Sys Rev Pharm 2022; 13(2): 93-97
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453 / DOI: 10.31858/0975-8453.13.2.93-97

Research Article

Intravenous Ibuprofen for Acute Pain: Systematic Review of Randomized Controlled Trial Study

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Article History: *Submitted: 07.02.2022* *Accepted: 21.02.2022* *Published: 28.02.2022*

ABSTRACT

Introduction: Acute postoperative pain still is a significant problem that occurs between 60 to 80% of patients according to the different series reported and it often remains undertreated.

Objective: This systematic review aimed to identify the benefit of Ibuprofen Intravenous in acute pain. Various methods are used to reduce pain, one of them by giving analgesics. Ibuprofen is a class of non-narcotic analgesic drugs that have antipyretic and anti-inflammatory properties.

Material and methods: The keywords used in the research process include: "Intravenous ibuprofen". Systematic research was done using PubMed database, included study has the following criterion. Study excluded if the study was not a Randomized Controlled Trial (RCT) study, the quality of RCT was measured using the Jadad score by two appraisers.

Result: There were 674 studies related to Intravenous Ibuprofen. After screening and checking for the eligibility, remains 7 studies. All studies have a good quality indicated by Jadad score of ≥ 3. The subjects in all studies were acute pain patients and compared Intravenous (IV) Ibuprofen with another analgesia or placebo. Intravenous Ibuprofen was considered to be safe in patients with acute pain. Intravenous Ibuprofen also improves the intensity of pain in all studies.

Conclusion: Intravenous Ibuprofen proved to be effective to reduce pain among patients with acute pain compared to placebo or other NSAIDs (Non-Steroidal Anti Inflammatory Drugs), especially ketorolac. It is also found to be safe without any serious adverse event.

Keywords: Ibuprofen, Acute pain, Intravenous, Analgesics, NSAID (Non-Steroidal Anti Inflammatory Drug)

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INTRODUCTION

Proof shows that about 80% of individuals experience postoperative agony and 75% of individuals report moderate or serious seriousness (Gan TJ, *et al.*, 2014). Medical procedure from upper and lower appendage, chest, mid-region, and spine/spine appendages has been related with higher torment levels (Sommer M, *et al.*, 2008). Many individuals get imperfect perioperative absense of pain, which influences personal satisfaction, capacity, and time for recuperation, and puts them in danger of creating intense post-careful confusions and persevering postoperative torment (Chou R, *et al.*, 2016). Intense postoperative torment actually is a huge issue that happens between 60 to 80% of patients as per the diverse series announced and it regularly remains undertreated. Narcotic analgesics are the backbone of intense torment therapy in the patient setting. Anyway they give no advantages to the fundamental pathophysiology of the interaction. Adjuvant specialists for torment treatment including Non-Steroidal mitigating Drugs (NSAIDs) ought to be utilized in mix with narcotics (Singla N, *et al.*, 2010).

Different techniques are utilized to lessen torment, one of them by giving analgesics. Ibuprofen is a class of non-opiate pain relieving drugs that have antipyretic and mitigating properties. Has a component as repressing the biosynthesis of prostaglandins, just as hindering the chemical Cyclooxygenase (COX) including COX-1 (Cyclooxygenase-1) and COX-2 (Cyclooxygenase-2). The propionic corrosive subordinate ibuprofen has pain relieving and mitigating properties through focal and fringe bar of COX-1 and COX-2 isoenzymes and can likewise have an impact through COX-free pathways. Intravenous ibuprofen opened up in 2009 and can be utilized for preemptive absence of pain. Studies completed in muscular medical procedure have shown preoperative and postoperative organization of IV ibuprofen decreased postoperative torment and narcotic need.

MATERIALS AND METHODS

The catchphrases utilized in the exploration interaction include: "Intravenous ibuprofen". Deliberate exploration was finished utilizing PubMed information base. *Figure 1* shows the rule choice interaction including the quantity of avoided diaries. Included investigation has the accompanying rules: (i) the examination was directed between 2015 to 2020, (ii) wrote in English, (iii) the examination was recognized the advantage of Intravenous Ibuprofen in intense torment. Any sort of intense aggravation is associated with this audit. The investigation is rejected if the examination was not a Randomized Controlled Preliminary (RCT) study and the full text was not accessible.

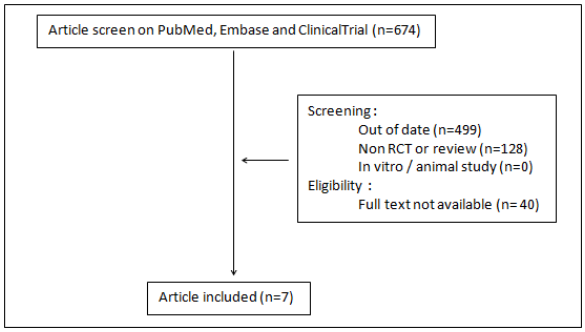

Figure 1: Selection process with a total of 674 articles from PubMed, Embase and Clinical trial, there are 499 out of date articles, 128 non-RCT or review articles and 40 full text articles not available. Then the total remaining journals are 7 articles

The nature of the RCT was estimated utilizing the Jadad score by two appraisers. Jadad score has 5 evaluation parts. One point will be added if the examination meets every part, along these lines the most extreme score is 5. The examination will be precluded on the off chance that it scores under 3. Subsequent to passing the evalu-

ation by utilizing the Jadad score, two creators looked into the investigation utilizing PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) agenda as the direction. PRISMA agenda has 27 things to evaluate the substance of efficient survey and meta-examination. Two creators work were settled by conversation between two audit creators. The factors evaluated include: analysis of incendiary agony, mediation, examination, number of subjects, length of the investigation, result, and results. The outcomes are portrayed by P value.

RESULTS

Figure 1 showed the detail of the choice cycle. There were 674 investigations identified with Intravenous ibuprofen. In the wake of screening and checking for the qualification, stays 7 investigations. The nature of each examination was assessed by utilizing the Jadad score.

Table 1 showed all examinations have a decent quality shown by Jadad score of ≥ 3. The most noteworthy score is in an examination by Martinez AG, *et al*., 2016. All examinations kept on being further audit.

Table 2 is synopsis of chose study. The subjects in all examinations were intense agony patients and contrasted IV Ibuprofen and another absence of pain or fake treatment.

Table 3 summed up the finish of each investigation. Intravenous Ibuprofen was viewed as protected in patients with intense agony. Intravenous Ibuprofen likewise works on the power of torment in all examinations.

Table 1: Quality of study by using jadad score

Authors and years	Was the study described as randomized?	Was the method used to generate the sequence of randomization described and appropriate?	Was the study described as double blind?	Was the method of double blinding described any appropriate?	Was there a description of withdrawal and dropout?	Total score
Liu X, *et al.*, 2018	Yes	No	Yes	Yes	Yes	4
Shaker SH and Borghei SA, 2018	Yes	Yes	No	No	No	2
Uribe, *et al.*, 2018	Yes	Yes	Yes	No	Yes	4
Veronica MD, *et al.*, 2016	Yes	Yes	Yes	No	Yes	4
Ciftci B, *et al.*, 2018	Yes	Yes	Yes	Yes	No	4
Haddadian A, *et al.*, 2018	Yes	Yes	No	No	Yes	4
Southworth S, *et al.*, 2009	Yes	Yes	Yes	No	No	3
Martinez AG, *et al.*, 2016	Yes	Yes	Yes	Yes	Yes	5

Table 2: Summary of selected studies

Authors and years	Diagnosis	Intervention	Control	Subject characteristics	Length of treatment	Outcome measure
Liu X, *et al.*, 2018	Post radical cervical cancer surgery	Group 1: ibuprofen 400 mg q.fi.d; Group 2: ibuprofen 800 mg q.i.d	Group 3: placebo q.i.d	N: 56 female; Group 1:45.9 ± 7.4 years; Group 2: 45.2 ± 8.6 years; Group 3: 45.6 ± 5.3 years	2 days	VASR (Visual Analogue Scale Report), VASM (Victorian Audit of Surgical Mortality), BCS (Bruggemann Comfort Scale), OPPS (Orpington Prognostic Score)
Shaker SH and Borghei SA, 2018	Renal colic pain	Group 1: Ibuprofen 800 mg q.i.d	Group 2: Ketorolac 30 mg q.i.d	N: 70 Male and female; Group 1: 38.29 ± 11.71 years; Group 2: 36.51 ± 11.64 years	60 minutes	VAS (Visual Analogue Scale)
Uribe, *et al.*, 2018	Post knee surgery	Group 1: Ibuprofen 800 mg q.i.d	Group 2: Ketorolac 30 mg q.i.d	N: 51 Male and Female; Group 1: 42.32 ± 12.37 years; Group 2: 44.6 ± 13.03 years	24 hours	VAS (Visual Analogue Scale)

Veronica MD, *et al.*, 2016	postoperative pain (Cesarean section)	Group 1 (n=25): Ibuprofen 800 mg diluted in 200 mL NaCl q.i.d	Group 2 (n=23): Ketorolac 30mg diluted in 200 mL NaCl q.i.d	N: 48 Female; Group 1: 33 ± 3.7 years; Group 2: 32 ± 5.8 years	48 hours	PCA (Patient-Controlled Absense of pain) attempts, PCA injections, Hgb (Hemoglobin concentration)
Ciftci B, *et al.*, 2018	Undergoing Laparoscopic Sleeve Gastrectomy (LSG) surgery.	Group 1 (n=30) : 800 mg of IV ibuprofen in 100 ml saline Solution q.8.h; Group 2 (n=30): 1000 mg of IV paracetamol in 100 ml saline Solution q.8.h	Group 3 (n=30) : 100 ml of saline solution q.8.h	N: 90 Female and male; Group 1: 50.16 ± 14.46 years; Group 2: 48.10 ± 16.01 years; Group 3: 43.93 ± 8.58 years	24 hours	VAS, fentanyl consumption doses of PCA, Rescue analgesia, adverse events
Haddadian A, *et al.*, 2018	distal radius fractures	Group 1: IV ibuprofen 400 mg infused for 30 min	Group 2: IV ketorolac 30 mg infused for 30 min	N: 150 97 males and 53 females ean age of 35.72 years	1 hour	Numeric rating scale (NRS)
Southworth S, *et al.*, 2009	elective, single-site orthopedic or abdominal surgery.	Group 1 (n=134) : Ibuprofen 400 mg IV q6h+morphine PCA 1-2 mg q5min; Group 2 (n=138): Ibuprofen 800 mg IV q6h+morphine PCA 1-2 mg q5min	Group 3 (n=134): Placebo+ morphine PCA 1-2 mg q5min	N: 406 319 women, 87 men; Group 1: 45 ± 13 years; Group 2: 46 ± 12 years; Group 3: 45 ± 11 years	48 hour	Morphine use in the first 24 hours after surgery, patient self-reports of pain scores at rest and with movement (VAS), Adverse events
Martinez AG, *et al.*, 2016	Post abdominal and orthopedic surgery	Group 1 (n=107): 800 mg IV-ibuprofen over a 15 minute period q.6.h	Group 2 (n=99): placebo (saline solution 200 ml) over a 15 minute period q.6.h	N: 206 Female and male; Group 1: 53.03 ± 14.45 years; Group 2: 53.49 ± 12.58 years	24 hours	Median morphine consumption within the first 24 hours following surgery, VASR, VASM

Table 3: Conclusion of the studies

Authors and years	Results
Liu X, *et al.*, 2018	Morphine usage is reduced in either Intravenous (IV) Ibuprofen 400 mg or 800 mg groups compared to placebo group. Tramadol use is reduced significantly in group IV Ibuprofen and shows no difference between 400 mg and 800 mg. There wasn't any difference in safety between groups in all aspects.
Shaker SH and Borghei SA, 2018	Pain severity is reduced within 60 minutes in both groups, IV Ibuprofen and IV Ketorolac was not show significant difference in pain score.
Uribe, *et al.*, 2018	IV Ibuprofen 800 mg shown reduce the usage of opioid within 24 hours post arthroscopy surgery and reduce postoperative pain.
Veronica MD, *et al.*, 2016	There is no superiority of IV ibuprofen over IV ketorolac for postoperative pain relief, nor a clinically meaningful difference in perioperative bleeding.
Ciftci B, *et al.*, 2018	IV ibuprofen resulted in lower pain scores compared to paracetamol by reducing postoperative opioid use in the first 24 h in patients undergoing LSG surgery.
Haddadian A, *et al.*, 2018	IV ketorolac 30 mg infusion is a safer and more effective method than IV ibuprofen 400 mg infusion for pain control in distal radius fracture following trauma.
Southworth S, *et al.*, 2009	Multimodal approach with morphine and ibuprofen 800 mg IV q6h might be more effective and better tolerated compared with morphine alone in the management of postoperative pain.
Martinez AG, *et al.*, 2016	Perioperative administration of IV-Ibuprofen 800 mg every 6 hours in abdominal surgery patient's decreases morphine requirements and pain score. Furthermore IV-Ibuprofen was safe and well tolerated.

DISCUSSION

Measurement

The essential end point in the investigation by Liu X, *et al*., 2018 is V-ASR (Visual Analogue Scale Report), VASM (Victorian Audit of Surgical Mortality), BCS (Bruggemann Comfort Scale), OPPS (Orpington Prognostic Score). VASR and VASM is Visual simple scale that used to gauge and assess torment in understanding with 100 mm territory (0=no aggravation to 100=exceptional torment). The thing that matters is VASR is the point at which the patients were resting, and VAS-M utilized when patients moved. BCS or Bruggemann Comfort Scale (4=no aggravation, 0=extraordinary agony) is an emotional estimation to realize patients solace after the medicine. OPPS by and large torment execution scale (0=no aggravation, 12=serious agony) this estimation was use to rating the aggravation in tolerant and had comparable utilization with VAS (Visual Analogue Scale) (VASR and VASM).

VAS is the solitary instrument utilized in RCT by Shaker SH and Ciftci B, *et al*., 2018. Visual Simple Scale (VAS) was use to quantify torment seriousness of the patients ill condition (Shaker SH and Borghei SA, 2018). VAS was estimated multiple times, once before medicine and twice after got prescription. This estimation could shown the mean agony change and contrasts between gatherings.

There were 3 results estimated in the examination by Veronica MD, *et al*., 2016. PCA (Patient-Controlled Absense of pain) and other health PCA endeavors, PCA infusions, Hgb (Hemoglobin fixation). From an overall perspective, Patient-Controlled Absense of pain (PCA) alludes to an interaction where patients can decide when and how much medicine they get, paying little heed to pain relieving procedure. PCA a technique for help with discomfort which utilizes dispensable or electronic mixture gadgets and permits patients to self-administer pain relieving drugs. PCA endeavors was the quantity of PCA solicitations, and PCA infusions was the quantity of PCA conveyed portions. PCA containing hydromorphone with 0.2 mg per conveyed portion, with a 10 min lockout and a greatest portion of 1.2 mg/h. Hgb (Hemoglobin fixation) was the security result variable, decline in Hemoglobin focus characteristic of perioperative dying

Study by Ciftci B, *et al*., 2018 was utilizing VAS, fentanyl utilization of a PCA, Rescue absense of pain, unfriendly occasions. The PCA gadget arranged with fentanyl was modified to a 10 mcq fixation, 10-min lockout, and 25 mcq bolus portion with no basal implantation, kept up with for 24 h. Salvage absense of pain was directed in line with the patients after medical procedure, Meperidine (0.25 mg/kg) was given to patients with a VAS score of 4 or above for salvage absense of pain, this was rehashed after 5 min if essential. Unfriendly Event was an occasion, preventable or non-preventable, that made damage a patient because of clinical consideration. This incorporates never occasions; emergency clinic obtained conditions; occasions that necessary life-supporting intercession; and occasions that caused delayed emergency clinic stays, super durable damage, or passing. The presence of antagonistic occasion was examined was queasiness, retching, tingling, and hypersensitive.

Numeric Rating Scale (NRS) is an aggravation scale instrument utilized in RCT by Haddadian A, *et al*., 2018). It comprises of several things and a numeric adaptation of the visual simple scale. The most widely recognized type of the NRS is a level line with an eleven point numeric reach. It is marked from zero to ten, with zero being an illustration of somebody with no aggravation and ten being the most noticeably awful aggravation conceivable. This kind of scale can be directed verbally. It can likewise be regulated by means of paper to be finished genuinely.

The essential end point in the examination by Southworth S, *et al*., 2009 was the mean measure of morphine managed during the initial 24 hours after a medical procedure on patient in the hospital. Optional endpoints included VASR, VASM and Adverse occasions, VASR and VASM was the mean changes in torment power very still and with development, as evaluated utilizing patient self-detailing with a 100 mm Visual Simple Scale (VAS) (0=no aggravation to 100=extraordinary agony). Essential and auxiliary result in research by Martinez AG, *et al*., 2016 and he also said that is same as essential and optional result in research by Southworth S, *et al*. 2009.

Liu X, *et al*., 2018, Shaker SH and Borghei SA, 2018, Ciftci B, *et al*., 2018, Southworth S, *et al*., 2018 and Martinez, *et al*., 2016 use VAS in their study to assess the pain. Veronica MD, *et al*., 2016 and Haddadian A, *et al*., 2018 did not use VAS for pain measurement.

Intravenous ibuprofen for pain treatment

The essential variable outcome is viability of Morphine decreased. In the initial 24 hours the use of Morphine were diminished in both Ibuprofen 400 mg (18.8 ± 3.1 mg) and 800 mg (17.6 ± 3.2 mg), the decreased among Ibuprofen bunches weren't show any huge unique yet between Ibuprofen 800 mg gathering and fake treatment bunch was show critical unique (p=0.04). In the auxiliary variable have the comparable outcome between gatherings. In view of VAS estimation Ibuprofen 800 mg bunches was altogether decline torment power (VASR p=0.049, VASM p=0.04) and no huge contrast between three gatherings. BCS score observed to be altogether higher in Ibuprofen 400 mg and 800 mg bunches as opposed to fake treatment gatherings (p=0.03). In OPPS score fake treatment bunch was altogether higher than Ibuprofen 800 mg bunch (p=0.02) (Liu X, *et al*., 2018).

The aggravation diminish of renal colic torment in Ibuprofen bunch wasn't shows huge distinction in torment score (VAS) with Ketorolac bunch (p=0.734). Incidental effect like queasiness and retching between two gatherings wasn't tracked down any critical contrasts. The lone huge outcome is the use of H2 blockers in Ibuprofen bunch because of epigastric agony, that wasn't uncovered in Ketorolac bunch (p=0.002) (Shaker SH and Borghei SA, 2018).

Patients who got ibuprofen logged more PCA endeavors (7.9 versus 5.0 mean; 4 versus 3 middle) (P=0.56), and more PCA conveyed portions (7.0 versus 4.3 mean; 4 versus 3 median) (P=0.59) than the people who got Ketorolac. Perioperative declines in Hemoglobin fixation likewise didn't vary between gatherings (P=0.38), even were it measurably critical, a 0.3 g/dL contrast of ascribed implies remains clinically immaterial. This purposelessness type affectability investigation contends against rehashing this examination with the full example size (Veronica MD, *et al*., 2016).

The utilization of salvage medicine in the Ibuprofen bunch was genuinely lower than different gatherings (P<0.001). Agony scores (VAS) in the Ibuprofen gathering and Paracetamol bunch at recuperation and at 2, 4, 8, 12, and 24 h were lower than those in the Placebo bunch (P< 0.001). Specifically, the VAS scores in the Ibuprofen bunch at the first 2 postoperatively were altogether lower than those in the Paracetamol bunch (P<0.001). Narcotic utilization in the Placebo bunch was essentially higher than different gatherings (P<0.001) (Ciftci B, *et al*., 2018).

A sum of 97 guys and 53 females with the mean time of 35.72 years were remembered for the investigation. There was not huge contrast in the normal agony scores estimated by Numeric Rating Scale (NRS) prior to recommending drugs. The decrease in torment was more huge in the ketorolac bunch 30 min after infusion (P<0.05) (Haddadian A, *et al*., 2018).

In the plan to-treat populace, middle morphine use was altogether decreased during the initial 24 hours after organization of the investigation drug in patients who got ibuprofen 800 mg IV q6 h (by 22% versus fake treatment; P=0.030). The utilization of ibuprofen 800 mg IV q6 h was related with huge decreases in torment very still and with development across 3 time-frames (1-24, 6-24, 12-24 hours) contrasted and fake treatment.

Ibuprofen 400 mg IV q6 h was related with critical decreases in torment very still and with development during the 6-to 24-hour and 12-to 24-hour time spans contrasted and fake treatment (Southworth S, *et al.*, 2009).

The essential result measure was middle morphine utilization inside the initial 24 hours following a medical procedure. The mean ± Scanning Electron Microscope (SEM) of morphine prerequisites was diminished from 29,8 ± 5,25 mg to 14,22 ± 3,23 mg (p=0,015) and brought about an abatement in torment very still (p=0,02) estimated by Visual Analog Scale (VAS) from mean ± SEM 3.34 ± 0,35 to 0.86 ± 0.24, and furthermore in torment during development (p= 0,02) from 4.32 ± 0,36 to 1.90 ± 0,30 in the ibuprofen treatment arm; while in the fake treatment bunch VAS score very still went from 4.68 ± 0,40 to 2.12 ± 0,42 and during development from 5.66 ± 0,42 to 3.38 ± 0,44 (Martinez AG, *et al.*, 2016).

Safety

No adverse event related with Ibuprofen in study by Liu X, *et al.*, 2018. The adverse event is associated with opioid analgesia, and it has also showed no significant difference between opioid group and opioid plus NSAIDs group.

Ibuprofen 800 mg could lead to epigastric pain event. In study by Shaker SH, Ketorolac group wasn't show any adverse event (Shaker SH and Borghei SA, 2018). Beside epigastric pain, another side effect either Ibuprofen and Ketorolac like nausea and vomiting weren't show.

In a study by Veronica MD, *et al.*, 2016 for efficacy and its safety outcomes, the mean values in the ibuprofen group were numerically higher, whereas the study hypotheses would require each to be numerically lower with its conditions. There were no drug-related adverse effects has been recorded for any patient during the study period, including allergic reactions, Gastro Intestinal (GI) ulcers, or GI perforations.

Ciftci B, *et al.*, 2018, stated incidence of nausea (P=0.012), itching (P=0.023) in the Ibuprofen group was lower than the other groups related conditions. There was no statistical difference seen between the groups in terms of the other adverse effects.

The prevalences of adverse events and abnormalities in laboratory measurements were not significantly different between patients who received IV ibuprofen and those who received placebo in the study by Southworth S, *et al.*, 2009.

No serious adverse event was reported in a trial by Martinez AG, *et al.* 2016. Similar treatment-emergent and related adverse events has also occurred across both study groups and there was no difference in the overall incidence of these events.

CONCLUSION

Intravenous Ibuprofen proved to be effective to reduce pain among patients with acute pain compared to placebo or other NSAIDs, especially ketorolac. It is also found to be safe without any serious adverse event.

CONSENT FOR PUBLICATION

Febrina Eva Susanto as a corresponding author hereby declares that I participated in the study and in the development of the manuscript titled "Intravenous ibuprofen for acute pain: Systematic review of Randomized Controlled Trial study".

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