Available online at www.jsan.org.np

Journal of Society of Anesthesiologists of Nepal

*Review Article*

# Intravenous ibuprofen as an adjunct in acute postoperative pain: A review

*Alisha Shrestha, Dong Huang*

*The third hospital of Xiangya, Central south university, Hunan, Changsha, China*

ARTICLE INFO

Article history
Received 18.10.2014
Accepted 06.02.2015
Published 26.02.2015

© Authors retain copyright and grant the journal right of first publication with the work simultaneously licensed under a Creative Commons Attribution License that allows others to share the work with an acknowledgment of the work's authorship and initial publication in this journal.

**Abstract**

**Background:** Postoperative pain can have a significant effect on patient recovery. Studies suggest that 82% patients experience some pain following surgery, of those 47% complaining of moderate pain, 39% experiencing severe to very severe pain. The failure to adequately treat postoperative pain is due to limitations of monotherapy with opioid analgesics. Intravenous ibuprofen is a nonsteroidal anti-inflammatory drug with anti-inflammatory, antipyretic, and analgesic properties that may be related to prostaglandin synthetase inhibition and have been shown to reduce opioid requirements with better postoperative pain management. This paper reviews analgesic outcomes of intravenous ibuprofen as an adjunct to opioid for acute postoperative pain in adults.

**Methods:** Relevant studies were searched using cochrane database of systematic reviews, embase and pubmed databases using key words about intravenous ibuprofen and postoperative pain that were appropriate to each database.

**Results:** Tools to assess pain intensity such as visual analog scale, verbal response scale and self-report of pain scores at rest and with movement have been studied. Multimodal approach with preemptive use of nonsteroidal anti-inflammatory drugs for treatment of postoperative pain is considered.

**Conclusion:** Randomized controlled trials and other studies concluded that postoperative pain control protocols can now consider inclusion of intravenous ibuprofen as an adjunct in multimodal approach to offer patients a significant analgesic benefit while reducing the risks associated with opioid administration.

**Keywords:** Acute pain; Ibuprofen; Intravenous administration; NSAIDs; Opioids; Postoperative pain.

**How to cite this article:** Shrestha A, Huang D. Intravenous ibuprofen as an adjunct in acute postoperative pain: A review. JSAN 2015;2:21-24.

*Corresponding author:*

*Alisha Shrestha, MD*

*The third hospital of xiangya, central south university, Hunan, changsha, 410013 China.*

*Telephone: +8618874260704, Email: alisha85@gmail.com*

*Prior presentation: at 8 th Pain conference of six central south province of China 2014*

*Hunan Changsha China*

## Introduction

Postoperative pain is the most important concerns of patients during recovery. About 80% of patient experience postoperative pain.[1] In order to improve quality of postoperative health care it is important to understand patient's attitude and concern about postoperative pain.[2] Postoperative pain is an acute pain. If not treated properly it may change into chronic pain.[3] Ineffectively treated pain may lead to anxiety, sleep disturbances, demoralization, mental disturbances and effect social health.[4,5] The advantages of effective postoperative pain management include patient comfort, satisfaction, reduce cost of care, earlier mobilization, reduce risk of deep vein thrombosis, faster recovery, and decrease likelihood of the development of neuropathic and chronic pain and fewer pulmonary and cardiac complications.[6] Postoperative treatment is difficult to treat with single agent. Multimodal approach has been taken into consideration and has been practiced for 36 years.[7] The failure to treat acute postoperative pain adequately in one part may be due to the use of monotherapy with opioids.[8] The concept of multimodal analgesia is targeted for good postoperative pain relief and it has emerged through understanding of benefits of the synergistic effect of multiple drugs.[9] Various analgesics act on different sites of nervous system resulting in synergistic analgesia with reduction in side effects of sole agent.[7]

The American Pain Society advocates for combination of therapy for optimal pain control.[10] The World Health Organization (WHO) includes NSAIDs in step 1 of the analgesic ladder for the treatment of mild to moderate pain. They are also included as adjuncts in the treatment of persistent and moderate to severe pain in steps 2 and 3, respectively.[1] Both the World Health Organization and the American Society of Anesthesiologists Task Force recommend NSAIDs such as ibuprofen as baseline therapy in multimodal approach to pain management which can minimize the risk of opioid-related side effects .[11]

Intravenous (IV) ibuprofen has been approved by the FDA in United States in June 2009 for the treatment of mild to moderate pain, moderate to severe pain in addition to opioid analgesics, and for reduction of fever. Since IV ibuprofen act in both the peripheral tissues and the central nervous system it has been the topic of interest to use it as an adjunct in postoperative pain management.[12] The efficacy and safety of intravenous ibuprofen for the management of pain was investigated in different clinical trials and has been accepted for alternative treatment option as an adjunct to opioid for acute postoperative pain management. IV ibuprofen can be used even for the most vulnerable patient populations with safety margins. Recently intravenous ibuprofen was approved for the treatment of symptomatic patent ductus arteriosus in preterm infants[13], critically ill patients[14] and treatment of fever and pain in burn patients.[15] In addition, the preemptive use of IV Ibuprofen as multimodal analgesia will prevent postoperative pain by hindering afferent input formation and prevent pain memory, thereby reducing analgesia requirement.[16] Main characteristics of preemptive analgesia is beginning before surgery and preventing central sensitization related to surgical trauma or inflammatory events.[17]

Oral ibuprofen has been associated with peripheral adverse effects like cardiovascular thrombotic events, gastrointestinal symptoms such as nausea, vomiting, flatulence, dyspepsia, anemia, bleeding, hypertension, bronchospasm, renal failure, fluid retention, peripheral edema, rash[18] and few CNS adverse effects such as dizziness, headache, vertigo and malaise.[19] But in clinical trials with IV ibuprofen these adverse events were not noted significantly. Therefore this review evaluates different studies and clinical trials that have been carried out over past few years on IV ibuprofen and its efficacy as an adjunct to opioid in postoperative pain management.

## Methods

We conducted our search on randomized clinical trials on IV ibuprofen in postoperative pain management using Cochrane Database of Systematic Reviews, EMBASE and PUBMED databases using appropriate key words for each database from 2009 till 2013.We found three randomized clinical trials on iv ibuprofen alone and one comparison of iv ibuprofen with combination of iv ibuprofen, acetaminophen and caffeine. Discussion on articles other than pain management including patent ductus arteriosus, hypoxic ischemic encephalopathy, fever, ibuprofen lysine, pediatric study, animal data and on oral ibuprofen were excluded.

## Results

In 2009, Southworth and his colleagues carried out multi-centered, double blind, randomized, placebo controlled clinical trials on 406 patients undergoing orthopedics and abdominal surgeries. Patients were divided into three groups and were given 400mg, 800mg of IV ibuprofen and placebo respectively every 6 hourly for 48 hours, the first dose beginning at the initiation of wound closure. All these patients had access to morphine by patient controlled analgesia (PCA) and IV Ibuprofen was added according to the need of the patient. The study showed that less morphine was required in 800mg group during first 24 hours as compared to placebo by 22% (p=0.03). There was no significant difference in 400mg and placebo groups. In addition patient with 800mg had significant reduction in pain by 30.6% at rest and 18% with movement across 3 time periods (1-24, 6-24, 12-24 hours) as compared to placebo measured through patient self assessment using visual analogue scale (VAS). Ibuprofen 400 mg IV was associated with significant reductions in pain at rest and with movement during the 6 to 24 hour and 12 to 24 hour time periods compared with placebo. Interestingly there were reductions in gastrointestinal adverse effects such as nausea, vomiting and constipation (400mg 74% [p=0.05], 800mg 71% [p=0.009], placebo 84%). This may be due to reduction in opioid use. No significant difference was

seen in pyrexia, renal toxicity, postoperative bleeding and wound complications in 400mg and 800mg as compared to placebo.[20]

In 2010, Singla N and his colleagues carried out another multi-centered, double blind, randomized, placebo controlled trial with 185 patients undergoing orthopedic surgery by using 800mg IV ibuprofen preemptively. First dose was given before induction of anesthesia then 6 hourly for 5 doses. Then it was given 8 hourly as needed for 5 days. The result was similar to previous study with 30.9% ($p<0.001$) less morphine requirement and reduction in pain at rest and with movement by 31.8% and 25.8% respectively as shown by mean area under curve in VAS (VAS-AUC with $p<0.001$).[21] There was 20.2% reduction in mean verbal response score (VRS) as compared to placebo. Similar treatment emergent adverse effects related to bleeding, coagulation and incidence of blood transfusion were seen in both groups with no significant difference. Whereas, vomiting was significantly more in IV ibuprofen group ($p=0.031$) and dyspepsia more in placebo group ($p=0.045$).

Another double blind, multi-centered, randomized, placebo controlled trial was done by Kroll and his colleagues in 2011 among 319 patients undergoing abdominal hysterectomy using 800mg IV ibuprofen initiated at wound closure then given 6 hourly for 8 doses. The result was also supportive with reduction in morphine use by 19% ($p \leq 0.001$). There was also significant reduction in pain at rest by 21% (AUC, 6 to 24 hours and 12 to 24 hours, $p < 0.001$) and with movement by 14% (AUC, 6 to 24 hours, $p = 0.010$ and 12 to 24 hours, $p \leq 0.001$) and early time of ambulation ($p = 0.018$) compared to placebo group as assessed by VAS.[22] There was no overall significant difference in adverse effects such as generalized or gastrointestinal bleeding, nausea, flatulence, pruritus, renal toxicity, respiratory, hematological and nervous system disorders in both groups. In addition there was no significant difference in heart rate, respiratory rate, systolic and diastolic blood pressure, temperature and death during 14 day study.

**Discussion**

Postoperative pain when not treated adequately may changes into chronic pain. This not only decreases the quality of life but also increases the cost. Adequate postoperative pain relief therefore has significant effect on patient recovery. Opioids are considered the treatment cornerstone for severe post-operative pain. In United States, more than 60% of the patients who have experienced moderate or severe post-operative pain have received morphine as a post-operative pain therapy.[10] These agents usually act upon μ-receptors in central and peripheral nervous system.[23] Opioids are useful in alleviating the sensation of pain, but do not improve the underlying disease process. Further their use is often limited by adverse effects including respiratory depression, sedation, allergic reactions, gastrointestinal events and dependency.[24] A multimodal approach to pain management is an effective means of achieving comprehensive pain relief by lowering the total dose of opioid required and thereby minimizing the potential for opioid-related adverse effects.[25] Consequently, over recent years there has been a high degree of interest in the development of opioid-sparing analgesic regimens.

Adjunctive agents for pain like NSAIDs may be used in combination with opioids. NSAIDs act by blocking cyclooxygenase COX-1 and COX-2 enzymes and prevent the sensitization of pain receptors at the site of injury. They consequently block inflammatory cascade and cyclooxygenase enzyme by inhibiting prostaglandin and thromboxane and reduce fever, pain, inflammatory response and platelet aggregation.[25] The anti-inflammatory properties of NSAIDs may be useful in promoting healing and resolution of pain. Combination therapy may help mitigate the side effects of both agents by reducing the total dose required.[26]

In above three randomized clinical trials it is concluded that IV ibuprofen has the highest efficacy when used in dose of 800mg in postoperative pain management with reduction in requirement and adverse effects of opioids. IV ibuprofen has significantly reduced pain at rest and during movement. Therefore, it has decreased longer hospital stay and reduced cost of care. However, all these studies had some limitations. These studies were based on adults of 18-70 years weighing >30kg who were anticipated for hospital stay >48 hours. The exclusion criteria were history of allergy or hypersensitivity to ibuprofen, aspirin, NSAIDs or cyclooxygenase-2 inhibitors, anemia, history of asthma or heart failure, pregnant or breastfeeding, at increased risk for bleeding including a platelet count <30,000 cells/μL, history of gastrointestinal bleeding within 6 weeks before surgery or history of bleeding diathesis, at increased risk for intracerebral hemorrhage, stroke, head trauma, idiopathic thrombocytopenic purpura, cerebral aneurysm or renal insufficiency (creatinine clearance <60 ml/min or oliguria defined as urine output <500 ml/24 h) or patients undergoing dialysis within 28 days before surgery, receiving warfarin, lithium, or a combination of angiotensin converting enzyme inhibitors and furosemide or if they received any analgesic, muscle relaxant, or sedative within 24 hours before administration of the study medication, previous history of opioid dependence, treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery[20,21] and patient needing epidural anesthesia and nerve blocks during postoperative period.

There are two intravenous NSAIDs approved in United States: IV ketorolac and IV ibuprofen. Other injectable NSAIDs such as Tenoxicam, Parecoxib and two formulations of Diclofenac are available outside United States. These agents are not discussed in this review. IV ibuprofen has advantage over IV ketorolac due to its balanced affinity on COX isoenzymes. IV ketorolac has high degree of COX 1 selectivity resulting in platelet dysfunction and increased incidence of perioperative bleeding. Further,

its use is limited by short term (<5 days) management of moderate to severe postoperative pain.[27] Similarly, selective COX 2 inhibitors increase risk of cardiovascular events such as acute myocardial infarction, coronary heart disease, stroke and death. Fraudulent data on previously published literature on COX 2 inhibitors led to retraction of various papers as well as drugs from the market resulting in need for additional new research in the proper pain management[28] and IV ibuprofen looks promising.

These studies were carried out in comparatively small portion of population. Therefore, we should consider safety criteria and drug interaction while using IV ibuprofen in patients with certain co-morbidities. But till date, as no grave complication has been reported with short term use of ibuprofen, we can consider to use it as an integral part of acute postoperative pain management. However, more clinical trials and further studies need to be carried out to establish the safety margins and efficacy of IV ibuprofen as multimodal analgesia in acute postoperative pain management.

**Conclusion**

Intravenous ibuprofen has a significant role as an adjunct to opioids in multimodal analgesia during post-operative pain management. It can reduce complications of opioids due to its opioid sparing effect and can promote patient satisfaction during recovery.

**Acknowledgement** We thank Wang Saiying and Duan Kaiming for their valuable contribution in literature search.

**Conflict of interest** There are no conflicts of interest.

**References**

1. Bookstaver PB, Miller AD, Rudisill CN, Norris LB. Intravenous ibuprofen: the first injectable product for the treatment of pain and fever. J Pain Res 2010;3:67-79.
2. 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;97:534-40.
3. Costantini R, Affaitati G, Fabrizio A, Giamberardino MA. Controlling pain in the post-operative setting. Int J ClinPharmacolTher 2011;49:116-27.
4. Sinatra R. Causes and consequences of inadequate management of acute pain. Pain Med 2010;11:1859-71.
5. Sherwood GD, McNeill JA, Starck PL, Disnard G. Changing acute pain management outcomes in surgical patients. Aorn J 2003;77:377-80.
6. Ramsay MA. Acute postoperative pain management. Proc 2000;13:244-7.
7. Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg 1993;77:1048-56.
8. Elvir-Lazo OL, White PF. Postoperative pain management after ambulatory surgery: role of multimodal analgesia. Anesthesiol Clin 2010;28:217-24.
9. White PF. Multimodal analgesia: its role in preventing postoperative pain. Curr Opin Investig Drugs 2008;9:76-82.
10. Gordon DB, Dahl JL, Miaskowski C, McCarberg B, Todd KH, Paice JA, et al. American pain society recommendations for improving the quality of acute and cancer pain management: American Pain Society Quality of Care Task Force. Arch Intern Med 2005;165:1574-80.
11. Practice guidelines for acute pain management in the perioperative setting. A report by the American Society of Anesthesiologists Task Force on Pain Management, Acute Pain Section. Anesthesiology 1995;82:1071-81.
12. Kokki H, Kumpulainen E, Lehtonen M, Laisalmi M, Heikkinen M, Savolainen J, et al. Cerebrospinal fluid distribution of ibuprofen after intravenous administration in children. Pediatrics 2007;120:1002-8.
13. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2013;30.
14. Morris PE, Promes JT, Guntupalli KK, Wright PE, Arons MM. A multi-center, randomized, double-blind, parallel, placebo-controlled trial to evaluate the efficacy, safety, and pharmacokinetics of intravenous ibuprofen for the treatment of fever in critically ill and non-critically ill adults. Crit Care 2010;14:30.
15. Promes JT, Safcsak K, Pavliv L, Voss B, Rock A. A prospective, multicenter, randomized, double-blind trial of IV ibuprofen for treatment of fever and pain in burn patients. J Burn Care Res 2011;32:79-90.
16. Sittl R, Irnich D, Lang PM. Update on preemptive analgesia : options and limits of preoperative pain therapy. Anaesthesist 2013;62:789-96.
17. Dahl JB, Kehlet H. The value of pre-emptive analgesia in the treatment of postoperative pain. Br J Anaesth 1993;70:434-9.
18. Titchen T, Cranswick N, Beggs S. Adverse drug reactions to nonsteroidal anti-inflammatory drugs, COX-2 inhibitors and paracetamol in a paediatric hospital. Br J Clin Pharmacol 2005;59:718-23.
19. Hoppmann RA, Peden JG, Ober SK. Central nervous system side effects of nonsteroidal anti-inflammatory drugs. Aseptic meningitis, psychosis, and cognitive dysfunction. Arch Intern Med 1991;151:1309-13.
20. 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;31:1922-35.
21. 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;11:1284-93.
22. Kroll PB, Meadows L, Rock A, Pavliv L. A multicenter, randomized, double-blind, placebo-controlled trial of intravenous ibuprofen (i.v.-ibuprofen) in the management of postoperative pain following abdominal hysterectomy. Pain Pract 2011;11:23-32.
23. Somogyi AA, Barratt DT, Coller JK. Pharmacogenetics of opioids. Clin Pharmacol Ther 2007;81.429-44.
24. Pasternak GW. Opiate pharmacology and relief of pain. J Clin Oncol 2014;32:1655-61.
25. Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. Curr Opin Anaesthesiol 2009;22:588-93.
26. Simon LS. Nonsteroidal anti-inflammatory drugs and their risk: a story still in development. Arthritis Res Ther 2013;15:24.
27. Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. Proc Natl Acad Sci U S A 1999;96:7563-8.
28. Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. Circulation. 2007;115:1634-42.