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Reduction of Postoperative Pain by Addition of Intravenous Acetaminophen after Total Hip Arthroplasty: A Retrospective Cohort Study

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We evaluated the analgesic effects of multimodal pain control in which intravenous acetaminophen (IV APAP) was added to the standard protocol for Japanese patients who had undergone a total hip arthroplasty (THA). We performed a retrospective cohort study of 180 patients aged 66.4 ± 10.5 years (30% male) who had undergone a THA (Oct. 2014 to Feb. 2015) at our hospital. The control patients were administered the standard analgesic protocol: flurbiprofen axetil as a continuous intravenous infusion and oral celecoxib (NAPAP; n = 109). The patients in the new analgesic protocol group received IV APAP in addition to the standard analgesic protocol (APAP; n = 71). The primary outcome was the maximum value of postoperative pain the patients reported on a numerical rating scale (NRS) during the first 24 h post-surgery. A univariate analysis and multivariate analyses adjusted for age, sex, the stage of hip osteoarthritis, preoperative pain, and surgical time showed that the maximum postoperative pain NRS scores during the first 24 h after surgery was significantly lower when the APAP protocol was used. The addition of IV APAP to the current standard multimodal analgesia protocol for Japanese patients who have undergone a THA may decrease the patients' postoperative pain.

Key words: intravenous acetaminophen, postoperative pain, total hip arthroplasty, osteoarthritis

Postoperative pain control is important for patients who have undergone a total hip arthroplasty (THA). Poor postoperative pain control increases the risk of postoperative comorbidities, delaying physical therapy and prolonging hospitalization [1-4]. Moreover, poor control of acute postoperative pain can lead to the development of chronic pain [1]. The American Society of Anesthesiologists (ASA) recommends the multimodal control of postoperative pain, and the ASA presented guidelines on the management of postoperative pain [5]. Various analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs), opioids, local anesthesia, and acetaminophen are useful for multimodal analgesia, and they can reduce the amount of analgesics used as well as the risk of adverse events. This allows physicians to implement safe, high-quality pain management to patients in the perioperative period [6-8]. However, NSAIDs increase the incidence of digestive symptoms, and opioids are associated with adverse effects such as nausea and vomiting, pruritus, anuresis, massive sedation, respiratory failure, and ileus [9, 10].

Acetaminophen is used for patients (from children to the elderly) who have symptoms of pain or fever. Oral and suppository versions of acetaminophen are

commercially available in Japan. With differing levels of pain or fever, patients may have difficulty using such oral or suppository agents, and intravenous acetaminophen (IV APAP) offers a new option for such patients; it is considered a helpful agent for pain management. IV APAP has been commercially available since 2002 in the U.S., and has been introduced in 80 countries worldwide. The Japanese Ministry of Health, Labor, and Welfare approved IV APAP as a commercial agent in 2013.

The administration of IV APAP in the perioperative period of orthopedic surgery, including THA, decreases the patient's postoperative pain, length of stay, and hospitalization costs, as it reaches higher blood levels more rapidly compared to other formulations [3,4,11-16]. The use of IV APAP also reduces the amount of opioids and other rescue agents used [17-20]. However, most of these previous studies were of Western patient populations, and no studies have evaluated the postoperative effects of IV APAP in Japanese patients. We conducted the present study to compare the effects of postoperative analgesia and the risk of adverse events in the postoperative period for Japanese patients receiving multimodal pain control with and without IV APAP. We also investigated whether the analgesic effect of IV APAP was dependent on the severity of hip osteoarthritis (OA).

Patients and Methods

Study design and settings.   This study was conducted in accord with the Declaration of Helsinki and approved by the Ethics Committee of our hospital (approval no. 2015-04-15). Formal patient consent was not required for this retrospective study.

We performed a retrospective cohort study to evaluate that IV APAP in addition to the standard analgesic protocol would be more effective than the standard analgesic protocol. Patients who had undergone a THA on one side during the period from October 2014 to February 2015 at Saga University Hospital were included in this study. We excluded the cases of the patients who had any pain in any other part of the body, hepatic or renal disorders, psychiatric disorders, or drug dependence; patients who had taken an NSAID in the 12 h before surgery, or were administered any analgesic agent during the operation or had a severe consciousness disturbance during the postoperative period.

THA and postoperative analgesic protocols.   All patients were prescribed rilmazafone hydrochloride hydrate (Rhythmy®; Kyowa Pharmaceutical, Osaka, Japan) 2 mg as premedication at bedtime on the day prior to surgery, and all received lactate Ringer's solution (Lactec® Injection; Otsuka Pharmaceutical, Tokyo) intravenously when entering the operating room. Each THA was performed under spinal anesthesia. The spinal anesthesia was induced using a standard technique: 0.5% isobaric bupivacaine was administered in a single shot using a 27-G pencil-type spinal needle at the L3-L4 vertebral level. Some patients were received midazolam (2-3 mg IV) for conscious sedation. All patients received multimodal analgesia after the completion of surgery.

Our hospital officially adopted the use of IV APAP in November 2014. In January 2015, we implemented a new pain management protocol in which IV APAP was added to the existing pain management protocol. Patients who had undergone a THA during the period from October to December 2014 were administered flurbiprofen axetil (Ropion®; Kaken Seiyaku, Tokyo) 50 mg as a continuous intravenous infusion and celecoxib (Celecox®; Astellas Pharma, Tokyo) 400 mg per day orally, as the standard analgesic protocol. We defined these patients as the control group (NAPAP group).

The patients who comprised the new analgesic protocol group (*i.e.*, the APAP group who underwent a THA in January-February 2015) received IV APAP (Acelio® Intravenous Injection; Terumo, Tokyo) at 1,000 mg for patients with body weights ≥ 50 kg and 15 mg/dl for patients with body weights < 50 kg as an intravenous infusion every 6 h within the first 24 h after surgery, in addition to the existing analgesic protocol.

When a patient in either the NAPAP or APAP group required one or more additional analgesic agents for postoperative pain, he or she was administered diclofenac sodium (Voltaren® SUPPO®; Novartis Pharma, Tokyo) 50 mg, or acetaminophen (Calonal® Tablet; Ayumi Pharmaceutical, Tokyo) 200 mg rectally, or pentazocine (Sosegon® Injection; Maruishi Pharmaceutical, Tokyo) 15 mg intravenously as rescue drugs.

Data collection and outcomes.   We reviewed the patients' electronic medical charts to obtain data including the patient's age, sex, and body mass index (BMI) at the time of surgery. Laboratory and imaging test data such as the complete blood count, differential

leukocyte count, liver and renal function parameters, and X-ray findings of the hip joint were also collected. The severity of OA was graded using the Japanese Orthopedic Association criteria as follows: stage 1 (pre-OA stage), no osteoarthritic change; stage 2 (initial stage), slight narrowing of the joint space associated with sclerosis of the subchondral bone; stage 3 (advanced stage), narrowing of the joint space with cystic radiolucencies and small osteophytes; and stage 4 (end stage), almost no joint space and marked osteophyte formation [21, 22]. The surgical time, anesthesia procedure, anesthetic agents, and analgesic agents administered during the operation were recorded.

Each patient's postoperative consciousness level was measured using the Japan Coma Scale [23] immediately after surgery. The intensity of each patient's postoperative pain was measured with the use of a self-reported numerical rating scale (NRS); this was an 11-level scale with 0 = no pain, to 10 = worst pain imaginable [24]. The postoperative pain NRS score was measured by nurses at 0, 1, 6, and 24 h after surgery while the patient was at rest, and the scores were recorded on the patient's electronic medical chart. The postoperative pain NRS score at the time when a patient used rescue analgesic drugs was also recorded, as were the names and amounts of such drugs required, in the electronic medical charts. Lumbar pain NRS scores were determined in a similar manner. When the patient asked for a rescue analgesic due to postoperative pain, the patient's physician selected the type and amount of the rescue analgesic (*e.g.*, diclofenac sodium 50 mg) and administered it.

The primary outcome of this study was the maximum postoperative pain NRS score during the first 24 h post-surgery, In our research protocol, we planned to use the pain NRS scores measured at 0, 1, 6, 24 h after surgery and at the time that patients requested rescue analgesic drugs for their postoperative pain for our analysis. However, the pain NRS scores at those time points were often missing from the medical chart review and could not be used for analysis. We therefore used the maximum postoperative pain NRS score within 24 h after surgery from the medical chart review as the primary endpoint for our analysis.

Secondary outcomes were the maximum lumbar pain NRS score, the frequency of nurse calls, and the administration of analgesic rescue agents. The incidence of postoperative nausea or vomiting (PONV) was recorded as an adverse event. We defined PONV as postoperative nausea or vomiting during the first 24 h post-surgery.

Statistical analysis. We evaluated the characteristics of the NAPAP and APAP groups before surgery: age, sex, hip joint and lumbar pain NRS scores, analgesic medication, hip joint x-ray findings, diagnoses of hip pain, laboratory data, surgical time, and total amount of perioperative bleeding. We compared these parameters between the groups using the chi-square test or Fisher's exact test for categorical variables. For continuous variables, we used Student's *t*-test or the Mann-Whitney *U*-test to analyze numerical data. We also used the Mann-Whitney *U*-test to compare the maximum postoperative and lumbar pain NRS scores in the first 24 h after surgery, the frequency of nurse calls, and the use of rescue drugs. We performed a logistic regression analysis to calculate the odds ratio of the incidence of PONV. Multiple linear regression analyses were conducted to examine the differences in outcomes, the maximum postoperative pain NRS score, the postoperative lumbar pain NRS score, the frequency of using rescue drug and nurse calls between the APAP and NAPAP groups, with the patient's sex, age, severity of hip OA, and surgical time as other explanatory variables [25, 26]. We also performed sub-group analyses that were based on the severity of hip OA prior to surgery. We defined patients with pre-OA, initial OA or the advanced stage of OA as the mild-stage OA group, and the patients with end-stage OA as the severe-stage OA group. All statistical analyses were performed using Stata MP for Macintosh, ver. 13 (Stata, College Station, TX, USA).

Results

Our patient series was 180 Japanese THA patients (APAP: n = 71, NAPAP: n = 109) with the mean age 66.4 ± 10.5 years; 30% of the patients were male. There were no significant between-group difference in preoperative patient characteristics, including age, sex, hip joint pain NRS score, lumbar pain NRS score, the use of analgesic agents, type of analgesic medication, hip OA x-ray findings, diagnoses, and laboratory data. The surgical time and the total amount of bleeding were also not significantly different between the APAP and NAPAP groups (Table 1).

The univariate analysis revealed that the maximum

Table 1   The preoperative characteristics of all patients

	Overall (N = 180)	APAP (N = 71)	NAPAP (N = 109)	P value
Age, mean ± SD	66.4 ± 10.5	66.5 ± 9.7	66.4 ± 11.1	0.873
Sex (Male), no. (%)	30 (16.7)	12 (16.9)	18 (16.5)	0.946
Hip pain NRS, mean ± SD	5.5 ± 2.6	5.7 ± 2.8	5.4 ± 2.4	0.372
Lumbar pain NRS, mean ± SD	2.4 ± 2.4	2.5 ± 2.3	2.4 ± 2.4	0.597
Diagnoses of OA, no. (%)				0.335
Developmental dysplasia of hip	172 (95.6)	68 (95.8)	104 (95.4)	
Idiopathic osteonecrosis of femoral head	3 (1.7)	2 (2.8)	1 (0.9)	
Rheumatoid arthritis	2 (1.1)	1 (1.4)	1 (0.9)	
others	3 (1.7)	0 (0.0)	3 (2.8)	
Severity of OA hip, no. (%)				0.322
Initial stage	2 (1.1)	1 (1.4)	1 (0.9)	
Advanced stage	26 (14.4)	7 (9.9)	19 (17.4)	
End stage	149 (82.8)	63 (88.7)	86 (78.9)	
Analgesic agents, no. (%)				
Acetaminophen	4 (2.2)	0/71 (0.0)	4/109 (3.7)	0.155
Diclofenac sodium	6 (3.3)	1/71 (1.4)	5/109 (4.6)	0.405
COX-2 inhibitor	57 (31.7)	27/71 (38.0)	30/109 (27.5)	0.139
Pregabalin	5 (2.8)	4/71 (5.6)	1/109 (0.9)	0.080
Benzodiazepine	1 (0.6)	0/71 (0.0)	1/109 (0.9)	1.000
other	14 (7.8)	7/71 (9.9)	7/109 (6.4)	0.400
Laboratory data, mean ± SD				
WBC ($\times 10^3$/μl)	6.2 ± 1.9	6.2 ± 1.8	6.2 ± 1.8	0.613
Hemoglobin (g/dl)	13.1 ± 1.4	13.1 ± 1.4	13.1 ± 1.4	0.976
AST (IU/l)	22.3 ± 6.6	22.3 ± 7.0	22.3 ± 6.5	0.876
ALT (IU/l)	17.7 ± 9.4	18.6 ± 9.0	17.2 ± 9.7	0.162
Creatinine (mg/dl)	0.75 ± 0.70	0.63 ± 0.18	0.83 ± 0.88	0.056
Surgical time (min), mean ± SD	46.5 ± 12.9	47.4 ± 13.5	45.9 ± 12.6	0.361
Total bleeding (ml), mean ± SD	482.0 ± 174.8	482.0 ± 165.9	481.9 ± 181.2	0.946

APAP, administration of intravenous acetaminophen; NAPAP, no administration of intravenous acetaminophen; SD, standard deviation; NRS, numerical rating scale; OA, osteoarthritis; WBC, white blood cell; AST, aspartate transaminase; ALT, alanine aminotransferase.

postoperative pain NRS score during the first 24 h post-surgery was significantly lower in the APAP patients compared to the NAPAP patients (APAP: 4.2 ± 3.0, NAPAP: 5.1 ± 2.9, $p = 0.032$). The maximum lumbar pain NRS score and the frequency of nurse calls were not significantly different between the groups. The frequency of the use of rescue drugs was also significantly lower in the APAP group (APAP: 1.0 ± 0.9, NAPAP: 1.4 ± 1.2, $p = 0.026$; Table 2).

The multivariate analyses adjusted for age, sex, the severity of OA of the hip, and the surgical time showed that the maximum postoperative pain NRS score during the first 24 h post-surgery was significantly lower with the use of the APAP protocol compared to the use of NAPAP (beta coefficient [β]: −0.93, 95% confidence interval [CI]: −1.79 to −0.08, $p=0.033$). The frequency

of using rescue drugs in the APAP group remained significantly lower than that in the NAPAP group (β: −0.34, 95%CI: −0.65 to −0.03, $p = 0.032$). The maximum lumbar pain NRS score (β: 0.43, $p = 0.334$) and the frequency of nurse calls (β: 0.39, $p = 0.244$) were not significantly different between the groups. The risk of PONV in the APAP group was lower than that in the NAPAP group but not significantly so (adjusted odds ratio: 0.80, 95%CI: 0.22 to 2.95, $p = 0.739$) (Table 3).

The subgroup analysis based on the severity of the patients' hip OA revealed that the postoperative and lumbar pain NRS scores were not significantly different among the patients with mild hip OA but were lower in the APAP group among the patients with severe hip OA (Table 4).

Table 2   Comparison of postoperative outcomes between the APAP and NAPAP groups: Univariate analysis

	APAP (N = 71)	NAPAP (N = 109)	P value
Postoperative pain NRS, mean ± SD	4.2 ± 3.0	5.1 ± 2.9	0.032
Lumbar pain NRS, mean ± SD	5.0 ± 2.9	4.4 ± 3.0	0.234
Frequency of rescue drugs, mean ± SD	1.0 ± 0.9	1.4 ± 1.2	0.026
Rescue drugs, no. (%)			
Acetaminophen	6 (8.5)	7 (6.4)	0.769
Diclofenac sodium	39 (54.9)	66 (60.6)	0.536
COX-2 inhibitor	1 (1.4)	1 (0.9)	1.000
Pregabalin	0 (0.0)	3 (2.8)	0.279
Opioids	6 (8.5)	25 (22.9)	0.015
Frequency of Nurse calls, mean ± SD	2.3 ± 2.3	1.9 ± 2.0	0.436
PONV, no. (%)	4 (5.6)	7 (6.4)	1.000

APAP, administration of intravenous acetaminophen; NAPAP, no administration of intravenous acetaminophen; SD, standard deviation; NRS, numerical rating scale; PONV, postoperative nausea and vomiting.

Table 3   The analgesic effect of adding IV APAP, based on the multivariate analysis

	β [a]	95% CI		P value
Primary outcome				
Postoperative pain NRS	−0.93	−1.79	−0.08	0.033
Secondary outcome				
Postoperative lumbar pain NRS	0.43	−0.45	1.31	0.334
Frequency of using rescue drugs	−0.34	−0.65	−0.03	0.032
Frequency of nurse calls	0.39	−0.27	1.06	0.244
	AOR*	95% CI		P value
PONV	0.80	0.22	2.95	0.739

[a]Multivariate linear regression analyses adjusted for age, sex, severity of osteoarthritis of hip, preoperative pain of hip, surgical time
β, Beta coefficient; CI, confidence interval; NRS, numerical rating scale; PONV, postoperative nausea and vomiting; AOR, adjusted odds ratio.
*Multivariate logistic regression analyses adjusted for age, sex, severity of osteoarthritis of hip, preoperative pain of hip, surgical time

Discussion

We investigated whether the intensity of postoperative pain could be changed by the addition of IV APAP as multimodal analgesia among patients with hip OA who had undergone a THA. The multivariate analyses adjusted for age, sex, the severity of hip OA, preoperative pain, and surgical time showed that the postoperative pain NRS score in the patients who received IV APAP in addition to the standard multimodal analgesia was lower compared to the scores of the patients who did not receive additional APAP. This result corresponded with those of studies that evaluated the effect of IV APAP in Western populations [12,13,18,27], suggesting that the analgesic effect of IV APAP in Japanese patients is similar to that in Western patients.

The frequency of rescue drug use during the first 24h post-surgery was lower in the APAP group than in the NAPAP group. Singla *et al.* reported that administering IV APAP after a THA decreased the dosage of rescue drugs required to less than half of that required when a placebo was administered [17]. An intravenous infusion produces a rapid elevation in the plasma concentration of acetaminophen and obtains a stable analgesic effect compared with that obtained by oral or rectal administration [11]. For the present study's patients, IV APAP was administered every 6h within the first 24h post-surgery, in addition to the standard analgesic protocol; the analgesic effect achieved by this approach was stable in the early post-surgical phase and the frequency of using rescue drugs was decreased.

On the other hand, the lumbar pain NRS score and

Table 4   Subgroups analysis based on the severity of the patients' hip osteoarthritis

A. Mild stage of OA

	Beta coefficient[a]	95% CI		P value
Primary outcome				
Postoperative pain NRS	0.03	−2.84	2.90	0.982
Secondary outcome				
Postoperative lumbar pain NRS	−0.63	−3.29	2.04	0.630
Frequency of using rescue drugs	−0.22	−1.10	0.66	0.603
Frequency of nurse calls	−1.29	−3.70	1.13	0.281

B. Severe stage of OA

	Beta coefficient[a]	95% CI		P value
Primary outcome				
Postoperative pain NRS	−1.12	−2.03	−0.20	0.017
Secondary outcome				
Postoperative lumbar pain NRS	0.58	−0.38	1.54	0.234
Frequency of using rescue drugs	−0.36	−0.71	−0.01	0.041
Frequency of nurse calls	0.67	−0.03	1.37	0.059

[a]Multivariate liner regression analyses adjusted for age, sex, severity of osteoarthritis of hip, surgical time
OA, osteoarthritis; CI, confidence interval; NRS, numerical rating scale; PONV, postoperative nausea and vomiting; AOR, adjusted odds ratio.

the frequency of nurse calls were not decreased in these THA patients. No study to date has evaluated the effect of administering IV APAP for lumbar pain on the frequency of postoperative nurse calls. The postoperative lumbar pain of the patients in this study was higher than the preoperative lumbar pain. The risk factors for the development of back pain after neuraxial anesthesia include the lithotomy position, multiple attempts at block placement, duration of surgery >2.5h, BMI ≥32 kg/m², and a history of back pain [28]. We suspect that these risk factors were related to the strength of the postoperative lumbar pain in our patient series.

Factors other than the surgical procedure such as total bed-time after surgery and the presence or absence of osteoporosis may strongly affect the intensity of lumbar pain. With regard to the frequency of nurse calls, we did not ascertain the reasons that patients called nurses after their surgery, and it is possible that some of the patients called nurses for reasons other than pain.

The prevalence of PONV during the first 24h post-surgery was not significantly different between the NAPAP and APAP groups. Karvonen et al. reported that the incidence of adverse events such as nausea and vomiting did not increase after the administration of acetaminophen for the patients received with major orthopedic surgery [20]. It is commonly believed that the incidence of PONV depends on the dose of opioids used [9,29]. In our study, the attending physicians chose the type of rescue drugs used for postoperative pain control; they administered diclofenac sodium (50 mg) in almost all cases, rather than opioids. This may explain the lack of a significant difference in the incidence of PONV between the NAPAP and APAP groups. Since the administration of IV APAP in addition to the standard analgesics decreases the dose of opioids required, it also facilitates the safe control of postoperative pain. On the other hand, the postoperative pain intensity reported by our patients was higher than in previous studies. This might be related to the avoidance of opioids for postoperative pain management in our series. Physicians need to consider both the advantages and disadvantages of the use of opioids for postoperative pain control [6,30].

In our subgroup analysis based on the severity of hip OA, the intensity of postoperative pain as indicated by the NRS and the frequency of rescue drugs after surgery were both markedly decreased with added IV APAP among the patients with severe OA. In another study, patients with mild hip OA had stronger postoperative pain and decreased physical activity compared to patients with severe hip OA [31]. Thus, in the present study the effect of adding IV APAP might have been

greater among the patients with severe hip OA. It is not possible to make this conclusion, however, because the number of patients with mild hip OA was small. Further evaluations of a larger number of patients are required to confirm the analgesic effects of IV APAP in such patients.

There are some limitations to this study. First, we may not have adjusted for all possible subclinical confounders, as we performed a retrospective observational study to evaluate the analgesic effect of IV APAP. The intensity of pain has been shown to be modified not only by the severity of the primary disease, but also by the psychological state of the patients [32]. It would have been ideal to adjust for the mental conditions of patients, such as depression. The patients in this study were enrolled by continuous sampling, and their pre-operative characteristics did not differ significantly between the groups; we therefore believe that there were no major distinctions between our NAPAP and APAP groups.

Secondly, the NRS score might not be accurate, as the postoperative pain NRS score, which was the primary outcome of this study, was rated by the patients themselves, and this may be less accurate in the case of elderly and severely demented patients [24]. The mean age of patients of this study (approx. 66 years) was not particularly old; we thus believe that the accuracy of the NRS score may be acceptable. In addition, in our initial research protocol, we had planned to use the postoperative pain NRS scores measured at $0, 6, 12, 24$ h after surgery for the analysis, but we could not do so because there were many missing values from the medical chart review. Therefore, we could not refer sufficiently to the time course of the intensity of the postoperative pain.

Finally, it is possible that the study suffered from a selection bias. We performed this study at a single university hospital; patients with severe disease may thus have been more likely to be enrolled in this study. The analgesic effect of IV APAP for postoperative pain should be evaluated in a multicenter study in order to test the generalizability of these results.

In conclusion, the intravenous administration of APAP in addition to the standard multimodal analgesia for Japanese patients who had undergone a THA may decrease the postoperative pain NRS score and the frequency of using rescue drugs during the first 24 h post-surgery. This multimodal analgesia also appears to be safe, as it did not increase the incidence of adverse events such as PONV.

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