Doi: 10.5152/TJAR.2019.10476

Original Article
Paediatric Anaesthesia

Turkish Journal of Anaesthesiology & Reanimation

# Intraoperative Single-Dose Intravenous Acetaminophen for Postoperative Analgesia After Skin Laser Irradiation Surgery in Paediatric Patients: A Small Prospective Study

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***Cite this article as:*** Kuroki S, Nagamine Y, Kodama Y, Kadota Y, Kouroki S, Maruta T, et al. Intraoperative Single-Dose Intravenous Acetaminophen for Postoperative Analgesia After Skin Laser Irradiation Surgery in Paediatric Patients: A Small Prospective Study. Turk J Anaesthesiol Reanim 2019; 47(3): 192-8.

## Abstract

**Objective:** Acetaminophen is an analgesic that shows efficacy in postoperative pain relief in children. Many drugs such as opioids, non-steroidal anti-inflammatory drugs, and/or acetaminophen have been used in paediatric skin laser irradiation surgery for postoperative pain relief. However, acetaminophen has some advantages over opioids, and opioids are being used less often. We aimed to demonstrate the effectiveness of intravenous (IV) acetaminophen during surgery for postoperative pain in paediatric skin laser irradiation.

**Methods:** The present study is a small, prospective, double-blinded, randomized controlled trial. Paediatric patients (1–12 years old with an American Society of Anesthesiologists physical Status I and II), scheduled for skin laser irradiation for a nevus or haemangioma between October 2014 and April 2016 were randomized into the acetaminophen (n=9) and placebo (saline, n=8) groups. The observational face scale (FS) and the Behavioural Observational Pain Scale (BOPS) scores were recorded on emergence from anaesthesia, and 1, 2, and 4 hr post-surgery.

**Results:** Patient characteristics were not significantly different except with regard to the irradiation area and surgery time. The observational FS and BOPS scores of the acetaminophen group were lower than those of the placebo group; median (minimum–maximum) at each recording time: 1 (0–2) – 0 (0–2) – 0 (0–1) – 0 (0–2) vs. 2 (0–4) – 0 (0–2) – 0 (0–2) – 0 (0–1) and 1 (0–3) – 1 (0–3) – 1 (0–2) – 0 (0–1) vs. 2 (0–4) – 3 (0-5) – 1 (0–4) – 0 (0–3), p=0.07 and p=0.003, respectively. No differences in post-surgical analgesic use or adverse events were observed.

**Conclusion:** In this study, we showed that the IV acetaminophen group had lower observational FS and BOPS scores in the early postoperative period; however, further studies including a large number of patients are required to confirm our findings.

**Keywords:** Intravenous acetaminophen, pediatrics, prospective study, skin laser irradiation

## Introduction

Skin laser therapy is used as a treatment method for paediatric congenital nevus or haemangioma (1, 2). Laser therapy performed during childhood has the following advantages: [1] thinner skin results in a more effective treatment, and [2] the laser irradiation area is still small. Most skin laser irradiation surgery in paediatric patients is performed under general anaesthesia because children do not tolerate the pain caused by laser irradiation. Many analgesic drugs such as opioids, non-steroidal anti-inflammatory drugs, and/or acetaminophen have been used for postoperative pain relief. However, opioids are being used less often because of significant adverse effects, such as respiratory depression, nausea, vomiting, slow gastrointestinal function, and sedation. Thus, non-opioid intravenous (IV) pain medications are often used in conjunction with or instead of opioids when appropriate to reduce overall opioid consumption.



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Received: 01.09.2018 Accepted: 27.10.2018
Available Online Date: 19.02.2019

Acetaminophen shows efficacy in postoperative pain relief and is suitable for use in children (3, 4). In Japan, IV acetaminophen has been used since 2013. IV acetaminophen is indicated in paediatric patients, whereas the indication of most analgesic drugs for paediatric patients is not documented on the drug package insert. However, the efficacy of IV acetaminophen for postoperative analgesia after skin laser irradiation surgery is still unknown. This study demonstrated the availability of IV acetaminophen in paediatric skin laser therapy.

## Methods

### Participants

This study was approved by the hospital ethics committee for human studies (Ethical Committee Number 2014-012). After written informed parental consent and children's (≥6 years) informed assent were obtained, patients aged 1–12 years, with an American Society of Anesthesiologists' physical Status of I and II, and scheduled for elective skin laser irradiation surgery under general anaesthesia were screened for enrolment into this study. Exclusion criteria were the following: patients aged <1 year or ≥13 years, any renal or hepatic impairment, any neurological disorder impairing an accurate pain assessment, an allergy to acetaminophen, or lack of informed consent from the parents.

Patients were assigned randomly to the placebo group (saline, made by Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) or the IV acetaminophen (Acelio, TERUMO Co. Ltd., Tokyo, Japan) group using a simple randomization method with a random number table prepared by a pharmacist from the Division of Clinical Trials who did not manage the anaesthesia or assess the data. All study treatments were prepared by a clinician unaware of the patient's allocated study group in identical infusion pumps, and the treatment volumes were equal. IV infusions were administered by a blinded attending physician. In the acetaminophen IV group, patients <2 years old received 7.5 mg $kg^{-1}$, and patients ≥2 years old received 15 mg $kg^{-1}$ IV acetaminophen infusion within 15 minutes during surgery. All patients were administered 0.3 mg $kg^{-1}$ pentazocin during the induction of general anaesthesia as adjunctive and to prevent emergence excitement (5, 6). They also received a steroid ointment and cooling of the irradiated area after surgery. Anaesthesia was induced slowly and was maintained by oxygen, nitrous oxide, and sevoflurane.

### Data collection

The primary outcomes were the observer-reported face scale (observational FS) and the Behavioural Observational Pain Scale (BOPS, Table 1). The observational FS was reported by nurses using the Wong–Baker Faces Pain Rating Scale, which consists of six facial expressions on a scale from 0 ("no pain") to 5 ("hurts worst") (7). The BOPS was developed in 1996 as a simplified hybrid of two well-known behavioural pain scales, the Princess Margaret Hospital Pain Assessment Tool and the Children's Hospital of Eastern Ontario Pain Scale (8). The BOPS score was derived by assessing three variables indicative of pain in children (facial expression, vocalization, and body movements). Each variable was divided into three grades, 0, 1, or 2, to keep the scale as simple as possible. The sum of these variables in the BOPS ranged between 0 and 6 points. Based on clinical experience and the method of score construction, a decision was made that scores >2 points would necessitate administration of an analgesic. Secondary outcomes were consciousness, respiration, oxygen administration, nausea/vomiting, and postoperative analgesic drugs. These data were recorded at emergence from general anaesthesia and 1, 2, and 4 hr after surgery by individual anaesthesiologists and nurses in the paediatric or dermatology ward.

### Statistical analysis

All data are presented as the mean±standard deviation, numbers, or median (minimum–maximum). A statistical analysis was performed using the JMP 11 (SAS Institute, Inc., Cary, NC, USA). Categorical data were examined using a chi-squared test or Fisher's exact test to compare the groups. A Student's t-test was used to compare the group means, and a two-way analysis of variance, where the factors were groups (2 levels) and recording time points (4 levels), was used to compare the observational FS and BOPS scores between the groups. The relationship between two variables was evaluated by Pearson's correlation. A p-value <0.05 was considered to be statistically significant.

**Table 1. Behavioural observational pain scale**

| Score | Facial expression | Verbalization | Body position |
|---|---|---|---|
| 0 | Neutral/positive facial expression, composed, calm | Normal conversation, laugh, crow | Inactive, laying with all extremities relaxed, or sitting or walking |
| 1 | Negative facial expression, concerned | Completely quiet or sobbing and/or complaining, but not because of pain | Restless movements, in a shifting fashion, and/or touching wound or wound area |
| 2 | Negative facial expression, grimace, distorted face | Crying, screaming, and/or complaining about pain | Lying rigid and/or drawn up with arms and legs to the body |

The facial expression, verbalization, and body position were used for pain evaluation.

**Table 2 . Patient characteristics**

| | Placebo (n=8) | Acetaminophen IV (n=9) | p |
|---|---|---|---|
| Age (year) | 3±2 | 4±1 | 0.55 |
| **Age structure** | | | |
| 2/3/4/5/6/7 years | 3/2/2/0/0/1 | 1/2/1/3/2/0 | 0.20 |
| Height (cm) | 97.0±11.1 | 104.1±7.9 | 0.52 |
| Weight (kg) | 15.3±3.4 | 17.0±1.2 | 0.73 |
| Male/Female | 1/7 | 3/6 | 0.31 |
| Laser field (%) | 5.6±3.3 | 1.7±1.4 | 0.006 |
| Laser (shots) | 1651±2466 | 137±91 | 0.08 |
| Operation time (min) | 38±27 | 10±7 | 0.01 |
| Anaesthesia time (min) | 82±25 | 60±17 | 0.051 |

Data are presented as the mean±standard deviation or as numbers.

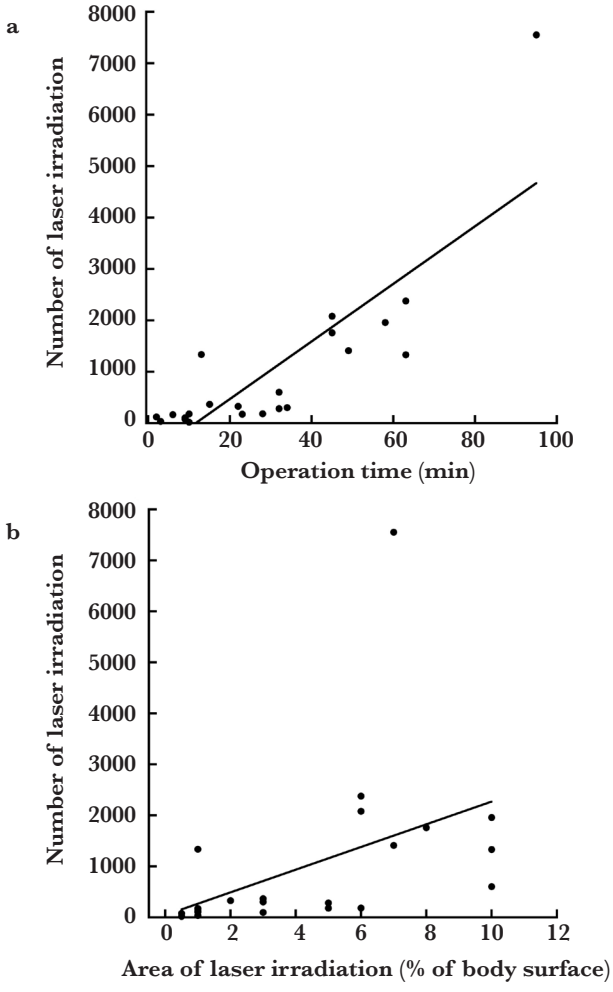


**Figure 1. a, b. (a) Correlation between the surgical time and laser operation time. The surgical time and laser operation time were in direct proportion to each other: y=−648.69+55.97x; $R^2$=0.698; p<0.0001. (b) Correlation between the laser irradiation area and the number of laser shots. The area of irradiation and the number of laser shots were in direct proportion to each other: y=44.78+222.76x; $R^2$=0.206; p=0.0295**

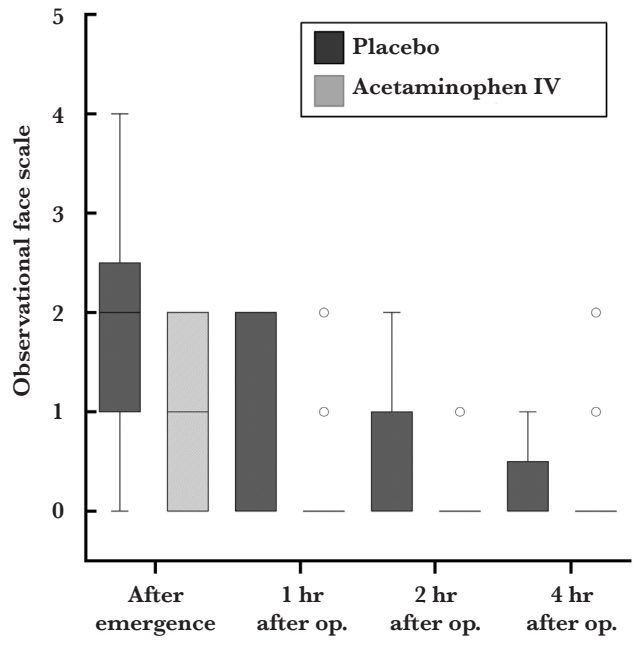


**Figure 2. Observational face scale. This is a box-and-whiskers plot of the observational face scale scores of children treated post-surgically with acetaminophen or a placebo. The bottom and top of the box are the first and third quartiles, and the band inside the box is the median. The whiskers show the range of data excluding outliners. Open circles are outliers**
**Op: operation**

## Results

Patients were recruited between October 2014 and April 2016. A total of 23 patients were prospectively enrolled, and six were excluded due to missing data. Finally, eight patients in the placebo group and nine in the acetaminophen IV group were included into the study. Patient characteristics are shown in Table 2. Patient characteristics were not significant-

**Table 3 . Postoperative pain scores and recovery variables**

| | Placebo (n=8) | Acetaminophen IV (n=9) | p |
|---|---|---|---|
| **Emergence from general anaesthesia** | | | |
| Observational FS | 2 (0–4) | 1 (0–2) | |
| BOPS | 2 (0–4) | 1 (0–3) | |
| **1 hour after operation** | | | |
| Observational FS | 0 (0–2) | 0 (0–2) | |
| BOPS | 3 (0–5) | 1 (0–3) | |
| Conscious/unconscious | 4/4 | 7/2 | 0.23 |
| Respiration rates (/min) | 23±5 | 21±2 | 0.30 |
| $SpO_2$ (%) | 97±1 | 97±1 | 0.90 |
| Oxygen administration Yes/No | 1/7 | 4/5 | 0.15 |
| Nausea Yes/No | 1/7 | 0/9 | 0.27 |
| Vomiting Yes/No | 2/6 | 1/8 | 0.45 |
| **2 hours after operation** | | | |
| Observational FS | 0 (0–2) | 0 (0-1) | |
| BOPS | 1 (0–4) | 1 (0-2) | |
| Conscious/unconscious | 5/3 | 6 /3 | 0.86 |
| Respiration rates (/min) | 24±6 | 20±3 | 0.11 |
| $SpO_2$ (%) | 97±1 | 98±1 | 0.76 |
| Oxygen administration Yes/No | 0/8 | 2/7 | 0.16 |
| Nausea Yes/No | 0/8 | 0/9 | - |
| Vomiting Yes/No | 0/8 | 0/9 | - |
| **4 hours after operation** | | | |
| Observational FS | 0 (0–1) | 0 (0–2) | |
| BOPS | 0 (0–3) | 0 (0–1) | |
| Conscious/unconscious | 8/0 | 8/1 | 0.33 |
| Respiration rates (/min) | 28±13 | 20±3 | 0.11 |
| $SpO_2$ (%) | 98±1 | 97±1 | 0.76 |
| Oxygen administration Yes/No | 0/8 | 1/8 | 0.33 |
| Nausea Yes/No | 0/8 | 0/9 | - |
| Vomiting Yes/No | 0/8 | 0/9 | - |
| **The use of analgesic drugs within 24 hour after operation** Yes/No | 1/7 | 0/9 | 0.27 |

FS: face scale; BOPS: Behavioural Observational Pain Scale; $SpO_2$: oxygen saturation

ly different; the exceptions were the laser field and surgery time. The number of laser shots, surgical time, and the area of laser irradiation were in a direct proportion to each other (Figure 1).

**Efficacy of IV acetaminophen for postoperative analgesia**

Observational FS and BOPS scores are shown in Figures 2 and 3, and in Table 3. The observational FS scores of the acetaminophen IV group tended to be lower than those of the placebo group (groups: $F_{1,60}$=3.39, p=0.07; recording times: $F_{3,60}$=6.90, p<0.001; groups × recording times interaction: $F_{3,60}$=0.96, p=0.42, respectively). In addition, the BOPS scores of the acetaminophen IV group were significantly lower than those of the placebo group (groups: $F_{1,60}$=9.44, p=0.003; recording times: $F_{3,60}$=4.22, p=0.009; groups × recording times interaction: $F_{3,60}$=0.31, p=0.82, respectively). The median scores of the observational FS and BOPS in both groups were low (no pain) at all-time intervals. The observational FS and BOPS scores were in direct proportion to each other (Figure 4).

Although one patient in the placebo group used an acetaminophen suppository for postoperative analgesia, the use of analgesic drugs within 24 hr after operation was not significantly different between the two groups (Table 3).

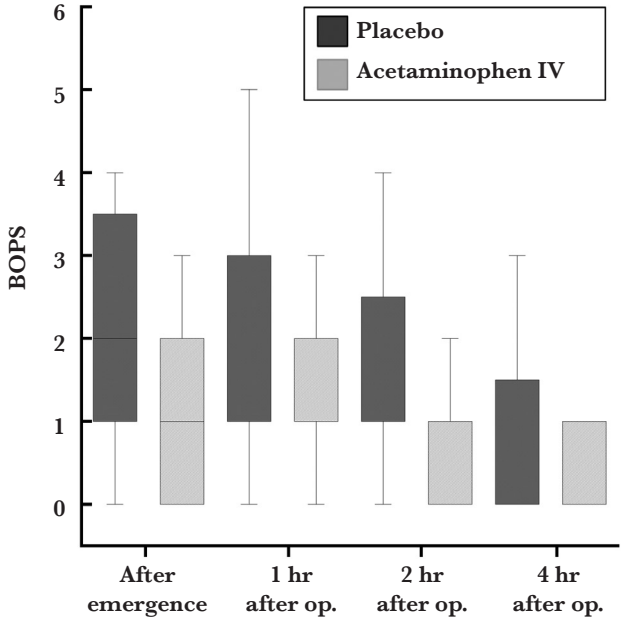


**Figure 3. Behavioural Observational Pain Scale. This is a box-and-whiskers plot of the Behavioural Observational Pain Scale (BOPS) scores of children treated post-surgically with acetaminophen or a placebo. The bottom and top of the box are the first and third quartiles, and the band inside the box is the median. The whiskers show the data range**
**Op: operation**

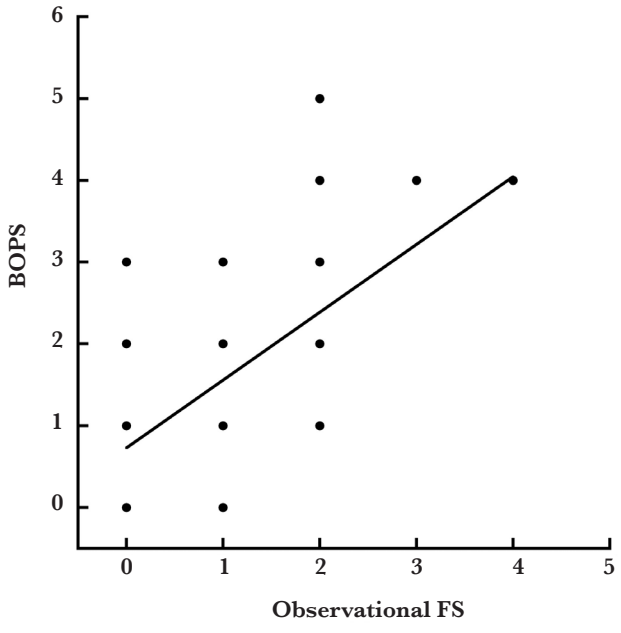


**Figure 4. Correlation between the observational face scale and Behavioural Observational Pain Scale. The observational face scale and Behavioural Observational Pain Scale were in direct proportion to each other: $y=0.73+0.83x$; $R^2=0.375$; $p<0.0001$**

**Adverse events**

Postoperative consciousness, respiration rate, oxygen saturation ($SpO_2$), oxygen administration, nausea, and vomiting at all-time intervals in the two groups are shown in Table 3. They were not significantly different between the two groups at any time point. Hepatic function disorder due to IV acetaminophen is rare with therapeutic doses (9-13), but it may occur. Because blood tests are not routinely performed after skin irradiation surgery, hepatic enzyme levels were not measured in this study. However, signs suggestive of a hepatic function disorder, such as jaundice, were not observed in the acetaminophen IV group.

## Discussion

Our practical study demonstrated that intraoperative IV acetaminophen was effective and safe for postoperative analgesia after paediatric skin laser irradiation surgery. In this study, the acetaminophen IV group had lower pain scores than the placebo group in the early postoperative period (up to 2 hr), except for emergence. To schedule this study, we retrospectively investigated analgesic medications for irradiation therapy during surgery before IV acetaminophen could be used in our hospital (5). The most frequently used drugs were pentazocin, acetaminophen suppository, and flurbiprofen axetil. Pentazocin was used in 45% of patients, and it was suggested that pentazocin was used to prevent emergence excitement due to volatile anaesthesia (6). Thus, both groups in this study received a low dose (0.3 mg $kg^{-1}$) pentazocin during the induction of general anaesthesia as an adjunctive and to prevent emergence excitement. As a result, observational FS and BOPS scores may become similar to low levels at emergence between groups. Recently, several randomized controlled trials revealed that acetaminophen was effective for the reduction of postoperative pain, reduction of postoperative opioid use, and was safe for perioperative pain management in paediatric patients (14-19). However, some studies failed to prove the advantage of IV acetaminophen (20-22). In these studies, all patients received intraoperative opioids for adjunctive anaesthesia. Thung et al. reported that an intraoperative dose of morphine (0.1 mg $kg^{-1}$) as a common analgesic regimen was adequate for many paediatric patients undergoing adenotonsillectomy, thereby mitigating the ability to see any additional effect from a single intraoperative dose of IV acetaminophen (20).

Oral acetaminophen has reportedly been associated with liver function disorders, especially in overdose (>4000 mg $day^{-1}$), or with liver dysfunction, because 90% of the absorbed dose of oral acetaminophen is metabolized in the liver. However, IV acetaminophen may reduce hepatotoxicity because it does not undergo the first-pass metabolism in the liver (3), and several studies reported that IV acetaminophen may not in-

crease postoperative complications in adults (9-11). The most common adverse events (incidence >5%) due to IV acetaminophen administration in adults were nausea (34%), vomiting (15%), headache (10%), and insomnia (7%); in paediatric patients, they were nausea, vomiting, constipation, pruritus, agitation, and atelectasis (13). Although there was a high incidence of nausea and vomiting, it was reported that IV acetaminophen actually reduced postoperative nausea and vomiting due to the reduction of postoperative pain: the relative risk (95% confidence interval) was 0.73 (0.60–0.88) for nausea and 0.63 (0.45–0.88) for vomiting (23).

It is important to note that our study has certain limitations. [1] The sample size was small. [2] The laser field and the surgical time of the acetaminophen IV group was respectively smaller and shorter than that of the placebo group. Although in our setting the laser field or surgery time became correlated poorly with pain scores (laser field vs. observational FS: $R^2$=0.003, laser field vs. BOPS: $R^2$=0.016, surgery time vs. observational FS: $R^2$=0.006, surgery time vs. BOPS: $R^2$=0.009), the acetaminophen IV group could have experienced less invasive surgery than the placebo group. [3] Both groups in this study received a low dose pentazocin as adjunctive and to prevent emergence excitement. As a result, although our study setting (placebo group also received analgesic drug during surgery) was easy to be accepted by parental guardians, pentazocin may influence observational FS and BOPS scores, especially at emergence. [4] Because postoperative hepatic enzyme levels were not measured in this study, there might be increasing hepatic enzyme levels without jaundice.

## Conclusion

Intraoperative single-dose IV acetaminophen combined with 0.3 mg $kg^{-1}$ pentazocin was effective and safe for postoperative analgesia after paediatric skin laser irradiation surgery. However, our results should be replicated in a large-scale trial.

**Ethics Committee Approval**: Ethics committee approval was received for this study from the hospital ethics committee for human studies (Ethical Committee Number 2014-012; Chairperson, Professor Koichiro Itai) on April 23, 2014.

**Informed Consent:** Written informed parental consent and children's (≥ 6 years) informed assent were obtained in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions**: Concept – S.Ku., I.T., T.M.; Design – S.Ku., I.T., T.M.; Supervision – S.Ku., T.M.; Resources – S.Ku., I.T., T.M.; Materials – Y.N., Y.Ko., Y.Ka., S.Ko.; Data Collection and/or Processing – Y.N., Y.Ko., Y.Ka., S.Ko.; Analysis and/or Interpretation – Y.N., Y.Ko., Y.Ka., S.Ko.; Literature Search – T.M.; Writing Manuscript – T.M.; Critical Review – S.Ku., I.T., T.M.; Other – S.Ka., M.A.

**Acknowledgements:** This study is attributed to the Departments of Anesthesiology and Dermatology, University of Miyazaki Hospital. The authors would like to thank Rie Ohno (pharmacist, Division of Clinical Trials), Noriko Hidaka, and Toshiko Watanabe (research assistant and secretary, Department of Anesthesiology) for their assistance in patient randomization and data collection during this study. In addition, the authors sincerely thank Yoshiki Kuroda, MD, PhD (Department of Public Health, Faculty of Medicine, University of Miyazaki) for expert statistical analysis.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

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