ORIGINAL ARTICLE

A Randomized, Placebo-Controlled, Double-Blind Study that Evaluates Efficacy of Intravenous Ibuprofen and Acetaminophen for Postoperative Pain Treatment Following Laparoscopic Cholecystectomy Surgery

Mursel Ekinci[1] · Bahadır Ciftci[1] · Erkan Cem Celik[2] · Emine Arzu Köse[1] · Muhammet Ahmet Karakaya[1] · Yasar Ozdenkaya[3]

Abstract

Background Ibuprofen is a NSAID that has anti-inflammatory, antipyretic, and analgesic effects. The oral form of the drug has been used safely for a long time and is one of the most preferred NSAIDs. It has been shown that ibuprofen is effective in the treatment of postoperative pain; however, there have not been sufficient studies on ibuprofen. We evaluated and compared the influence of IV forms of ibuprofen and acetaminophen on pain management and opioid consumption on patients undergoing laparoscopic cholecystectomy surgery.

Methods Patients were stratified into three groups. Group I (group ibuprofen, $n = 30$) was administered 800 mg of IV ibuprofen; group A (group acetaminophen, $n = 30$) was administered 1000 mg of IV acetaminophen; and group C (control group, $n = 30$) was given 100 ml of saline solution. We evaluated opioid consumption and VAS scores postoperatively.

Results Pain scores in group I and group A at all time periods were lower than those in group C ($p < 0.05$). Group I had significantly lower VAS scores than those in group A at all time periods postoperatively ($p < 0.05$). Those in group C had significantly higher opioid consumption than the other groups ($p < 0.05$). Opioid consumption in group I at all time periods postoperatively was significantly lower than those in group A ($p < 0.05$). Group I had statistically lower rescue medication than the other groups at all time periods.

Conclusion Our study suggested that IV ibuprofen resulted in lower pain scores and reduced opioid use compared with acetaminophen postoperatively in the first 24 h in patients undergoing laparoscopic cholecystectomy surgery.

Keywords Laparoscopic cholecystectomy · Analgesia · Ibuprofen

Introduction

Postoperative pain is an undesirable condition that may affect patient comfort and cause complications in the postoperative period. In the literature, it has been reported that acute postoperative pain occurs in 60–80% of patients.[1,2] Effective postoperative analgesia management can prevent most complications such as respiratory, cardiovascular complications, delayed mobilization, and prolonged hospitalization.[3,4]

Laparoscopic cholecystectomy is considered as the gold standard technique for surgical treatment of gall bladder stones.[5] Tissue trauma may be severe, as the ports used in the laparoscopic technique passes through the muscles and ligaments. Pain may occur due to this tissue trauma, and the most important component of this pain is inflammatory pain.[6]

✉ Bahadır Ciftci
bciftci@medipol.edu.tr

Mursel Ekinci
drmurselekinci@gmail.com

[1] Present address: Department of Anesthesiology and Reanimation, Istanbul Medipol University, Bagcilar, 34000 Istanbul, Turkey

[2] Department of Anesthesiology and Reanimation, Erzurum Regional Training and Research Hospital, Yakutiye, 25070 Erzurum, Turkey

[3] Department of General Surgery, Istanbul Medipol University, Bagcilar, 34000 Istanbul, Turkey

Opioids have been widely used in the postoperative pain management, and they exert analgesic effects by affecting the central nervous system.[7] However, these agents do not block the inflammatory component of pain and do not affect the underlying pathology of the process.[8] Therefore, non-steroidal anti-inflammatory drugs (NSAIDs) should be used in combination with opioids for postoperative pain management. These agents block the conversion of arachidonic acid to prostaglandins and prevent the response of pain receptors to injury.[9] Multimodal analgesia treatment including NSAIDs and opioids can reduce the total amount of opioids required, and the pain can be treated effectively. Thus, opioid-related side effects (ORAE) can also be minimized.[10]

Paracetamol (Europe) and acetaminophen (USA) are the names of the same drug. This drug has been used safely for a long time. However, its mechanism of action has not been explained clearly until now. It has analgesic and antipyretic effects like NSAIDs, but it does not have anti-inflammatory activity. For this reason, acetaminophen has not been evaluated as a NSAID agent. Acetaminophen effects both the peripheral (COX inhibition) and central (COX, serotonergic descending neuronal pathway) antinociception processes.[11]

Ibuprofen is a NSAID that has anti-inflammatory, antipyretic, and analgesic effects.[12] The oral form of the drug has been used safely for a long time and is one of the most preferred NSAIDs. It has been shown that ibuprofen is effective in the treatment of postoperative pain; however, there have not been sufficient studies on ibuprofen.[13–16]

The primary objective of the present study is to evaluate the efficacy of the IV forms of ibuprofen and acetaminophen on postoperative pain control and opioid requirement on patients undergoing laparoscopic cholecystectomy.

Materials and Methods

Ethical approval was obtained from the Istanbul Medipol University Committee for this randomized, double-blind, placebo-controlled study. Ninety patients in ASA 1–2 classifications, scheduled for laparoscopic cholecystectomy under general anesthesia, aged between 18 and 70 years, and planned hospitalization stay for at least 24 h were included in this study. Written informed consent was obtained from all patients. Demographic data were recorded included age, BMI, gender, ASA score, the duration of surgery, and anesthesia (in minutes).

Patients classed ASA 3 or above, with a history of study drugs allergy, diagnosed asthma or chronic obstructive pulmonary disease before, with a history of ischemic cardiomyopathy and heart failure, severe hepatic and renal failure, long-term non-steroidal anti-inflammatory and opioid analgesics, using oral anticoagulants, known with bleeding diathesis or platelet dysfunction, with a history of gastrointestinal diseases, with a history of neuropathic disease, who discontinued the study drugs and patient-controlled analgesia (PCA) device, and who are pregnant or breastfeeding were excluded from the study.

Before operation, the patients received information about the drugs in the study, visual analog scale (VAS) for pain evaluation, and how to use the PCA device. There were three groups randomized by closed envelope method (group ibuprofen, $n = 30$; control group, $n = 30$; group acetaminophen, $n = 30$). Group I was administered 800 mg of IV ibuprofen in 100 ml saline; group A was administered 1000 mg of IV acetaminophen; and group C was administered 100 ml of normal saline 30 min preoperatively. Everyone was unaware of randomization. Moreover, 2-mg intravenous midazolam was administered to all patients for premedication in the operation room. All patients including standard ECG, peripheral oxygen saturation (SpO_2), and non-invasive blood pressure were monitored classically. All measurements were recorded at 5-min intervals during surgery. Propofol 2–2.5 mg/kg iv and 0.5 mg/kg iv rocuronium for muscle relaxation were administered for anesthesia induction. Sevoflurane 2–3% in a mixture including oxygen and air (50% O_2/50% air) and remifentanil infusion intravenously 0.25 μg/kg/min were administered for maintaining anesthesia. All operations were administered by the same surgical team using the same technique. Meperidine 0.5 mg/kg iv was administered to all groups for approximately 20–30 min before the end of the surgery. Atropine 0.5 mg and neostigmine 1.5 mg iv were administered for muscle relaxation antagonism at the end of the operation. All patients were taken to the postoperative care unit (PACU) after extubation.

Postoperative Analgesia Management

Drugs were administered to all patients every 8 h at postoperatively 24 h. PCA device was attached to all patients in the PACU. The PCA device prepared with a dose of 10 mcq concentration fentanyl was programmed no basal infusion, 20 mcq bolus dose, and 20-min lockout time and continued for 24 h. In addition, the PCA is not standard practice in our clinic for laparoscopic cholecystectomy surgery. We performed this to compare opioid consumption for study. An anesthesiologist blinded to the study drugs and groups evaluated the patients at the postoperative period. The VAS (VAS 0 = no pain, VAS 10 = the most severe pain) was used for the postoperative analgesia assessment. Meperidine 0.25 mg/kg iv was administered for rescue analgesia if the VAS score was 4 and above. If necessary, the same dose was repeated after 5 min. The sedation level was measured with a four-point sedation scale (0—awake and eyes were open; 1—sleep but responsible to verbal stimuli; 2—difficult to wake; 3—sleepy not able to wake with shaking).

Table 1 Demographic data and comparison of operative procedures between group C, group P, and group I

	Group C (n = 30)	Group P (n = 30)	Group I (n = 30)	p
Age (years)	44.06 ± 8.32	42.46 ± 7.49	43.06 ± 7.88	0.732 $^\alpha$
BMI (kg/cm^2)	26.53 ± 1.54	25.73 ± 1.79	26.00 ± 1.92	0.209 $^\alpha$
Gender (M/F)	15/15	8/22	13/17	0.164$^\beta$
ASA (I/II)	18/12	14/16	11/19	0.192$^\beta$
Duration time of anesthesia	58.93 ± 6.07	57.10 ± 4.68	55.73 ± 4.89	0.066$^\alpha$
Duration time of surgery	46.50 ± 5.74	46.90 ± 5.28	46.00 ± 5.36	0.816$^\alpha$
Blood loss	59.16 ± 7.33	59.03 ± 6.81	58.73 ± 7.20	0.971$^\alpha$
Length of hospitalization	1.36 ± 0.99	1.26 ± 0.52	1.26 ± 0.82	0.858$^\alpha$
Preoperative diagnosis				0.314$^\beta$
Chronic cholecystitis	9	5	12	
Gallbladder polyp	1	1	0	
Cholelithiasis	20	24	18	
Pathologic diagnosis				0.522$^\beta$
Chronic cholecystitis	17	13	19	
gallbladder polyp	1	1	0	
Cholelithiasis	12	16	11	

Values are expressed mean ± standard deviation or number; *ASA*, American Society of Anesthesiologist

$^\alpha$ $p > 0.05$ one-way ANOVA between groups

$^\beta$ $p > 0.05$ chi-square test between groups

Adverse effects of the drugs used in the study (breathing depression, sedation/confusion, urinary retention, nausea, vomiting, pruritus, constipation, bleeding, and dyspepsia) were recorded.

Statistical Analysis

Power analysis was performed according to the total opioid consumption variable. It was determined that the effect size was 0.59 in the 95% confidence interval and the power was 0.99 in the significance level. This result indicates that the study sample is sufficient. The statistical data were analyzed by the IBM SPSS 20.0 software. The Kolmogorov–Smirnov test was used to evaluate the data distribution. The Pearson chi-squared test was used for comparing the categorical data

between groups. We used the one-way ANOVA followed by Tukey's tests to check the differences among groups, at a significance level of 5% for normally distributed continuous variables. Descriptive statistics was expressed as mean ± SD.

Results

Baseline demographic data showed no statistical difference between groups ($p > 0.05$) (Table 1).

Pain scores in group I and group A at all time periods were lower than those in group C ($p < 0.05$) (Table 2). Especially, those in group I had significantly lower VAS scores than those in group A at all time periods postoperatively ($p < 0.05$) (Table 2). Those in group C had significantly higher opioid

Table 2 The comparison of VAS values between group C, group P, and group I

	Group C (n = 30)	Group P (n = 30)	Group I (n = 30)	p
VAS recovery	6.96 ± 1.29	4.90 ± 1.12$^\alpha$	1.93 ± 1.74 $^{\alpha\,\beta}$	< 0.001
VAS 1st hours	5.60 ± 0.77	4.66 ± 0.80 $^\alpha$	1.76 ± 1.25 $^{\alpha\,\beta}$	< 0.001
VAS 2nd hours	4.53 ± 0.81	4.06 ± 0.78 $^\alpha$	1.73 ± 1.48 $^{\alpha\,\beta}$	< 0.001
VAS 4th hours	3.66 ± 0.80	3.33 ± 0.71 $^\alpha$	1.70 ± 1.36 $^{\alpha\,\beta}$	< 0.001
VAS 8th hours	3.96 ± 1.32	2.80 ± 0.71 $^\alpha$	1.43 ± 0.85 $^{\alpha,\,\beta}$	< 0.001
VAS 16th hours	3.06 ± 1.31	1.96 ± 0.66 $^\alpha$	0.86 ± 0.77 $^{\alpha,\,\beta}$	< 0.001
VAS 24th hours	1.70 ± 0.59	1.16 ± 0.79 $^\alpha$	0.26 ± 0.44 $^{\alpha,\,\beta}$	< 0.001

Values are expressed mean ± standard deviation; *VAS*, visual analog pain scale

$^\alpha$ $p < 0.05$ one-way ANOVA compared with group C

$^\beta$ $p < 0.05$ one-way ANOVA compared with group P

Table 3 The comparison of opioid consumption and rescue analgesia between group C, group P, and group I

	Group C (n = 30)	Group P (n = 30)	Group I (n = 30)	p
0-6th hours	192.83 ± 44.09	119.10 ± 22.27$^\alpha$	75.33 ± 31.40$^{\alpha,\beta}$	< 0.001
6-12th hours	167.66 ± 36.92	106.00 ± 17.29$^\alpha$	66.70 ± 26.74$^{\alpha,\beta}$	< 0.001
12-24th hours	205.83 ± 48.31	117.23 ± 30.59$^\alpha$	73.63 ± 41.21$^{\alpha,\beta}$	< 0.001
Total consumption	566.33 ± 126.23	342.33 ± 65.59$^\alpha$	215.66 ± 97.26$^{\alpha,\beta}$	< 0.001
Rescue analgesia (Y/N)	20/10	9/21[a]	1/29[a,b]	< 0.001

Values are expressed mean ± standard deviation or numbers

$^\alpha$ $p < 0.05$ one-way ANOVA compared with group C

$^\beta$ $p < 0.05$ one-way ANOVA compared with group P

[a] $p < 0.05$ chi-square test compared with group C; [b] $p < 0.05$ chi-square test compared with group P

consumption than the other groups ($p < 0.05$) (Table 3). Similar to VAS scores, opioid consumption in group I at all time periods postoperatively was significantly lower than those in group A ($p < 0.05$). Finally, those in group I had statistically lower rescue medication than the other groups at all time periods (Table 3).

In terms of adverse effects, the incidence of nausea and pruritus in group C occurred higher than the other groups ($p < 0.05$) (Table 4). Especially, those in group I had a lower incidence of nausea than those in group A ($p < 0.05$).

Renal insufficiency and higher creatinine levels were in the exclusion criteria of the study. So, these patients were not included. In addition, there were not any renal complications during the study.

Discussion

This study showed that the intravenous form of ibuprofen reduced the pain scores and opioid consumption in the 24-h postoperative period compared with acetaminophen. In addition, rescue analgesic utilization was significantly lower in those in the ibuprofen group.

Multimodal analgesia treatment is a pain management that is used to provide effective analgesia and reduce the incidence of ORAE. The primary objective of this treatment strategy is to provide adequate analgesia by using additive or synergistic effects between different analgesics.[17] This treatment strategy provides analgesia, reduces side effects, shortens the length of hospital stay, and results in faster recovery. The World Health Organization, American Pain Society, American Society of Anesthesiologists, and American Society of Regional Analgesia and Pain Medicine suggest this treatment strategy for postoperative pain management.[18] Severe, acute postoperative pain can be treated with multimodal analgesia, and the side effects of opioids can be reduced by reducing the required total analgesic dose. In our study, we aimed to use multimodal analgesia management by combining IV ibuprofen with low-dose opioids.

Laparoscopic surgery is advantageous compared with open surgery, as it has less tissue trauma and is minimally invasive; however, pain may occur quite commonly after laparoscopic surgery. In these cases, pain in the first hour after laparoscopy may be similar or even more severe than in open surgery.[19] If severe pain is not treated effectively in the first 24 h, the pain may be chronic with high risk.[20] Opioids have been widely used in the treatment of postoperative pain. However, adverse

Table 4 The comparison of incidence of adverse effects between group I, group P, and group C

	Group C (n = 50)	Group P (n = 50)	Group I (n = 50)	p*
Breathing depression	0	0	0	1.000
Sedation/confusion	0	0	0	1.000
Urinary retention	0	0	0	1.000
Nausea (Y/N)	12	9[a]	2[a,b]	0.010
Vomiting (Y/N)	8	8	2	0.082
Pruritus (Y/N)	7	3[a]	0[a]	0.016
Constipation	0	0	0	1.000
Bleeding	0	0	0	1.000
Dyspepsia	0	0	0	1.000

Values are expressed mean ± standard deviation; *$p > 0.05$; Y, yes; N. no

[a] $p < 0.05$ chi-square test compared with group C

[b] $p < 0.05$ chi-square test compared with group P

effects such as opioid-inducing hyperalgesia, tolerance, addiction, constipation, nausea, and vomiting limit the use of these agents alone.[7]

Preemptive analgesia is a treatment that is performed before tissue damage to prevent peripheral and central sensitization.[21] Postoperative hyperalgesia can be prevented by preventing sensitization. NSAIDs have been used for preemptive analgesia, and studies on using intravenous ibuprofen are still limited. In a study, Ahiskalioglu et al. administered ibuprofen 400 mg preemptively for laparoscopic cholecystectomy operation and emphasized that IV ibuprofen reduced opioid consumption.[14] Gozeler et al. administrated an IV ibuprofen 800 mg preemptively for septorhinoplasty operation and indicated that ibuprofen reduced postoperative pain scores.[22] In another study, Çelik et al. compared the efficacy of IV ibuprofen and acetaminophen. They performed the drugs preemptively for rhinoplasty operation and emphasized that IV ibuprofen provided more effective postoperative analgesia than acetaminophen.[23] In our study, we applied 800 mg iv ibuprofen 3×1; we started the drugs preemptively and continued postoperatively and compared ibuprofen with acetaminophen. According to this study's results, IV ibuprofen is superior to acetaminophen in terms of providing effective analgesia and reducing opioid consumption postoperative in the first 24 h. Thus, we emphasize that IV ibuprofen may be used as a part of multimodal analgesia.

Ibuprofen provides analgesia by inhibiting cyclooxygenase enzyme (COX-1 and COX-2). Primary effects (analgesia, antipyretic, and anti-inflammatory) occur due to COX-2 inhibition. The adverse effects occur due to inhibition of COX-1. Ibuprofen has a lower inhibition ratio of COX-1 to COX 2 compared with other NSAIDs. Thus, ibuprofen has lower adverse effects.[24] Acetaminophen is the first-step analgesic agent, mostly due to its lower adverse effects and safety. It is mostly preferred as the first-line agent in the pain treatment. It has been reported that acetaminophen is effective for postoperative analgesia treatment.[25,26]

In a meta-analysis by Moore et al., the efficacy of ibuprofen and acetaminophen was compared. Moreover, it has been reported that acetaminophen is the first-step treatment option for pain control, even though it is emphasized that ibuprofen is generally stronger than acetaminophen at standard doses.[27] They evaluated the oral forms of the drugs, and, in our study, we compared the IV forms of the two drugs.

The IV form of ibuprofen has been evaluated in different studies for the management of postoperative pain.[13,15,16] In these studies, 800 mg of IV ibuprofen was administered preoperatively and continued every 6 h postoperatively, and it has been reported that ibuprofen reduced opioid consumption compared with placebo. In our study, different from these studies, 800-mg dose was administered every 8 h and compared with acetaminophen. According to our results, IV

ibuprofen significantly reduces pain scores and opioid consumption compared with acetaminophen in the first 24 h postoperatively. There are two forms of IV ibuprofen: 400 mg and 800 mg. In a study, comparing 400 mg and 800 mg doses, it was reported that 800-mg ibuprofen administered every 6 h reduced the use of opioids and was well tolerated compared with the placebo group.[28] In our study, we found that the 800 mg dose-administered at every 8 h reduced the use of opioids compared with both acetaminophen and placebo group for laparoscopic cholecystectomy.

Adverse effects especially nausea, and pruritus was lower in the ibuprofen group due to the reduced use of opioids. Similarly, the requirement of rescue analgesic was lower in the ibuprofen group. We recommend ibuprofen because it reduces opioid consumption, thereby reducing the adverse effects of opioids.

This study has some limitations. First, we used only 800 mg of ibuprofen, which has two forms: 400 mg and 800 mg. Second, the 800-mg dose was used at every 8-h interval during 24 h postoperatively. We can use it at every 6-h interval. Our objective was to extend the time interval. Third, the sample size was detected according to the primary aim, that is, the reduction of opioid consumption. Lastly, ibuprofen and acetaminophen (Tylenol) can be used together as a fourth group for further multimodal analgesia treatment. However, we did not use this combination.

In conclusion, IV ibuprofen reduced pain scores and opioid consumption compared with acetaminophen in the first 24 h postoperatively after laparoscopic cholecystectomy surgery. In addition, it reduced the requirement of rescue analgesic and ORAE. Therefore, IV ibuprofen may have a more potent analgesic effect than IV acetaminophen in the postoperative pain treatment. Further studies may be essential to evaluate the efficacy of the IV form of ibuprofen.

Compliance with Ethical Standards

References

1. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: Results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth Analg.* 2003;97:534–540, table of contents.
2. Rathmell JP, Wu CL, Sinatra RS, Ballantyne JC, Ginsberg B, Gordon DB, et al. Acute post-surgical pain management: a critical

appraisal of current practice. Reg Anesth Pain Med. 2006; 31: 1–42. doi:https://doi.org/10.1016/j.rapmg.2006.05.002

3. Kehlet H, Holte K. Effect of postoperative analgesia on surgical outcome. Brish J Anaesth 2001;87:62–72.

4. American Society of Anesthesiologists Task Force on Acute Pain ManagementPractice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 2012;116:248–73.

5. Soper NJ, Stockmann PT, Dunnegan DL, et al. Laparoscopic cholecystectomy. The new 'gold standard'? Arch Surg 1992;127:917–21. discussion 921–913.

6. Donatsky AM, Bjerrum F, Go¨genur I. Surgical techniques to minimize shoulder pain after laparoscopic cholecystectomy. A systematic review. Surg Endosc. 2013;27:2275–82.

7. Oderda GM, Said Q, Evans RS, et al. Opioid-related adverse drug events in surgical hospitalizations: Impact on costs and length of stay. Ann Pharmacother. 2007;41:400–406.

8. Beilin B, Bessler H, Mayburd E, et al. Effects of preemptive analgesia on pain and cytokine production in the postoperative period. Anesthesiology. 2003;98:151–155.

9. Svensson CI, Yaksh TL. The spinal phospholipasecyclooxygenase-prostanoid cascade in nociceptive processing. Annu Rev Pharmacol Toxicol. 2002;42:553–583.

10. Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg. 1993;77:1048–1056.

11. Bebenista MJ, Nowak JZ. Paracetamol: Mechanism Of Action, Applications And Safety Concern. Acta Poloniae Pharmaceutica-Drug Research, Vol. 71 No. 1 pp. 11–23, 2014.

12. Scott LJ. Intravenous ibuprofen: in adults for pain and fever. Drugs 2012;72:1099–109.

13. Gago Martinez A, Escontrela Rodriguez B, Planas Roca A, et al. Intravenous ibuprofen for treatment of post-operative pain: a multicenter, double blind, placebo-controlled, randomized clinical trial. PLoS One 2016;11:e0154004.

14. Elif Oral Ahiskalioglu, MD, Ali Ahiskalioglu, Pelin Aydin, Ahmet Murat Yayik, Ayetullah Temiz. Effects of single-dose preemptive intravenous ibuprofen on postoperative opioid consumption and acute pain after laparoscopic cholecystectomy. Medicine (2017) 96:8.

15. Kroll PB, Meadows L, Rock A, et al. A multicenter, randomized, doubleblind, placebo-controlled trial of intravenous ibuprofen (i.v.-ibuprofen) in the management of postoperative pain following abdominal hysterectomy. Pain Pract 2011;11:23–32.

16. Singla N, Rock A, Pavliv L. A multi-center, randomized, double-blind placebo-controlled trial of intravenous-ibuprofen (IV-ibuprofen) for treatment of pain in post-operative orthopedic adult patients. Pain Med. 2010;11(8):1284–93.

17. Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. Curr Opin Anaesthesiol. 2009; 22: 588–593. https://doi.org/10.1097/ACO.0b013e328330373a PMID: 19606021

18. Ashburn MA, Caplan RA, Carr DB, et al. Practice guidelines for acute pain management in the perioperative setting. An updated report by the American Society of Anesthesiologists task force on acute pain management. Anesthesiology 2004; 100:1573–1581.

19. Ekstein P, Szold A, Sagie B, Werbin N, Klausner JM, Weinbroum AA. Laparoscopic surgery may be associated with severe pain and high analgesia requirements in the immediate postoperative period. Ann Surg. 2006;243:41–6.

20. Blichfeldt-Eckhardt MR, Ording H, Andersen C, Licht PB, Toft P. Early visceral pain predicts chronic pain after laparoscopic cholecystectomy. Pain. 2014;155(11):2400–7.

21. Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia I: physiological pathways and pharmacological modalities. Canadian journal of anaesthesia = Journal canadien d'anesthesie. 2001;48(10):1000–10.

22. Gozeler MS, Sakat MS, Kilic K, Ozmen O, Can A, Ince I. Does a single-dose preemptive intravenous ibuprofen have an effect on postoperative pain relief after septorhinoplasty? American journal of otolaryngology 2018.

23. Çelik EC, Kara D, Koc E, Yayik AM. The comparison of single-dose preemptive intravenous ibuprofen and paracetamol on postoperative pain scores and opioid consumption after open septorhinoplasty: a randomized controlled study. European Archives of Oto-Rhino-Laryngology; 2018. doi: https://doi.org/10.1007/s00405-018-5065-6

24. Kroll PB. Intravenous ibuprofen for postoperative pain. Pain Manag. 2012; 2:47–54. doi: https://doi.org/10.2217/pmt.11.68

25. Macario A, Royal MA. A literature review of randomized clinical trials of intravenous acetaminophen (paracetamol) for acute postoperative pain. Pain Pract 2011; 11: 290–6

26. McNicol ED, Tzortzopoulou A, Cepeda MS, Francia MB, Farhat T, Schumann R. Single-dose intravenous paracetamol or propacetamol for prevention or treatment of postoperative pain: a systematic review and meta-analysis. Br J Anaesth 2011; 106: 764–75

27. R.A. Moore, S. Derry, P.J. Wiffen, S. Straube, D.J. Aldington. Overview review: Comparative efficacy of oral ibuprofen and paracetamol (acetaminophen) across acute and chronic pain conditions. Eur J Pain 19 (2015) 1213—1223.

28. Southworth S, Peters J, Rock A, Pavliv L. A multicenter, randomized, double-blind, placebo-controlled trial of intravenous ibuprofen 400 and 800 mg every 6 hours in the management of postoperative pain. Clin Ther. 2009;31(9):1922–35.