

Randomized Trial

Synergistic Effect of Intravenous Ibuprofen and Hydromorphone for Postoperative Pain: Prospective Randomized Controlled Trial

Eun Jung Oh, MD, Hyun Joo Ahn, MD, PhD, Woo Seog Sim, MD, and Jin Young Lee, MD

From: Samsung Medical Centre,
Sungkyunkwan University School
of Medicine
Seoul, Republic of Korea

Address Correspondence:
Hyun Joo Ahn, MD, PhD
Associate professor
Samsung Medical Centre,
Sungkyunkwan University School
of Medicine
Department of Anesthesiology
and Pain Medicine
Samsung Medical Center
50, Ilwon-Dong, Kangnam-Gu
Seoul, 135-710
Korea
E-mail:
hyunjooahn@skku.edu

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Background: An intravenous form of ibuprofen has recently been approved by the Food and Drug Administration (FDA) and reports are rare on its co-administration with opioids.

Objectives: We researched whether an intravenous ibuprofen-hydromorphone combination is synergistic, additive, or infra-additive on postoperative pain.

Study Design: A parallel-group, 1:1:1 allocation, randomized, double-blind controlled trial.

Setting: University teaching hospital in Korea.

Methods: Ninety patients, undergoing breast surgery, were divided into one of the 3 groups (I, H, IH groups). Positive analgesic efficacy was defined as a numeric rating scale (NRS) ≤ 3 on a 0 – 10 NRS, 30 minutes after the drug administration. Drugs were administered by the Dixon's up-and-down method. Starting doses were ibuprofen (I) 50 mg, hydromorphone (H) 0.25 mg, or ibuprofen 25 mg + hydromorphone 0.125 mg (IH). The maximum doses were ibuprofen 800 mg, hydromorphone 2 mg, or ibuprofen 400 mg + hydromorphone 1 mg. Combination index (CI) (additive: 0.9 – 1.1, synergism: < 0.9 , antagonism: > 1.1), dose reduction index (DRI, a measure of how much the dose of each drug in a combination can be reduced), and isobologram were used to define the nature of their interaction.

Statistics: One way ANOVA, Kruskal Wallis test, and Chi square test, significance level $P < 0.05$.

Results: The median effective doses (ED50) of ibuprofen and hydromorphone were 1,447 mg and 1.5 mg, respectively. The median ED50 of the combination was ibuprofen 71 mg and hydromorphone 0.3 mg. Ibuprofen and hydromorphone showed a strong synergy (CI 0.2, DRI 20 and 5 for ibuprofen and hydromorphone at ED50).

Limitation: Analgesic efficacy was observed during post-anesthesia care unit (PACU) period only.

Conclusions: The combination of intravenous ibuprofen and hydromorphone produces a strong synergistic analgesia on postoperative pain.

Key words: Median effective dose, hydromorphone, pain, ibuprofen, postoperative

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Opioid analgesics are a mainstay in the management of post-operative pain. However, their use is often limited by adverse effects such as respiratory depression, sedation, pruritus, and nausea/vomiting. Adjuvant agents used

with opioids may help mitigate the side effects by reducing the total dose required. The World Health Organization also recommends a multimodal approach to the treatment of pain (1).

Non-steroidal anti-inflammatory drugs (NSAIDs)

are the most commonly used adjunctive agents and address a different pain pathway with opioids. Opioids interact with opioid receptors distributed in the brain and spinal cord dorsal horn providing pain relief (2,3). Whereas NSAIDs inhibit the production of cyclooxygenase (COX)-1 and COX-2 enzymes to block the conversion of arachidonic acid to prostaglandins such as PGE₂ and PGE₁. This inhibition prevents the sensitization of pain receptors at the site of injury (4). NSAIDs have not only an analgesic effect but also antipyretic and anti-inflammatory properties. Thus the combination of opioids and NSAIDs is expected to be more compatible for post-operative management.

Ibuprofen, a commonly used NSAID, was only available as an oral form until recently. The lack of a parenteral formulation has been an obstacle in use of ibuprofen for the post-operative period. But recently an intravenous form of ibuprofen has been approved (5). To our knowledge, there has been no study describing the nature of the interaction between ibuprofen and hydromorphone which is a widely used opioid with less concern for patients with renal or hepatic insufficiency.

Therefore, the present study was undertaken to find the analgesic efficacy through evaluating the median effective analgesic doses (ED₅₀) of ibuprofen, hydromorphone, and comparing it with their variable combination doses. We determined the opioid-sparing effect of ibuprofen using combination index (CI), dose reduction index (DRI), and isobolographic analysis.

Our hypothesis was co-administration of ibuprofen and hydromorphone produces a synergistic effect on post-operative pain.

METHODS

Study Population

The study was approved by our institutional review board and a written informed consent was obtained from patients undergoing breast surgery from June 2014 until December 2014. All recruited patients were American Society of Anesthesiologists (ASA) physical status I or II who were able to communicate and understand the pain scales.

Exclusion criteria were (i) any contraindication to the use of ibuprofen or hydromorphone, a history of allergy or hypersensitivity, a calculated creatinine clearance of < 75 mL/min, the presence or history of asthma, bleeding tendency, coronary artery bypass graft (CABG) surgery, heart failure, peptic ulcer disease, inflammatory bowel disease or any other gastrointestinal disorder,

and renal or hepatic disease; (ii) pregnancy; (iii) age younger than 18 years; (iv) intraoperative use of regional anesthesia; (v) intraoperative administration of analgesics other than remifentanyl; (vi) postoperative pain ≤ 3 on a numeric rating scale (NRS) in the post-anesthesia care unit (PACU).

Study Design

This was a parallel-group design, 1:1:1 allocation, randomized, double-blind (participants, observers, and assessors of outcomes), controlled study. Randomization was done prospectively to one of the 3 groups using a computer-generated table and concealed envelopes (I, H, IH groups).

Before surgery, the patients were instructed on how to use the NRS (with 0, no pain, to 10, the worst imaginable pain). All patients received total intravenous anesthesia consisting of propofol and remifentanyl. No patient received premedication. Routine intraoperative monitoring and a bispectral index (BIS) monitor (Aspect Medical System, Norwood, MA, USA) were placed before induction of general anesthesia. The patient received intravenous (i.v.) midazolam (2 mg) and pre-oxygenation. After lidocaine 40 mg was administered, propofol and remifentanyl were started and maintained by effect site target concentration (propofol: 3 – 4 mcg/mL, remifentanyl: 3 – 5 ng/mL using an Orchestra pump (Orchestra™ Fresenius Vial, France). Tracheal intubation was performed after rocuronium 0.6 mg/kg using a 7.0 (ID) tube and mechanical ventilation was started to maintain normocapnia during the operation. Hemodynamic variation was maintained within 20% of the preoperative value and BIS score between 40 and 50. At the end of operation, all patients were extubated after confirming full recovery of muscle power and obeying command. No opioids or analgesics except remifentanyl were administered during operation.

Pain assessment was done by an investigator who is not aware of the drugs given. As soon as the patient arrived at the PACU, the pain intensity was assessed using NRS. Thereafter, the pain assessment was performed every 5 minutes. As soon as the NRS reached > 3 (defined as T_0), the patients received analgesia according to the protocol.

At T_0 , patients in the ibuprofen group (Group I) received ibuprofen (Caldolor®, 400 mg/4 mL, DB Pharm Korea Co, Korea) in a 200 mL bag as a continuous i.v. infusion over 15 minutes and 10 mL saline i.v. as a bolus. Patients in the hydromorphone group (Group H) received hydromorphone (Dilid®, Hydromorphone HCL,

2 mg/mL, Hana Pharm Co, Korea) i.v. as a bolus in a 10 mL syringe and saline in a 200 mL bag as a continuous i.v. infusion over 15 minutes. Patients in the ibuprofen + hydromorphone group (Group IH) received ibuprofen in a 200 mL bag as a continuous i.v. infusion over 15 minutes and hydromorphone i.v. as a bolus in a 10 mL syringe.

The dose of ibuprofen, hydromorphone, or both received by a particular patient was determined using Dixon's up-and-down technique (6). In Group I, the patient received 50 mg, 100 mg, 200 mg, 400 mg, or 800 mg ibuprofen. In Group H, the patient received 0.25 mg, 0.5 mg, 1 mg, 1.5 mg, or 2 mg hydromorphone. In Group IH, the patient received ibuprofen 25 mg and hydromorphone 0.125 mg, ibuprofen 50 mg and hydromorphone 0.25 mg, ibuprofen 100 mg and hydromorphone 0.5 mg, ibuprofen 200 mg and hydromorphone 0.75 mg, or ibuprofen 400 mg and hydromorphone 1 mg. The first dose was given to the first patient and the next dose was given according to the following rule: if the patient responds positively (NRS ≤ 3), the dose is decreased one step for the next patient, and conversely, if the patient responds negatively (NRS > 3), the dose is increased one

step for the next patient (Fig. 1).

The efficacy of the drug was assessed by NRS of 3 or lower, 30 minutes after drug administration (T30). Participants who reported ineffective analgesia (NRS > 3) at 30 minutes were given rescue analgesics according to our PACU protocol.

Blinding was ensured using blinded syringes and bags freshly provided by an anesthesiologist who prepared the drugs according to the Dixon's up and down method and wasn't involved in the assessment of the drug's effect.

The dose-effect curves, combination index (CI), dose reduction index (DRI), and isobologram of co-administration groups were constructed using the multiple drug-effect equation suggested by Chou-Talalay using the Calcsyn program (BIOSOFT, Cambridge, United Kingdom) (7).

The CI shows the type of interaction of the combined drugs. A CI in the range of 0.9 and 1.1 is considered to be an additive action. A CI < 0.9 and CI > 1.1 indicate synergism and antagonism, respectively. The DRI is a measure of how much the dose of each

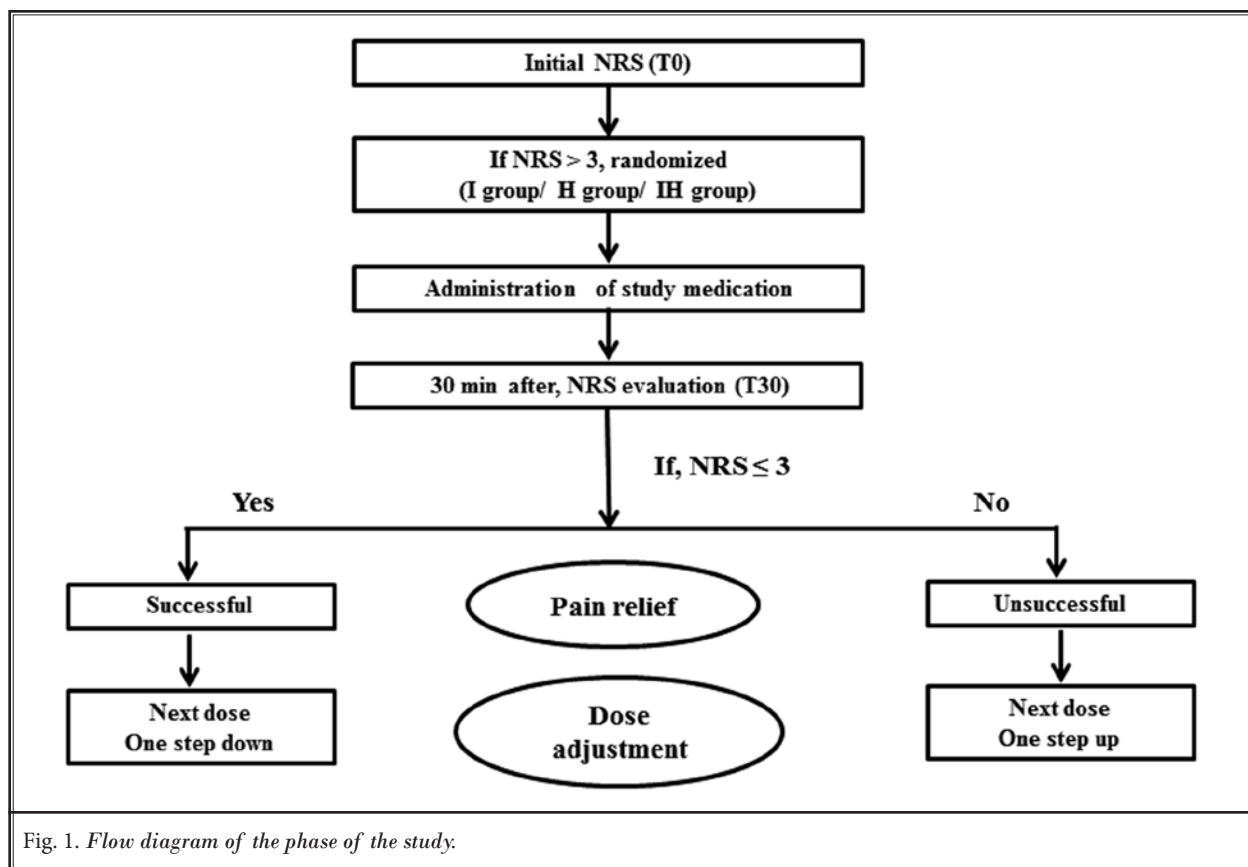


Fig. 1. Flow diagram of the phase of the study.

drug in a combination can be reduced at a given effect level compared with the doses of each drug alone. The isobologram is a graphical display, in which equipotent pairs of the doses of 2 drugs are connected by a line, which represents the additive activity between the 2 drugs. Synergism or antagonism was considered to exist between the 2 drugs if the dose of the combined drugs was lower or higher than this line, respectively (8).

In addition to NRS measurement, sedation (using a simplified 4-point scale, according to our hospital policy, where 0 = patient awake, 1 = respond only to verbal stimuli, 2 = respond only to physical stimulation, 3 = not arousable), desaturation ($SpO_2 < 94\%$), dizziness, nausea/vomiting, pruritus, and vital signs were collected at 15, 30, 45, and 60 minutes after the beginning of the infusion and every 30 minutes after, until discharge from the PACU. The highest temperature on POD0 and blood cell counts on POD1 were also recorded.

Data Analysis

The primary outcome variable was the CI at ED50 which shows interaction of the combined drugs. The number of participants needed per group was 30 ac-

ording to the method of Dixon (6).

The 3 groups were compared for patient characteristic data using the one way ANOVA, Kruskal Wallis test, and Chi square test. The occurrence of adverse events was compared between groups using the Chi square test with the Bonferroni correction.

RESULTS

We could not enroll all 30 patients in Group I because maximal dose of ibuprofen (800 mg) did not provide positive analgesic efficacy ($NRS \leq 3$) in 5 consecutive patients. Therefore, patient enrollment was stopped after 18 patients. All 30 patients finished the study in Group H. Two patients in Group IH were withdrawn from data analysis due to missing data. Hence data of 76 patients were analyzed (Fig. 2). The demographic and operational characteristics of the 3 groups were similar (Table 1).

NRS T0 was not different between the groups (I: 6.3 ± 1.7 H: 6.8 ± 2.1 , IH: 6.1 ± 1.9 , $P = 0.612$). The ED50 of ibuprofen was 1,447 (95% CI 603 – 3,477) mg. The ED50 of hydromorphone was 1.5 (95% CI: 1.1 – 2.1) mg. The ED50s of the combination were 71 (95% CI: 46 –

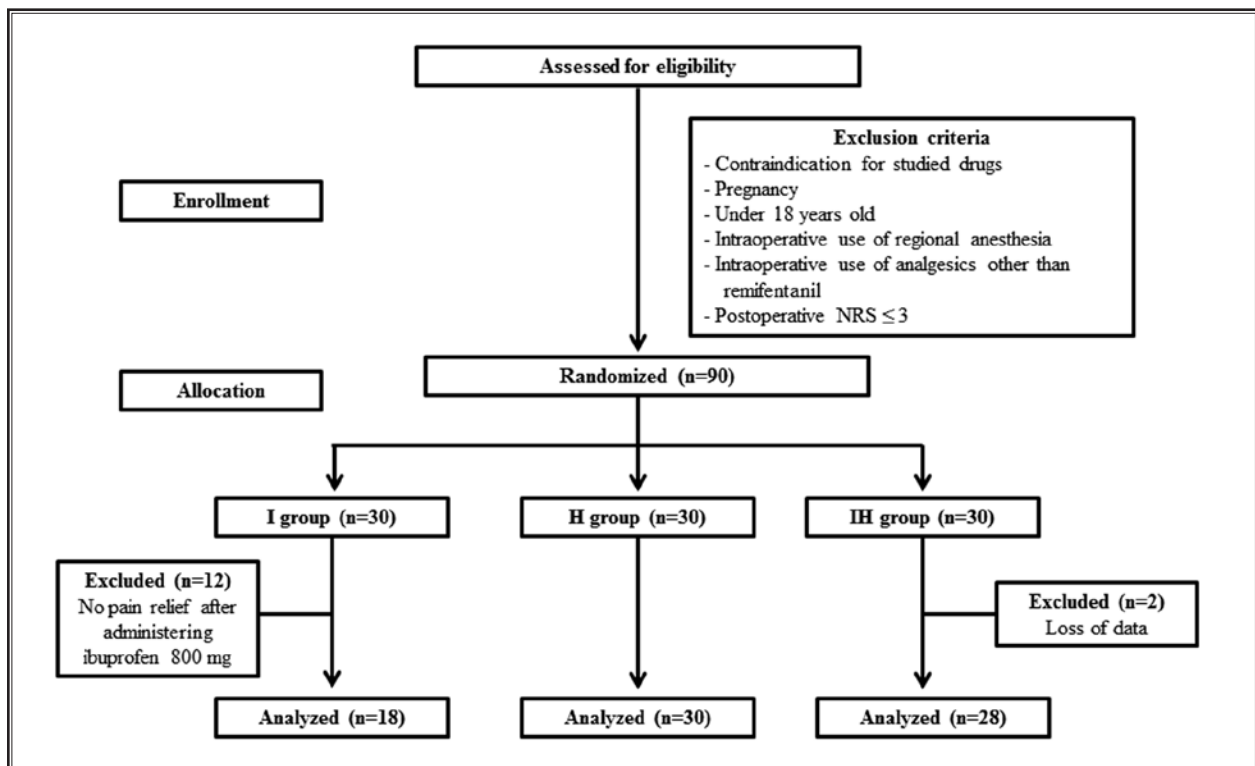


Fig. 2. Consort diagram.

Synergistic Effect of Ibuprofen and Hydromorphone

Table 1. Patients characteristics between I, H, and IH groups.

	I	H	IH	P-value
Age (years)	48 (9)	51 (8)	52 (9)	0.313
Body weight (kg)	57 (7)	59 (8)	57 (6)	0.563
BMI (kg/m ²)	23 (3)	24 (3)	23 (3)	0.265
Male/Female	0/18	0/30	1/27	0.420
ASA classification I/II (%)	61/39	67/33	68/32	0.888
Comorbidities (%)	6	8	7	0.817
Hypertension (%)	3	5	5	0.9912
Diabetes mellitus (%)	1	1	3	0.516
Thyroid disease (%)	3	3	1	0.319
Kidney disease (%)	0	0	0	0.196
Liver disease (%)	0	0	2	0.172
Duration of surgery (min)	86 (32)	93 (38)	99 (32)	0.452
Duration of anesthesia (min)	122 (32)	130 (39)	138 (34)	0.328
Propofol (mcg/mL)	3.8 (0.5)	3.7 (0.4)	3.7 (0.4)	0.739
Remifentanyl (ng/mL)	3.3 (0.5)	3.5 (0.5)	3.5 (0.6)	0.334
Baseline NRS pain intensity (0-10)	6.3 (1.7)	6.8 (2.1)	6.1 (1.9)	0.612
Baseline heart rate	73 (14)	77 (14)	78 (15)	0.380
Baseline blood pressure (mmHg)				
Systolic blood pressure	142 (20)	151 (19)	140 (24)	0.195
Diastolic blood pressure	76 (14)	85 (13)	76 (12)	0.651
Mean blood pressure	91 (13)	101 (12)	91 (14)	0.411
Operation name (1/2/3/4)	2/7/3/6	5/13/6/6	0/16/8/4	0.228

Data are mean (SD), number, or %. I, ibuprofen; H, hydromorphone; BMI, Body mass index.

Propofol remefentanyl, mean doses during administration. Operation name: 1, excisional biopsy; 2, partial mastectomy with/without lymph node dissection; 3, total mastectomy with/without lymph node dissection; 4, modified radical mastectomy.

109) mg for ibuprofen and 0.3 (95% CI: 0.2 – 0.5) mg for hydromorphone. ED₇₅ (75% effective dose) and ED₉₀ (90% effective dose) also showed the reduction of each drug when they were combined (Table 2, Fig. 3).

The drug interaction between ibuprofen and hydromorphone based on the combination index (CI) showed synergy in analgesia. A CI in the range of 0.9 and 1.1 is considered to be an additive action. A CI < 0.9 and CI > 1.1 indicate synergism and antagonism, respectively. CIs were 0.2 ± 0.1, 0.5 ± 0.2, and 0.9 ± 0.5 at ED₅₀, ED₇₅, and ED₉₀, respectively (Table 2).

The opioid sparing effect was evaluated by DRI. DRIs were 20, 15, and 10 for ibuprofen and 5, 3, and 1 for hydromorphone at ED₅₀, ED₇₅, and ED₉₀, respectively. This indicates 20 times, 15 times, and 10 times reduction of doses for ibuprofen and 5 times, 3 times and no reduction of doses for hydromorphone at each ED when they are administered together (Table 2).

According to CI and DRI, synergy was more appar-

ent at lower effective doses (ED₅₀ > ED₇₅ > ED₉₀).

Isobologram also showed the similar synergetic pattern (Fig. 4).

The incidence of adverse effects was higher in the H group compared to the other groups (*P* = 0.008). Incidence of desaturation (SpO₂ < 94%) and dizziness mostly contributed to the total incidence of adverse effects. Adverse effects were not observed in the I group (Table 3).

Vital signs during PACU stay were not different among the 3 groups. Temperature at T30 and the highest temperature on POD0 were not different among the 3 groups. Difference of hemoglobin values and platelet counts between pre-operative and POD1 were similar among the 3 groups (Table 4).

DISCUSSION

In this randomized double-blind controlled study, the ED₅₀s were 1,447 mg and 1.5 mg for ibuprofen

Table 2. ED₅₀, ED₇₅, ED₉₀, CI, and DRI.

	I	H	IH	CI	DRI
ED ₅₀	1,447 (602 – 3,477)	1.5 (1.1 – 2.1)	71 (46 – 109) *	0.2 (0.1)	20
			0.3 (0.2 – 0.5)*		5
ED ₇₅	3,125 (982 – 9,947)	2.2 (1.4 – 3.4)	215 (128 – 361) *	0.5 (0.2)	15
			0.8 (0.4 – 1.4)*		3
ED ₉₀	6,746 (1,584 – 28,736)	3.2 (1.9 – 5.5)	650 (268 – 1,574) *	0.9 (0.5)	10
			1.9 (0.7 – 5.3)*		1

Values are mean (95% confidence limit) or mean (SD). ED₅₀, Median effective dose; ED₇₅, 75% effective dose, ED₉₀, 90% effective dose; CI, combination index; DRI, dose reduction index; I, ibuprofen; H, hydromorphone. *: $P < 0.05$ compared to the single drug administration.

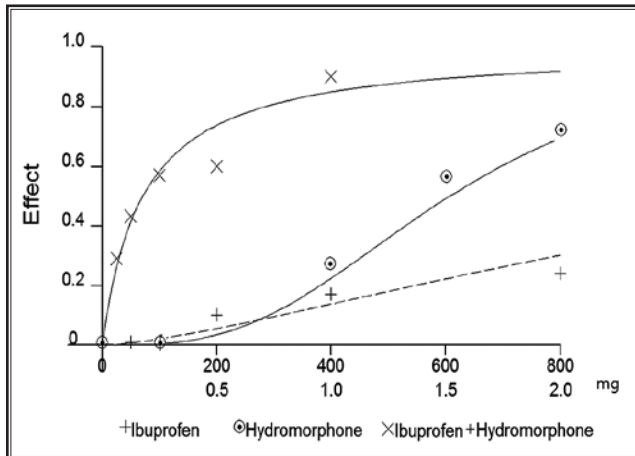


Fig. 3. Dose effect curve.

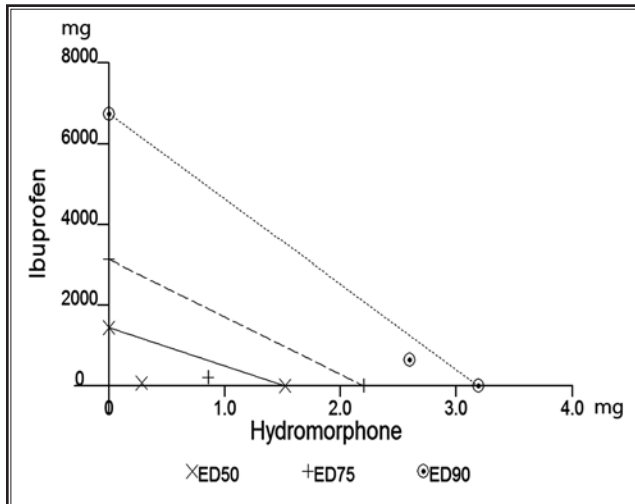


Fig. 4. Isobolographic representation of the combination of ibuprofen and hydromorphone. The ED₅₀, ED₇₅, ED₉₀ for single administration were placed on the X- and Y-axes. The lines connecting both ED₅₀ (solid line) ED₇₅ (long dashed line) ED₉₀ (short dashed line) represents the theoretical line of additivity. The x, +, o in the middle of the graph depict the experimentally derived ED₅₀, ED₇₅, and ED₉₀ in each group. The isobologram shows the synergistic interaction.

and hydromorphone single administration. ED₅₀s of combined drugs were 71 mg and 0.3 mg for ibuprofen and hydromorphone, respectively. CI and isobolographic analysis demonstrated that ibuprofen and hydromorphone had a favorable synergistic effect when administered in combination especially at lower doses.

Combining analgesics is a way to maximize the analgesic effect with lower doses and consequently minimize the adverse effect during pain control (9).

However, combining opioid with non-opioid analgesics is not always synergistic. Interaction between morphine and either nefopam (10) or tramadol (11) has been shown to be infra-additive. Paracetamol and morphine showed only an additive effect (12). A systemic review suggested pain intensity and reduction of morphine related adverse effects significantly decreased only with NSAIDs (13).

Until recently, ketorolac (Toradol®; Roche Laboratories, Nutley, NJ, USA) was the only NSAID available in parenteral form in North America. Additional parenteral options are available outside North America such as tenoxicam (Mobiflex®; Roche Laboratories, United Kingdom), parecoxib (Dynastat®; European Union), and 2 formulations of injectable diclofenac (Dyloject®; Javelin Pharmaceuticals, United Kingdom and Voltarol®; Novartis, United Kingdom). Although ketorolac is widespread in clinical practice, it is not labeled for the treatment of fever and contraindicated for preoperative administration, along with limited use for no more than 5 days. An intravenous form of ibuprofen has recently been approved and is the only i.v. antipyretic currently available and is currently one of 2 injectable NSAIDs available for the treatment of pain.

In our study, we showed strong synergy between ibuprofen and hydromorphone. The ED₅₀s of a single administration was relatively high such as 1,447 mg and 1.5 mg for ibuprofen and hydromor-

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Table 3. *Adverse effects.*

	I (n = 18)	H (n = 30)	IH (n = 28)	P-value
Sedation	0	0	0	0.196
SpO2 < 94%	0	4	2	0.249
Dizziness	0	7	3	0.061
Nausea	0	1	0	0.460
Vomiting	0	0	2	0.172
Pruritus	0	0	0	0.196
Side effects, total	0	12	7	0.008

Values are number of patients. I, ibuprofen; H, hydromorphone. $P = 0.002$: I vs. H. $P = 0.064$: I vs. IH. $P = 0.542$: H vs. IH with the Bonferroni correction.

Table 4. *Vital signs, hemoglobin, and platelets between I, H, and IH groups.*

	I	H	IH	P-value
HR (bpm)	62.3 (7.9)	65.7 (10.7)	65.3 (9.6)	0.472
MBP (mmHg)	89.7 (13.7)	92.7 (13.8)	85.4 (12.2)	0.115
Temperature (°C)				
T ₃₀	36.7 (0.5)	36.7 (0.4)	36.6 (0.4)	0.783
POD0	36.4 (0.3)	36.5 (0.3)	36.6 (0.5)	0.348
Hemoglobin diff (g/dL)	0.8 (0.8)	1.0 (1.1)	1.2 (1.3)	0.764
Platelet diff (×1000, /μL)	35.5 (38.8)	21.7 (35.7)	23.6 (46.0)	0.689

Data are mean (SD). I, ibuprofen; H, hydromorphone; T30: 30 minutes after drug administration; POD, post-operative day; diff, Preoperative–POD1.

phone. We did not administer opioids or other analgesics except continuous infusion of remifentanyl during operation. Remifentanyl is related to acute opioid tolerance and opioid-induced hyperalgesia (14). The ED50 of hydromorphone may have increased due to intraoperative remifentanyl infusion and abrupt stop. Ibuprofen only provided 29–22% decrease of NRS at the maximum dose of 800 mg. A study done in orthopedic surgery also showed 800 mg of ibuprofen reduced pain score only by 20%. However, post-operative morphine consumption was significantly reduced by ibuprofen co-administration (15).

Besides an analgesic effect, NSAIDs provide antipyretic anti-inflammatory properties. The antipyretic effect of NSAIDs is induced by interleukin (IL)-1 and IL-6 in the hypothalamus and inhibits the production of prostaglandins and resets the thermoregulatory system, leading to vasodilation and increase heat loss. The anti-inflammatory effects of NSAIDs result from inhibition of COX-1 to block the conversion of arachidonic acid to prostaglandins (16). Reduction of fever and inflammation not only offers substantial benefit to a patient's well-being but the metabolic compromise of sustained fever may potentiate risks associated with common comorbidities encountered in hospitalized patients.

Acetaminophen and ibuprofen have been the primary agent of choice for patients with fever. Data have demonstrated equal efficacy between the 2. However, ibuprofen offered pharmacokinetic advantages in early onset and durable antipyretic effects (17). However, we could not observe significant benefit on fever in the groups containing ibuprofen. That's probably because most patients did not develop significant fever postoperatively in our study. Operations related to high inflammatory reaction may receive a more beneficial effect from ibuprofen addition and further studies are required on this.

Another advantage of the synergistic interaction was to decrease the well-known opioid side effects. Marret and colleagues (18) showed in their meta-analysis that combining NSAIDs with morphine PCA reduced postoperative nausea, vomiting, and sedation by 30%. In our study, Group H seemed to develop more frequent dizziness and desaturation, and total adverse effects were higher in Group H than in the other groups. Our study was to determine EDs and drug interaction using various doses of drugs. Further studies on adverse effects are required using fixed equi-analgesic doses.

There were several limitations in our study. First, we could not enroll 30 patients in Group I because the

maximal dose of ibuprofen (800 mg) did not provide positive analgesic efficacy (NRS ≤ 3) in 5 consecutive patients. Second, as a limitation of Dixon's up and down method, the EDs would be over-estimated if the patients who are sensitive to pain are placed in the earlier part of patient allocation. Third, many anesthesiologists administer intra-operative opioids such as fentanyl and it would reduce EDs of ibuprofen and hydromorphone of our study. However, synergy between the 2 drugs would still exist. Forth, as our assessment was limited to the PACU period, a significant pain relief or reduction in adverse effects cannot be excluded after PACU discharge. Fifth, adverse gastrointestinal and renal ef-

fects associated with long-term NSAID use were also beyond our scope. In previous studies, however, neither gastrointestinal nor renal adverse effects have been demonstrated with i.v. ibuprofen (15,19-21). Finally, we excluded patients with serious cardiovascular thrombotic events, myocardial infarction, and stroke from our study. NSAIDs may increase risk in those patients and we should be careful with multimodal analgesic approaches including NSAIDs in this population.

In conclusion, the combination of the i.v. ibuprofen and hydromorphone produces a strong synergistic analgesia for postoperative pain.

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