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Effect of single dose preoperative intravenous ibuprofen on postoperative pain and opioid consumption: a systematic review and meta-analysis.

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Running title: Preoperative IV ibuprofen and pain

** This is a Master’s thesis of Su Yeon Kim.

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Effect of single dose preoperative intravenous ibuprofen on postoperative pain and opioid consumption: a systematic review and meta-analysis

Running title: Preoperative IV ibuprofen and pain
Abstract

**Background:** Ibuprofen, a well-known analgesic, is commonly used as a component of multimodal analgesic approach for postoperative pain. This systematic review and meta-analysis aimed to investigate whether single-dose preoperative intravenous ibuprofen can reduce postoperative pain and opioid consumption.

**Methods:** Databases of PubMed/MEDLINE, Embase, Cochrane Library (CENTRAL), and Web of Science were searched to identify relevant studies published up to May 2020. Randomized controlled trials comparing the effect of preoperative single-dose of intravenous ibuprofen with control group using saline on postoperative pain and opioid consumption after surgery under general anesthesia were included in this meta-analysis.

**Results:** Six studies involving 366 participants were finally included in this meta-analysis. Single administration of intravenous ibuprofen before surgery significantly reduced postoperative pain score on scale of 0-10 at 1 h (MD, -1.64, 95% CI [-2.56 to -0.72], P < 0.001, $I^2 = 95\%$), at 4-6 h (MD, -1.17, 95% CI [-2.09 to -0.26], P < 0.001, $I^2 = 94\%$) and at 24 h (MD, -0.58, 95% CI [-0.99 to -0.18], P < 0.001, $I^2 = 90\%$). Cumulative fentanyl consumption were also reduced significantly in ibuprofen group compared to placebo up to postoperative 4-6 h (MD, -56.35 μg, 95% CI [-101.10 to -11.60], P < 0.001, $I^2 = 91\%$) and 24 h (MD, -131.39 μg, 95% CI [-224.56 to -38.21], P < 0.001, $I^2 = 95\%$).

**Conclusions:** Preoperative single-dose intravenous ibuprofen can reduce postoperative pain and opioid consumption until 24 h postoperatively. However, considering high degree of heterogeneity, further research is needed to confirm this effect.

**Keywords:** Anesthesia and analgesia; Ibuprofen; Postoperative pain; Preoperative period.
Introduction

Poorly controlled postoperative pain may negatively affect patient’s clinical outcomes, such as postoperative complications and rehabilitation [1,2]. Multimodal analgesia is strongly recommended for effective management of postoperative pain rather than using opioids alone [3,4]. In addition, multimodal analgesia is one of the key components of the enhanced recovery after surgery protocol, which aims to achieve early recovery through diverse approaches. Through multimodal analgesia, patients will experience less opioid-induced adverse effects, early recovery and early discharge by reducing perioperative use of opioids [5].

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been an important part of a multimodal regimen for postoperative analgesia [6]. In combination with opioids, NSAIDs reduce opioid consumption and opioid-related side effects such as nausea and vomiting [7].

Ibuprofen is an NSAID which inhibits cyclooxygenase enzymes, which converts arachidonic acid to prostaglandin H₂, a mediator of inflammation, pain, and fever. Among widely used NSAIDs, ibuprofen is less likely to increase gastrointestinal adverse events and cardiovascular risk [8,9]. Ibuprofen is preferred in various types of surgeries and patient populations because of its safety profile.

Although ibuprofen has a long history of use as an oral analgesic, intravenous ibuprofen has been used in clinical practice only for over 10 years, since the approval by the United States Food and Drug Administration in 2009. In case of adults, it is recommended to administer 400-800 mg of intravenous ibuprofen every 6 hours as necessary with a maximum limit of 3200 mg per day [10].

The usefulness of multiple doses of IV ibuprofen in conjunction with opioids has been reported in the perioperative setting [11,12]. However, limited data are available on its usefulness when ibuprofen is administered preoperatively through intravenous route.

Recently, a single dose of preoperative intravenous ibuprofen was suggested as an intervention
to enhance the effectiveness of postoperative analgesia, however, inconsistent results have been
presented [13-18].

The objective of this study was to determine the effect of preoperative single-dose intravenous
ibuprofen on the severity of postoperative pain and opioid consumption by meta-analysis of the data
from previous randomized controlled studies.
Materials and Methods

Study design

This meta-analysis followed the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) (Appendix 1). The study was registered in the “International Prospective Register of Systematic Reviews” (PROSPERO) (https://www.crd.york.ac.uk/PROSPERO, no. CRD42020166141).

Information sources and search strategy

Two authors (SK and KK) searched the PubMed/MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science databases. The search terms included variants of terms, such as “ibuprofen”, “intravenous”, “postoperative pain”, “analgesia”, “opioid”, “fentanyl”, “morphine” and “patient controlled analgesia” as well as Medical Subject Heading or Embase Subject Heading terms (Appendix 2).

There was no limitation on year of publication, but we limited the search to randomized controlled trials conducted on humans. The language of the article was limited to English and Korean. The date of the last search was May 12, 2020.

Study selection and eligibility criteria

After searching the articles from the databases listed above, two authors (SK and KK) selected the studies independently. Selection was composed of the following three steps: using title, abstract and full text of the articles. Two authors first selected the articles based on the title, then the abstract, and for the remaining articles, two authors reviewed the full text of each article for the final selection. In case of disagreement, two authors discussed an agreement on the final selection of the articles.
The inclusion criteria were as follows: (1) patients under general anesthesia, (2) ibuprofen was administered intravenously, (3) ibuprofen was administered preoperatively, which is defined as before surgical incision, (4) control group using placebo was reported with results, and (5) primary outcomes of original articles were postoperative pain scores or opioid consumption.

Studies were excluded based on the following criteria: (1) articles not written in English or Korean, (2) patients not under general anesthesia, (3) ibuprofen was not administered intravenously, (4) ibuprofen was administered after the skin incision or multiple administration, (5) did not include appropriate postoperative outcomes, (6) non-randomized clinical trials, (7) non-human studies, and (8) did not compare with the appropriate control group. We also excluded articles that were not available in full text.

**Risk of bias in individual studies**

Based on “risk of bias” of the Review Manager software version 5.3 (The Cochrane Collaboration, UK), two authors (SK and KK) evaluated the quality of articles independently. A third author (SL) was included to resolve disagreements when needed. Seven categories were included for assessing the risk of bias; random sequence generation and allocation concealment for detecting selection bias, blinding of participants for performance bias, blinding of outcome assessor for detection bias, incomplete outcome data for attrition bias, selective reporting for reporting bias, and other bias that were not covered by the above categories. We specified the adequacy of the sample size calculation as “other bias”, the seventh category. The risk of bias was rated as “high”, “low” or “unclear” in each original article. The agreement of two independent raters regarding the risk of bias for seven categories was evaluated using Cohen’s kappa. Authors interpreted the Cohen’s kappa values based on Cohen’s suggestions as follows: (1) below 0.00: no agreement, (2) 0.00-0.20: slight agreement, (3) 0.21-0.40: fair agreement, (4) 0.41-0.60: moderate agreement,
Data collection process and extracted items

Two authors (SK and KK) extracted data from the articles and cross-checked the data to avoid missing any information or extracting incorrect information. The extracted information included patient age, study design, publication year, authors’ first name, type of surgery, timing and dosage of study drug, and measured outcomes. The measured outcomes were as follows: postoperative pain score, postoperative analgesic regimen and analgesic consumption. Two independent authors (SK and KK) extracted data from the text, tables, and graphs. The Cohen’s kappa was used to assess the agreement of two authors on extracted data and the values were interpreted in the similar manner as the risk of bias.

We extracted pain scores at postoperative 1, 4-6, and 24 hours to reflect immediate, early and late postoperative pain, respectively, for the analysis of pain scores. If the pain score was not measured at 6 hour postoperatively in original articles, we used pain scores measured at postoperative 4 hour after replacement [13,15-17]. Cumulative opioid consumption up to postoperative 4-6 hour and 24 hours were included. We extracted data of cumulative opioid consumption at 6 hour postoperatively, and if data were not available at 6 hour, we extracted data measured at postoperative 4 hour after replacement [16,17].

To analyze the intensity of postoperative pain, pain scores measured by the visual analogue scale (VAS) or numerical rating scale (NRS) were extracted from each study. When the studies evaluated pain scores during movement and resting state simultaneously, we only used scores assessed at the resting state. If the studies used opioids other than fentanyl, we converted them into fentanyl equivalents [14,18].
Statistical analysis

Summary measures

Pain scores were extracted with the mean and standard deviation at the specified time points. We also extracted the mean and standard deviation of cumulative opioid consumption in the similar manner.

Synthesis of results

The VAS and NRS scores were strongly correlated [19], and pain scores were measured on same scale of 0-10 in all included studies. In addition, we converted opioid consumption into fentanyl equivalents (μg). Therefore, we calculated the data of mean differences (MDs) for continuous outcomes (postoperative pain scores or amount of cumulative opioid consumption). We calculated the 95% confidence intervals (CIs) for all estimates. A random-effect model was used for all trial results because of the possibility of different effect sizes across the studies. To measure heterogeneity among the trials, Higgins' $I^2$, the heterogeneity statistic Cochrane’s Q, and corresponding and P values were calculated. We considered $I^2 > 50\%$ as significant heterogeneity.

Sensitivity analysis was performed by leave-one-out analyses using meta and dmetar packages under R software (version 3.6.3, R Foundation for Statistical Computing, Austria).

Publication bias was not assessed in this meta-analysis because the included studies were less than 10.

We used Review Manager (RevMan, version 5.3, The Cochrane Collaboration) and R software (version 3.6.3, R Foundation for Statistical Computing, Austria) for all the analyses.
Results

Study selection and characteristics

Authors obtained 1,534 articles after an initial database search from PubMed (n = 154), Embase (n = 880), the Cochrane Library (n = 348) and Web of Science (n = 152). We excluded 350 duplicated articles. Two authors reviewed the articles independently, and subsequently, excluded 109 reports based on the title and 1011 articles based on the abstract. Final full text reviews were performed on the remaining 64 articles. Of 64 articles, 58 were excluded for the following reasons: patients not under general anesthesia (n = 6), multiple administration of drug (n = 3), drug not administered intravenously (n = 15), drug administered after skin incision (n = 7), do not provide appropriate postoperative outcomes (n = 5), non-randomized clinical trials (n = 11), placebo not provided (n = 2), could not attain full text (n = 1), and gray literature (n = 8). We evaluated the risk of bias and extracted data from the final six articles (Fig. 1).

The characteristics of the final six studies are shown in Table 1. All articles were randomized clinical trials. The types of surgeries were diverse, including laparoscopic cholecystectomy [16,17], septorhinoplasty [13,18], pancreaticoduodenectomy [14], and thyroidectomy [15]. Ibuprofen was administered intravenously in all the studies; however, the doses were different; one study administered 400mg of ibuprofen [17], while other studies injected 800mg of ibuprofen. Furthermore, opioids used in these articles were diverse from fentanyl [13,15-17], and morphine [14] to tramadol [18]. The timing of measurement of pain scores and opioid consumption also varied among the studies.

Quality assessment of included studies (risk of bias within studies)

The risk of bias assessment indicated that all included studies were low biased (Figs. 2 and 3). All trials were evaluated as having a low risk for random sequence generation. Of all included
studies, 66.6% were assessed as “unclear” in allocation concealment, 16.6% in blinding of participants and personnel, and 16.6% in blinding of outcome assessment, 66.6% in selective reporting and 16.6% in other bias categories. Other bias was the only category assessed to have a “high” risk of bias, with proportion of 16.6%. Only two trials [14,18] were clear about allocation concealment, while other trials (66.6%) did not describe the allocation concealment method in detail. With respect to blinding of patients, one study [18] did not mention the term “double-blinded” nor describe its method of blinding. Furthermore, it did not specify blinding of the outcome assessor method, so we assessed it as “unclear”. Only two studies [14,16] provided information regarding protocols written in advance. All studies were rated as “low” in other bias, except two trials: one study [15] without calculation of required sample size and power analysis rated as “unclear”, and the other [18] with inappropriate power analysis rated as “high”.

Agreement between two raters for assessing the risk of bias was moderate (Cohen’s kappa = 0.52).

Meta-analysis

One study [14] reported the effects of intraoperative remifentanil infusion along with preoperative ibuprofen on postoperative pain and opioid consumption. Patients in this study received intraoperative remifentanil infusion targeting 4 ng/mL or 1 ng/mL as effect-site concentration, with or without preoperative ibuprofen administration. In this study, we extracted the data from subgroups with low remifentanil infusion only because most of the other articles included in our meta-analysis did not use opioid infusion or used a low infusion rate of opioid during surgery.

Pain scores at 4 hour postoperatively were extracted in four reports [13,15-17] since data at 6 hour were not available. One study [15] on opioid consumption was not included in the analysis.
of opioid consumption owning to lack of information, and opioid consumption at postoperative 4 hour in two studies [16,17] were used because there were no data available at postoperative 6 hour.

Agreement between two raters for data extraction was substantial (Cohen’s kappa = 0.63).

**Pain intensity at postoperative 1 hour**

A meta-analysis of six studies [13-18] (n = 366; 185 in ibuprofen group and 181 in control group) showed that pain scores measured at 1 hour postoperatively were significantly reduced in the preoperative ibuprofen group (MD, -1.64, 95% CI [-2.56 to -0.72], P < 0.001, $I^2 = 95\%$) (Fig. 4A). In the sensitivity test, the pain score measured postoperative 1 hour postoperatively was lower (MD, -1.94, 95% CI [-2.30 to -1.57], P < 0.001, $I^2 = 29\%$) than the estimated pooled effect with consistent direction and significance after excluding outlier study [14]. It can be concluded that the results were robust. In addition, there was an effect of reducing heterogeneity to an acceptable level.

**Pain intensity at postoperative 4-6 hour**

A meta-analysis synthesizing six studies [13-18] (n = 366; 185 in ibuprofen group and 181 in control group) showed that preoperative ibuprofen group reported lower pain intensity with a statistical significance (MD, -1.17, 95% CI [-2.09 to -0.26], P < 0.001, $I^2 = 94\%$) (Fig. 4B). In sensitivity analysis, the effects of pain intensity at 4-6 hour reduced (MD, -0.79, 95% CI [-1.29 to -0.30], P = 0.0016, $I^2 = 61\%$) compared to pooled effect after excluding one trial [18], which was an outlier in this analysis. However, the results were also reliable because direction and significance were maintained. Although the heterogeneity decreased, it is still of moderate intensity; hence, the results should be interpreted carefully.
Pain intensity at postoperative 24 hour

A meta-analysis with data from six studies [13-18] (n = 366; 185 in ibuprofen group and 181 in control group) demonstrated that pain scores of the ibuprofen group were lower than those of the control group (MD, -0.58, 95% CI [-0.99 to -0.18], P < 0.001, $I^2 = 90\%$) (Fig. 4C).

In the sensitivity analysis, the pain score of the ibuprofen group measured at postoperative 24 hour was still effective (MD, -0.75, 95% CI [-1.17 to -0.32], P < 0.001, $I^2 = 88\%$) than the estimated effect after excluding one trial [14], an outlier. As the direction and significance of results were maintained, the results were regarded as robust.

Accumulative opioid consumption at postoperative 4-6 hour

A total of four studies [14,16-18] (n = 275; 139 in ibuprofen group and 136 in control group) showed data on accumulative opioid consumption at postoperative 4-6 hour. Preoperative ibuprofen administration significantly reduced opioid consumption (MD, -56.35 μg, 95% CI [-101.10 to -11.60], P < 0.001, $I^2 = 91\%$) (Fig. 5A). The sensitivity analysis did not show any outlier.

Accumulative opioid consumption at postoperative 24 hour

Meta-analysis of five studies [13,14,16-18] (n = 326; 165 in ibuprofen group and 161 in control group) showed that cumulative opioid consumption at postoperative 24 hour was lower in the ibuprofen group (MD, -131.39μg, 95% CI [-224.56 to -38.21], P < 0.001, $I^2 = 95\%$) (Fig. 5B).

In the sensitivity analysis, the effect size of cumulative opioid consumption at 24 hour increased (MD, -170.70μg, 95% CI [-265.63 to -75.76], P < 0.001, $I^2 = 95\%$) after excluding one trial [14], which was indicated to be an outlier.
Discussion

Recently, the multimodal analgesic approach has been in the spotlight as a way to reduce pain. Supplemental analgesics can be administered before, during or after surgery. Although some studies have shown the effect of preoperative drug administration on postoperative pain and opioid consumption [20,21], limited data are available regarding when specifically ibuprofen is administered preoperatively through the intravenous route.

In this meta-analysis, data showed statistically significant reductions in postoperative pain scores and opioid consumption when ibuprofen was administered intravenously before surgery.

Postoperative pain scores were reduced at all analyzed time points (postoperative 1, 4-6, 24 hour) after a single dose of ibuprofen. The MDs in postoperative pain scores reduced as time went by; -15.21, -10.82, and -6.58, for postoperative 1, 4-6, 24 hour respectively. Therefore, it can be inferred that the effect of preoperative single-dose administration of ibuprofen decreases as time passes; however, it is still effective until postoperative 24 hour. This result is interesting considering that the mean duration of ibuprofen is around 6-8 hours.

The half-life of intravenous ibuprofen is around 2 hour [22]. Pain scores and opioid consumption measured in the original articles included in our meta-analysis were assessed at postoperative 24 hour, which meant that more than 24 hours had passed since the preoperative administration of single-dose ibuprofen. This meant that the effect of ibuprofen persisted even when the plasma concentration of ibuprofen was almost 0. In this regard, it is speculated that preoperative administration of ibuprofen may have preemptive effect as well. Preemptive analgesia limits pain response by suppressing initial pain sensitization [23].

Moreover, our study reported that preoperative ibuprofen significantly reduced postoperative opioid consumption, while other study [21] reported that flurbiprofen, a similar NSAID, did not reduce opioid consumption.
Although we could not conduct subgroup analysis according to the dose of ibuprofen in this meta-analysis, it would be interesting and meaningful to compare whether the effect of ibuprofen varies depending on the doses (400 mg or 800 mg). In addition, comparison between ibuprofen and other analgesics in various settings, including patient characteristics, such as age or weight, type and length of surgery, and anesthetic techniques regarding type and doses of anesthetics used, may contribute to the determination of the optimal multimodal analgesia.

Opioid-related side effects, such as postoperative nausea and vomiting, can be expected to be reduced as opioid consumption was reduced when ibuprofen was administered preoperatively, as reported by another study using flurbiprofen [24]. In our meta-analysis, we could not analyze the effect of preoperative ibuprofen on postoperative nausea and vomiting since the included articles reported outcomes in different ways from one another. One article [13] reported the number of patients who experienced nausea and vomiting, while others [15-18,25] reported events of nausea and vomiting. In addition, some articles [13,16,17,25] counted nausea and vomiting as one criterion, while others [15,18] counted them as two different events. Therefore, we concluded that outcomes of postoperative nausea and vomiting cannot be synthesized appropriately for the meta-analysis.

In this meta-analysis, heterogeneity in all study outcomes were quite high. Such high heterogeneity could be a result of various study designs, types of surgeries, anesthetic techniques, doses of anesthetic drugs, or drugs that were administered simultaneously, such as remifentanil or gabapentin [14,16]. The doses and type of rescue drugs and standards of timing of rescue drug administration were also different between trials.

In this study, heterogeneity was reduced after excluding one study [18] from all the analyses (results not shown). Unlike others, this study used tramadol to control postoperative pain. Tramadol targets opioid receptors and inhibits the reuptake of noradrenaline and serotonin [26].

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The unique mechanisms of action of tramadol may have contributed to the high heterogeneity.

There are some limitations in our meta-analysis. First, only a few studies were included in our meta-analysis. Although we did not limit publication year when we selected articles, only a few studies were included. This could be because there were few published articles on this topic, or the inclusion criteria of our meta-analysis were very strict and limited. Second, heterogeneity between studies was high in all the analysis of postoperative outcomes, possibly caused by several factors, such as different surgery types and different doses of study drug or combination drugs. We tried to conduct subgroup analysis to determine the cause of high heterogeneity; however, owning to the small number of included studies, we could not classify the studies into homogenous subgroups. Third, data and analysis of opioid consumption could have been more accurate if rescue analgesia was included in opioid consumption; however, this was not performed owning to lack of information. All studies recorded the number of patients who required rescue analgesia, not the number of rescue analgesia administrations. Therefore, we could not calculate the exact amount of rescue analgesics injected.

In conclusion, preoperative single-dose intravenous ibuprofen can reduce pain and opioid consumption until postoperative 24 hour. We expect that these findings can contribute to multimodal analgesia by increasing the efficiency of postoperative pain management.

However, the analysis reported high heterogeneity within trials, probably owning to variations in study designs and small sample sizes. Further studies with similar design are needed to increase the reliability of evidence and conclude regarding the effect of preoperative administration of ibuprofen on postoperative pain intensity and opioid consumption.
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<table>
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<th>Source</th>
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RCT: randomized controlled trial, IV: intravenous, VAS: visual analogue scale, PACU: post-anesthesia care unit, PO: per os; by mouth, NRS: numerical rating scale
Fig. 1. Flow diagram of study selection.
**Fig. 2.** Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies.
**Fig. 3.** Risk of bias summary: review authors’ judgements about each risk of bias item for each included study. +, low risk; ?, unclear; -, high.
Fig. 4. Forest plot: Effect of ibuprofen on postoperative pain scores. (A) Postoperative 1 hour. (B) Postoperative 4-6 hour. (C) Postoperative 24 hour. CI: confidence interval, SD: standard deviation.
Fig. 5. Forest plot: Effect of ibuprofen on opioid consumption. (A) Postoperative 4-6 hour. (B) Postoperative 24 hour. CI: confidence interval, SD: standard deviation.