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Efficacy of repeated administration of intravenous acetaminophen for pain management after total knee arthroplasty

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Intravenous acetaminophen is an integral component of multimodal postoperative pain management. This prospective study aims to assess the efficacy of the repeated administration of intravenous acetaminophen and the impact on postoperative patient satisfaction with postoperative pain management after total knee arthroplasty (TKA). We enrolled 98 patients scheduled for unilateral TKA. Patients were randomly assigned to receive either 1000 mg of intravenous acetaminophen at 6-hour intervals (AAP group) or not to receive intravenous acetaminophen (control group). All patients underwent single-shot femoral nerve block after general anesthesia, as well as intraoperative periarticular infiltration of analgesia prior to implantation. The primary outcome was the postoperative numerical rating scale (NRS) pain score at rest. The NRS score was measured just before the administration of study drugs, immediately after arrival in the ward (time 0), and at 6, 12, 18, 24, and 48 h (time 1 to time 5, respectively) postoperatively. We also evaluated the mean doses of rescue opioid use for 24 h postoperatively. At time 5, the AAP group had significantly improved mean NRS score than controls (3.0 vs. 4.0; $P < 0.01$). Rescue opioid use was significantly lower in the AAP group for 24 hours compared to controls (0.3 µg vs. 0.9 µg; $P < 0.01$). Repeated intravenous acetaminophen administration after TKA may provide better analgesia and reduce opioid use.

Keywords: acetaminophen, postoperative pain, knee, arthroplasty.

INTRODUCTION

Total knee arthroplasty (TKA) is the world standard procedure for relieving pain and restoring function. However, in questionnaire-based evaluations of patient satisfaction regarding the outcomes of hip and knee arthroplasty, patients undergoing primary TKA reported inferior outcomes compared to those undergoing primary total hip arthroplasty[1]. Furthermore, around 65-100% (median: 88.9%) of patients were satisfied with TKA, with most patients reporting >80% satisfaction[2].

The previously reported factors affecting patient satisfaction after TKA include sex, age, high preoperative expectations, and postoperative alignment[3]. Moreover, chronic pain following TKA is thought to affect postoperative satisfaction[4]. Instability, malrotation of the tibial or femoral components, impingement of the popliteus tendon, and central sensitization are some of the reasons for chronic pain following TKA[5,6]. And the intensity of early postoperative pain should also be managed because it was found to increase the risk of chronic pain after TKA[5,7].

The current options for controlling early postoperative pain in TKA include preoperative femoral nerve block[8,9,10], intraoperative infiltration with local anesthetic[11,12], and repeated administration of intravenous acetaminophen[13,14,15]. However, there is a paucity of information regarding the efficacy of repeated administration of intravenous acetaminophen in Japanese patients[15], and its impact on the satisfaction of patients undergoing primary TKA remains unknown. Therefore, this prospective study aimed to evaluate the efficacy of repeated administration of intravenous acetaminophen and the impact on postoperative patient satisfaction with postoperative pain management in Japanese patients.

MATERIAL AND METHODS

This was a single-center, randomized, single-blinded controlled clinical trial which assesses the efficacy of repeated intravenous acetaminophen in patients undergoing unilateral TKA under general anesthesia. This study received approval from the Institutional Review Board prior to patient recruitment. All patients gave written informed consent to be included in the study. Before participant enrolment, the trial was registered as a randomized control trial titled "Efficacy and Safety of repeated administration of intravenous acetaminophen injection for pain management after total knee arthroplasty" with the University Hospital Medical Information Network (registration number UMIN 000031692). All TKA surgeries were completed by two orthopedic surgeons. Data was then collected by nursing staff.

All patients underwent single-shot femoral nerve block after general anesthesia and intraoperative periarticular infiltration of analgesia prior to implantation. Levobupivacaine hydrochloride was used in the femoral nerve block (50 mg injection) and in the periarticular infiltration of analgesia (150 mg pericapsular injection). All patients received intravenous patient-controlled analgesia with fentanyl at an underlying infusion rate of 0.3 μg/kg/h, and a bolus dose of 5 or 10 μg (a lockout time of 5 or 10 min) for up to 24 h postoperatively. As additional rescue analgesia, non-steroidal anti-inflammatory drugs (NSAIDS; 50 mg flurbiprofen axetil, 25 mg diclofenac sodium suppository, and 60 mg loxoprofen sodium) were administered intravenously starting the day after surgery. In addition, 400 mg/day celecoxib and 3000 mg/day acetaminophen were routinely administered orally for 7 days after TKA, followed by 200 mg/day of oral celecoxib for 7 additional days.

Two surgeons performed all surgeries. All patients received a cemented prosthesis. Postoperative rehabilitation was started from the day after surgery in both groups.

Male and female patients 20 years of age or older undergoing unilateral TKA under general anesthesia were eligible for this study. Eligible patients gave written informed consent. The exclusion criteria were as follows: 1) those who had an American Society of Anesthesiologists physical status IV or higher; 2) those who were scheduled for simultaneous bilateral TKA, additional procedures, or revision procedures; 3) those who were allergic to medications included in the standard postoperative protocol; 4) those who had renal insufficiency and a history of liver disease; and 5) those with known allergy/hypersensitivity to acetaminophen or celecoxib.

A total of 98 eligible subjects were randomized to two groups using a computerized random number generator prior to their surgery. The intravenous acetaminophen group (AAP group, n = 49) received repeated 1000 mg intravenous acetaminophen. In the AAP group, 1000 mg acetaminophen was administered intravenously (with an exception for patients under 50 kg, who were given 15 mg/kg) immediately after returning to the ward and every 6 hours thereafter on the day of the TKA. The control group (n = 49) did not receive intravenous acetaminophen. The medications were prepared by the nursing staff for each subject based on group randomization, and these were also administered by the nursing staff after admission in the hospital ward. We ensured that the patients were blinded to the group assignment during the study period.

The primary outcome was the postoperative numerical rating scale (NRS) pain score at rest. The NRS score ranges from 0 to 10 (indicating no pain to extreme pain). The NRS score was measured just before the administration of study drugs, immediately after arrival in the ward (time 0), and at 6, 12, 18, 24, and 48 h postoperatively (time 1 to time 5, respectively). The secondary outcome was the patients' postoperative satisfaction at 24 h, 48 h, which was assessed by asking them to grade their level of satisfaction (i.e.,., very dissatisfied, dissatisfied, neutral, satisfied, or very satisfied) and using the visual analog scale (VSA). The VAS score ranges from 0 to 100 (i.e., very dissatisfied to very satisfied). The use of rescue analgesia was recorded immediately after returning to the ward and within 48 h postoperatively. We determined the number of actual doses of rescue analgesia (i.e., opioids and NSAIDs) administered and the number of patient requests for it. Postoperative pain

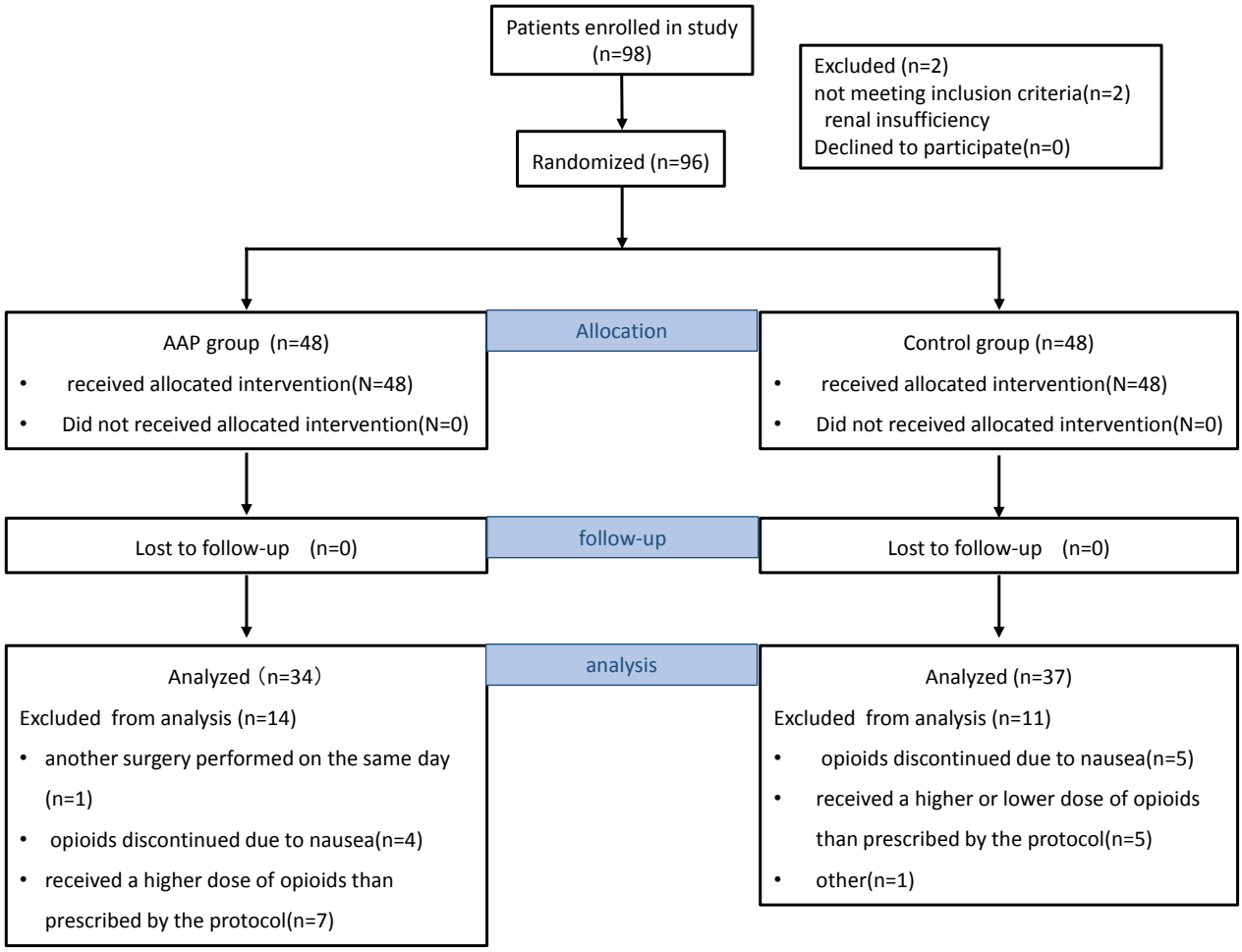

Fig. 1 — Patient recruitment and analysis.

scores, satisfaction scores, drug administration, and dosing of all medications were recorded by the nursing staff. Any complications occurring during the course of the trial were recorded with particular emphasis on impaired liver function defined as transaminase level twice upper limit[16]. Routine laboratory testing was performed 1, 4 and 7 days after TKA.

Comparisons between the study groups were performed using the Wilcoxon sum rank test for continuous variables and chi-square test for categorical variables. All tests were two-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using the JMP ver 14.0 software (Tokyo, Japan).

This study was conducted in accordance with the Declaration of Helsinki and was approved by our Institutional Review Board. Informed consent was obtained from all patients included in the study.

RESULTS

A total of 98 TKAs during the study period were eligible for inclusion in the study. The flowchart presented in Figure 1 outlines the trial. After 2 TKAs were excluded, the remaining 96 TKAs were randomly assigned to either the AAP group or the control group. In the AAP group and control group, respectively, 14 and 11 patients were excluded due to the following reasons: the patient had a different surgery performed on the same day (AAP group, n = 1), the patient had opioids discontinued due to nausea and postoperative delirium within 24 hours (AAP group, n = 4; control group, n = 5), and the patient received a higher or lower dose of opioids than prescribed by the protocol (AAP group, n = 7; control group, n = 6). Baseline patient demographics including age, body mass index, gender, diagnosis, range of motion, pain VAS and

Table I. — Baseline data of AAP and control groups

	AAP(n=34)	Control (n=37)	*P* value
Age, mean (SD)	73.3 (7.9)	74.3 (7.6)	0.773
Female, n (%)	31 (77.5)	15 (71.4)	0.600
Height and weight, mean (SD)			
Weight (kg)	59.2 (11.6)	57.7 (10.4)	0.865
Height (cm)	152.5 (8.6)	150.9 (9.3)	0.525
BMI (kg/m^2)	25.3 (4.0)	25.2 (3.5)	
Weight<50 kg, n (%)	9 (22.5)	4 (19)	0.754
Diagnosis			
OA/RA, n (%)	34 (85.0)/6 (15.0)	20 (95.2)/1 (4.8)	0.233
Preoperative pain VAS, mean (SD)	55.3 (31.9)	64.6 (25.9)	0.273
Preoperative flexion angle, mean (SD)	119.6 (13.9)	111 (9.0)	0.037
Preoperative extension angle, mean (SD)	-8.9 (8.4)	-13.6 (15.9)	0.570
AAP; acetaminophen, SD; Standard Deviation, BMI; body mass index, OA; osteoarthritis, RA; rheumatoid arthritis.			

Table II. — Numerical rating scale pain score at rest

	AAP group (n=34) Mean (SD)	Control group (n=37) Mean (SD)	*P* value
time 0	4.0 (3.2)	3.4 (3.1)	0.499
time 1 6h	3.0 (3.0)	3.4 (2.9)	0.568
time 2 12h	3.1 (3.0)	3.9(2.8)	0.265
time 3 18h	3.5 (2.9)	4.6 (3.3)	0.163
time 4 24h	3.8 (2.2)	4.3 (2.8)	0.574
time 5 48h	3.0(1.7)	4.0(2.3)	0.034*
*significant, AAP: acetaminophen, SD: Standard Deviation.			

Table III. — Patient satisfaction

	AAP group (n=34) Mean (SD) or %(n)	Control group (n=37) Mean (SD) or %	*P* value
Satisfied' or 'very satisfied			
24h (%)	58.1 (18)	50 (18)	0.625
48h (%)	70.6 (24)	66.7 (24)	0.800
Vas(0-100mm)			
24h	71.5(19.2)	63.6 (26.7)	0.318
48h	76.9 (19.2)	73.9 (21.3)	0.763
AAP: acetaminophen, SD: Standard Deviation.			

preoperative alignment were similar across both groups (Table I).

Primary Outcome

The mean NRS scores at time 0, 1, 2, 3, and 4 were not significantly different between the AAP and control groups. However, the APP group had significantly improved mean NRS scores at time 5 compared to the control group (Table II).

Secondary Outcome

The AAP and control groups had no significant differences in VAS score as well as in the number of patients who reported being "satisfied" and "very satisfied" (Table III). However, the AAP group had a significant decrease in the use of rescue analgesia and in the number of patients who requested rescue analgesia. Furthermore, rescue opioid use within 24 hours was significantly lower

Table IV. — Rescue analgesia

	AAP group (n=34) Mean (SD) or %(n)	Control group (n=37) Mean (SD) or %	*P* value
Mean number of rescue analgesia			
0-24h	0.8 (1.4)	2.3 (2.5)	0.001*
0-48h	0.9 (1.5)	2.5 (2.5)	0.002*
Number of patients requested rescue analgesia			
0-24h (%)	29.4 (10)	70.3 (26)	0.001*
0-48h (%)	38.2 (13)	73.0 (27)	0.003*
Rescue opioid consumption			
0-24h (µg)	0.3 (0.6)	0.9 (1.2)	0.012*
AAP: acetaminophen, SD: Standard Deviation.			

Table V. — Complications

	AAP group (n=34) % (n)	Control group (n=37) %(n)	*P* value
Impaired liver function	88.2 (4)	73 (10)	0.106
Infection			
superficial	0 (0)	0 (0)	1.000
deep	1 (2.9)	2 (5.4)	0.606
Transient peroneal nerve palsy	0 (0)	0 (0)	1.000
AAP: acetaminophen.			

in the AAP group compared to the control group (Table IV).

There was no significant difference in the incidence of complications such as liver dysfunction between the two groups. Liver function was restored without treatment in all cases (Table V).

DISCUSSION

Our study demonstrates that the pain scores at 48h postoperatively, the use of rescue analgesia, the number of patients who requested rescue analgesia, and rescue opioid use were all significantly lower in the AAP group versus controls after TKA treated with multimodal pain management. Although these findings did not achieve statistical significance in this cohort, postoperative pain scores at 24 h postoperatively were lower in the AAP group compared to controls. It is important to manage early postoperative pain, because its intensity is directly related to the risk of developing postsurgical chronic pain after TKA[7].

In recent years, multimodal pain management strategies after TKA have become widespread because uncontrolled postoperative pain has many deleterious effects, including on the incidence of deep venous thrombosis, on the effectiveness of rehabilitation programs for early recovery of function, and on the number of patients who seek total joint arthroplasty[12]. Intravenous acetaminophen produces a much higher plasma drug concentration compared to oral administration[14], making it useful for postoperative pain management, especially after elective major orthopedic surgery[16]. There have been several reports on the use of acetaminophen for acute postoperative pain in TKA[13,15,17-19]. For instance, Kelly et al.[17] reported that intravenous acetaminophen did not significantly decrease postoperative opioid use, but their analysis included procedures other than primary TKA, such as total knee revisions. Nwagbologu et al.[19] and O'Neal et al.[15] also reported no significant differences in opioid use, but in these studies, acetaminophen was only given as a single dose of 1000 mg. In contrast, repeated administration of

1000 mg intravenous acetaminophen injection has been reported to provide effective analgesia and reduce opioid requirements[13,18]. These findings are likely because the effect of acetaminophen is dose-dependent. Repeated intravenous infusion of acetaminophen has been shown to be effective, with significantly higher pain relief scores at 6 h compared to placebo[16].

In our study, postoperative pain scores were significantly lower in the AAP group, and rescue opioid use was also significantly lower for 24 hours in the AAP group compared to controls. We believe that repeated intravenous acetaminophen administration after TKA may provide better analgesia and reduce opioid use. Although opioids are useful for postoperative pain, they are associated with adverse events such as nausea, vomiting, and respiratory depression. Furthermore, even short-term infusion may cause hyperalgesia around the surgical site on withdrawal[21].

In the present study, rescue opioid use was significantly decreased in the AAP group. Although the results of this study did not prove that repeated administration of intravenous acetaminophen affects patient satisfaction in the early postoperative period, we believe that this can still reduce acute postoperative pain. Decreasing opioid use may be significant in the prevention of persistent postoperative pain.

Our prospective study has some limitations. First, we did not administer intravenous normal saline as a placebo. This is a major limitation, and we cannot deny that it may have influenced the results. Second, an intravenous dose of 15 mg/kg acetaminophen was used for patients with body weight <50 kg, in accordance with the Japanese dosage guidelines. However, we believe its influence on pain score was small, considering the age, weight, and number of patients with body weight <50 kg. Nevertheless, we suggest that repeated administration of intravenous acetaminophen plays a role as part of multimodal postoperative pain management for TKA.

CONCLUSION

In conclusion, repeated intravenous acetaminophen administration after TKA may provide better analgesia and reduce opioid use.

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