

	Group 1	Group 2	Group 3	P*
Gender Male Female	 1 11	 2 10	 3 9	
Age (years)	65.8 ± 4.7	63.5 ± 9.3	67.0 ± 5.7	0.449
Body mass index (kg/m^2)	27.2 ± 3.8	26.0 ± 2.9	26.2 ± 3.2	0.642

* ANOVA One Way test

Table 2. *Numeric rating scale walking and 2-minute walking test length comparison at hours 24 postoperative significance.*

	Group 1 vs Group 2	Group 1 vs Group 3	Group 2 vs Group 3
NRS Walking [c]	< 0.001	0.204	< 0.001
2MWT [d]	< 0.001	< 0.001	1.000

c post-hoc Bonferoni test, *P* significant < 0.05
d post-hoc Mann Whitney, *P* significant < 0.05

Table 3. *Comparisons: opioids requirement, pain score, and 2-minute walking test at hours 24 postoperative.*

	Group 1	Group 2	Group 3	*P*
Opioid requirements at hours 24 post-operative, mg	7.5 (30-36.0)	15.0 (4.5-28.5)	9.0 (0.0-24.0)	0.391 [a]
NRS				
Rest	2.7 ± 1.0	2.0 ± 0.0	2.2 ± 0.5	0.089 [b]
Walking	4.8 ± 0.5	7.3 ± 1.2	5.6 ± 0.5	< 0.001 [b]
Knee full flexion	6.5 ± 1.1	7.2 ± 0.6	7.3 ± 2.0	0.320 [b]
2MWT, meters	6.0 (2-16)	0.0 (0-4)	0.0 (0-4)	< 0.001 [a]

a Kruskal Wallis test, *P* significant < 0.05
b ANOVA One Way test, *P* significant < 0.05

timodal analgesia in combination with paracetamol and ibuprofen did not show statistically significant differences when compared to the administration of paracetamol or ibuprofen. However, when compared using the median value, the group that received the paracetamol-ibuprofen combination showed the lowest total requirement when compared to the group that received paracetamol only or ibuprofen only.

Lamplot et al (14) showed a total daily dose of morphine of 40.5 ± 12.7 mg was required in the first 24 hours of surgery for a control group that used morphine only for analgesia. In a randomized clinical study conducted by Gupta et al (13) which compared the total morphine consumption via PCA morphine within 120 hours duration, the total morphine consumption in the group of patients given the paracetamol-ibuprofen combination was lower when compared to the group given ibuprofen only ($P < 0.001$). A Thybo et al (15) publication of multimodal analgesia in patients undergoing total hip arthroplasty procedures showed a decrease in morphine consumption in patients given a combination of oral paracetamol and oral ibuprofen in the first 24 hours postoperatively.

Paracetamol works on the central nervous system, although the mechanism of action is still controversial. Based on several papers, it works through inhibition of prostaglandin production and activation of the serotonergic pathway, and as an indirect cannabinomimetic (16-19). Ibuprofen causes reversible, nonselective inhibition of the COX-1 and COX-2 enzymes and prevents sensitization of pain receptors at the site of injury (20-22). The use of a combination of paracetamol and ibuprofen, which works at 2 different pain induction locations, is expected to improve the ability of adequate pain management.

This study used paracetamol and ibuprofen in injection dosage forms. The administration of 1000 mg of intravenous acetaminophen rapidly increases plasma concentration and results in higher peak concentrations than 1000 mg oral acetaminophen (23-25). Administration of intravenous ibuprofen results in a maximum plasma concentration (C-max) which is twice the oral dose, and the time required to reach C-max (t-max) is much faster than the oral dose (26). The administration of paracetamol and ibuprofen in injection dosage forms is expected to accelerate the start of analgesia faster and more effectively than using oral dosage forms.

This study uses a numeric rating scale (NRS) to assess the pain scale. This pain scale is interpreted at intervals of 0 (no pain), 1-3 (mild pain), 4-6 (moderate pain), 7-10 (severe pain). The results of the NRS assessment of the walking phase of this study show there are statistically significant differences when administering a combination of paracetamol and ibuprofen compared to administering paracetamol only or ibuprofen only. Clinically, the mean NRS results in the group given the combination of paracetamol-ibuprofen and the group given ibuprofen only showed a scale of 4-6 (moderate pain). This result is different from the group given paracetamol only, with a scale of 7-8 (severe pain).

Ong et al (27) displayed data showing multimodal analgesia with a combination of oral paracetamol and oral NSAIDS can provide a superior analgesic effect when compared with unimodal analgesia. Gupta et al (13) assessed the pain scale using VAS; on the third postoperative day, the group that received the iv combination of paracetamol-ibuprofen showed a lower pain scale compared to the group that got iv ibuprofen only ($P = 0.002$). The results of pain assessment using NRS walking phase and knee flexion in this study indicate that the administration of a combination of paracetamol-ibuprofen is more adequate in the management of pain compared to those given paracetamol only or ibuprofen only.

This study used 2MWT at postoperative hour-24 to evaluate patient ambulatory. The 2MWT is a performance-based test that evaluates postoperative recovery (28). The results showed that there were statistically significant differences in the comparison of 2MWT between individuals who received the paracetamol-ibuprofen combination, compared with those who received only paracetamol or ibuprofen. Significant differences in these 3 groups indicate that the administration of the paracetamol and ibuprofen

can help patients begin early ambulation to speed up the recovery period after TKA.

Yakkanti et al (29) show that early ambulation after TKA surgery significantly reduces the length of stay. Lamplot et al (14) in multimodal pain management studies using parameters of the development of physical therapy (lifting limbs, rising from bed, walking with assistance > 50 ft, walking without assistance > 50 ft, climbing stairs) to assess the speed of recovery of patients after TKR surgery, showed that groups of patients with multimodal administration analgesia recovers faster and activates earlier than the group of patients who use PCA hydromorphone only ($P < 0.01$). Our research shows that patients who experience an adequate pain management effect from the administration of the paracetamol-ibuprofen combination are helped with early ambulation.

Limitation

The limitation of this study is that morphine PCA was used limited to the first 24 hours postoperatively when the patients lay in bed with limited movement. At hour-24, PCA morphine was stopped, the patient was then asked to walk and bend the knee, so the total morphine requirement measured in this study illustrates the consumption of morphine in the resting phase. Further research is needed to assess the total requirement of morphine at 48 hours and 72 hours with a measured activity program to assess the combination of paracetamol-ibuprofen at the time of activity.

Conclusion

The combination of paracetamol and ibuprofen is clinically better in reducing the requirement of morphine and providing adequate pain management to help early ambulation after TKA when compared with the administration of paracetamol only or ibuprofen only.

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