2019

Is Intranasal Ketorolac Both Safe and Effective in Reducing Acute Postoperative Pain for Patients over 18 Years of Age That Require Inpatient Hospitalization?

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Is intranasal ketorolac both safe and effective in reducing acute postoperative pain for patients over 18 years of age that require inpatient hospitalization?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 14, 2018

ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not intranasal ketorolac is both safe and effective in reducing acute postoperative pain for patients over 18 years of age that require inpatient hospitalization.

STUDY DESIGN: Review of three double-blind randomized controlled trials (RCTs) were used, all are from 2008 to present and all are in the English language.

DATA SOURCES: Data sources include articles that were published on both PubMed and Cochrane databases and were selected based on their relevance to the research question as well as patient measured outcomes.

OUTCOMES MEASURED: Outcomes measured include efficacy of the drug measured through Visual Analog Scale (VAS), Pain Intensity Differences (PID) and Summed Pain Intensity Differences at 6 hours (SPID6) as well as safety measured through self-reported adverse events or change in clinical status.

RESULTS: The study by Moodie et al.[6] showed a significant increase of 64.9 ($p=0.0015$) in SPID6 scores between intranasal ketorolac and placebo. Brown et al.[7] also showed a significant increase of 46.1 ($p=0.007$) in the SPID6 scores between the groups. Finally, Singla et al.[8] additionally demonstrated a significant increase of 27.6 ($p=0.03$) in SPID6 scores between the two groups.

CONCLUSIONS: All three studies demonstrated that intranasal ketorolac is both safe and effective in reducing pain postoperatively.

KEY WORDS: Intranasal ketorolac; postoperative pain

INTRODUCTION

Postoperative pain is one of the most common side effects that follows a surgical procedure and can also be one of the most challenging to manage. As many as 80% of patients admit to acute pain after surgery but under 50% report sufficient pain control before and after discharge.[1] Long term consequences of inadequately controlled pain can include increased post-surgical complications, decreased quality of life and persistent chronic pain.[1] The estimated economic burden of pain cost the United States between $560-$665 billion, including lost productivity and healthcare costs, which was reported in 2010.[2] The exact number of healthcare visits per year is unknown, however, about 10.3 million inpatient surgeries were performed in 2014 so an estimated 8.2 million stays per year would have required post-operative pain management.[3]

Pain is a broad definition that describes the body's physiological response to nerve stimulation or tissue damage and involves both physical and emotional responses from the body.[4] Although the pain pathway is quite complex, tissue damage from injury or surgery triggers nociceptors in the nerve endings to send electrical signals to the brain. These electrical signals are received to the brain on varying intensities based on their threat to the tissue.[4] The brain will then send adaptive responses to the tissue, such as reflex mechanisms and/or inflammatory mediators, to prevent further injury and start repairing the damage. Acute pain occurs from some known direct insult to the body, such as an injury or surgical procedure.[4] Chronic pain occurs over months or even years at a time and can occur from improperly controlled acute pain even once the original injury has healed.[4] Each individual experiences and perceives pain differently and can lead to various challenges when properly treating and managing acute pain postoperatively.

Adequately controlling acute pain postoperatively through analgesic therapy is key in order to prevent stressful physiologic responses and adverse health consequences. For example, if patients are in too much pain to get out of bed and ambulate after surgery, they are at a significantly higher risk for acquiring complications such as blood clots, pneumonia, atelectasis, etc.[5] The mainstay of treatment for postoperative pain is opioid analgesics; this can be given intravenously (IV), such as through patient-controlled analgesic (PCA) pumps, or given orally.[5] Some of the most common opioid analgesics used are morphine, fentanyl, hydromorphone, and hydrocodone.[5] Other nonnarcotic oral or IV drugs given alone or in combination with opioids to control pain include acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDS), and/or gabapentin.[5] Epidural or peripheral nerve infusion can also be given to control pain for certain procedures that involve larger areas of nerve involvement, such as abdominal procedures.[5]

Practitioners must be mindful when prescribing narcotic medications due to the possibility of over-sedating their patients, which can lead to potentially fatal side effects such as respiratory depression and apnea.[5] Opioid medications are also highly addictive leading to regulation and hesitation by health care providers when prescribing narcotic medication, especially long term. Ketorolac is a non-steroidal anti-inflammatory medication that has been proven to provide potent analgesic effects, similar to morphine, to control moderate to severe pain after surgery.[6,7,8] The intranasal (IN) route provides additional benefits since it is quickly absorbed into the bloodstream but does not require an intravenous line to be administered.[6,7,8]

OBJECTIVE

The objective of this selective EBM review is to determine whether or not intranasal (IN) ketorolac is both safe and effective in reducing acute postoperative pain for patients over 18 years of age that require inpatient hospitalization.

METHODS

The studies selected for this EBM review were found using PubMed and Cochrane Library databases to incorporate three placebo-controlled, double-blind RCTs that included adults over the age of 18 that were undergoing surgery with inpatient postoperative care. The intervention being observed in each study was intranasal ketorolac; Moodie et al.[6] and Brown et al.[7] used 30 mg of IN ketorolac in a 100 µL solution while Singla et al.[8] used 31.5 mg of IN ketorolac in a 100 µL solution. All studies were compared to a matched placebo that was similar in container shape, medication color, and administration. Patients still had access to morphine for pain and could receive back-up pain medication if study drug was not adequate for pain control. Outcomes measured in these studies was efficacy in pain reduction through summed pain intensity differences at 6 hours (SPID6) taken through patient reported visual analog scales (VAS) for pain and pain intensity differences (PID) as well as safety through reports of adverse events or change in clinical state.

All three RCTs were found in peer-reviewed journals and were published in English during or after 2007. Articles were then selected based on relevance to the clinical question and if their results focused on patient-oriented outcomes (POEMS). Inclusion and exclusion criteria for this review were applied to all three articles. Inclusion criteria were adults over 18 years of age that underwent an inpatient surgical procedure that required subsequent inpatient care and pain management. Exclusion criteria included subjects under 18 years of age and studies that comprised of other treatment modalities other than standard of care compared to the study drug. Table 1 demonstrates all specific inclusion and exclusion criteria for each study. Values reported for pain reduction were given in p-values in all three studies while a CI was given for Singla et al.[8] and safety was reported by calculating number needed to harm (NNH) for each study.

Table 1. Demographics & Characteristics of included studies

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Moodie[6] (2008)	RCT	84	> 18 years of age (mean age 53)	-Over 18 years old and weighing between 100 to 300 pounds -Pain intensity score >40 mm out of 100mm (VAS scale) -expected inpatient stay over 48 hours -Negative Pregnancy Test -Willingness to comply and complete posttreatment visit	-Allergy, sensitivity or contraindication (CI) to the use of NSAIDS (active bleeding/PUD, renal impairment, etc.) -Use of any IN product w/in 24 hours -Current URI, past or present cocaine use, or other respiratory tract condition or abnormality that would interfere with medication absorption or reporting adverse events -Clinically significant abnormality on screening test (w/in one month) -Pregnancy or breastfeeding	17	30-mg IN ketorolac given to subjects every 8 hours through 40 hours
Brown[7] (2009)	RCT	300	Range of 19-81 years old (mean age 52)	- Over 18 years of age undergoing major surgery and expected to stay in the hospital for at least 48 hours and up to 5 days	-Allergy, sensitivity, or CI to NSAIDs or opiate analgesics -GI bleeding disorder -Current URI or other conditions that interferes with intranasal absorption -Use of other IN products w/in 24 hours -Pregnancy or breastfeeding	90	30-mg IN ketorolac administered three times daily for up to 5 days
Singla[8] (2010)	RCT	321	Range of 18-64 years old (Mean age 46)	-Ages 18-64 undergoing major abdominal surgery (US and New Zealand) under general analgesia expected to remain in the hospital for at least 48 hours and up to 5 days	-Recent or current PUD/GI bleeding -Allergies, sensitivities or CI to study drugs -Current URI that could interfere with drug absorption -Use of any other IN product w/in 24 hours -Pregnancy or breastfeeding	20	31.5-mg IN ketorolac given every 6 hours for the first 48 hours and then up to 4 times per day

OUTCOMES MEASURED

Outcomes measured in all three studies were pain reduction through the VAS, PID and SPID6 scores while also measuring safety through adverse events (AE). All studies had patients rate their pain on the VAS with "0" being absolutely no pain and "100" being worst pain imaginable. Treatment began when their first VAS was greater than or equal to 40 and measured again at certain time intervals, usually at 30 minutes and then hourly, for a minimum of 6 hours and up to 2 to 5 days (as needed). The PIDs were then calculated by taking their baseline score and subtracting their pain score at certain time intervals after the drug was administered. All weighted PID scores were then analyzed to get the SPID6 results which is a sum of all PID scores for the first 6 hours. Greater difference in the SPID6 values between IN ketorolac and the placebo indicates a greater treatment effect. Safety was measured through adverse events reported by the patients or by change in clinical status (such as vitals, appearance, etc.) and then measured through NNH.

RESULTS

Three double-blind, placebo-controlled RCTs were evaluated to assess if intranasal ketorolac is both safe and effective for reducing postoperative pain in patients over 18 years of age that require inpatient hospitalization. Moodie et al.[6] and Brown et al.[7] measured 30 mg of IN ketorolac and Singla et al.[8] measured 31.5 mg of IN ketorolac, all to a matched placebo. All studies also measured adverse events in both groups. Table 1 above provides all inclusion and exclusion criteria.

In Moodie et al.[6] study, 84 subjects were enrolled to either receive placebo or 30 mg IN ketorolac.[6] Baseline characteristics were marginally similar, however, there was a slight trend toward older, white men in the placebo group compared to the experimental.[6] The intervention

for the experimental group was 30 mg of IN ketorolac (2 x 100 µL of 15% solution).[6] Both the experimental drug and matched placebo were given in an IN metered device to administer 100 µL of aerosolized medication per nostril.[6] Nurses on the post-surgical units would educate patients on correct administration so that they were able to self-administer throughout the study. General anesthesia was given to all patients prior to and during surgery. All patients had access to a PCA morphine pumps and rescue opioid medications for pain after surgery though no subjects requested rescue medications. VAS and PID scores were calculated at multiple time intervals for two days, but for the purpose of this analysis, only the first 6 hours were included (at 30 minutes and then 1,2,3,4,5, & 6 hours).[6] SPID6 results were analyzed with the Kruskal-Wallis test between the two groups.[6] The SPID6 score for the experimental group was 195.5 while the SPID6 score for the placebo group was 130.6 with a difference in SPID6 scores of 64.9 ($p= 0.0015$).[6] Table 2 has a summary of the results below. Safety was also assessed by total adverse events (AE) and calculating the NNH. AE were compared upon both treatment groups using the chi-square (χ^2) test or Fisher's exact test, as applicable.[6] The IN ketorolac group had a AE frequency rate of 95.2% while the placebo group has a AE frequency rate of 97.6%.[6] Nausea and pyrexia were the most common AE overall but there was a 28.6% decrease of pyrexia in the ketorolac group compared to placebo.[6] Nasal passage irritation was one of the only AE much higher in the ketorolac group (16.7%) compared to placebo (11.9%).[6] The NNH was calculated at -50 which means that 1 less patient will experience an adverse event with IN ketorolac compared to the placebo for every 50 patients treated. Table 3 has the results below.

Table 2: Mean Baseline VAS Scores and Difference in SPID6 Values

	Mean Baseline VAS Score (SEM)	SPID6 Values (SEM)	Difference between SPID6 Values	P-Value
Experimental Group	52.0 (1.5)	195.5 (12.1)	64.9	P=0.0015
Control Group	51.4 (1.7)	130.6 (14.4)		

Table 3: Comparison of Occurrences in Adverse Events between Ketorolac and Placebo

Control event rate (CER)	Experiment event rate (EER)	Relative risk increase (RRI)	Absolute risk increase (ARI)	Number needed to harm (NNH)
0.976	0.952	-0.025	-0.024	-50

In Brown et al.[7] study, 300 patients were initially enrolled in the study in a 2:1 ratio (ketorolac to placebo, respectively) but only 210 patients (133/199 in the ketorolac group and 72/101 in the placebo group) completed all 5 days of dosing.[7] Most common reasons for withdrawal were adverse events, concurrent illness and/or lab abnormality (33/199 in ketorolac group and 14/101 in placebo group).[7] A last observation carried forward approach was taken for the subjects who withdrew early.[7] Demographics and vital signs were similar between both groups. Most patients were middle-aged white women undergoing a total hysterectomy or hip replacement, though other invasive surgical procedures were included.[7] The experimental group intervention was 30 mg of IN ketorolac (100 μL solution) administered in a meter-pumped spray delivery system with one spray per nostril.[7] The placebo drug was similar in all aspects except containing the active drug, ketorolac. Study nurses would educate patients on correct administration so that they were able to self-administer throughout the study when comfortable to do so. Participants had access to a morphine PCA pump and backup analgesics in this study while some partook in a single-dose trial without backup analgesics, however, this was not evaluated in this analysis. The PID ratings were analyzed with one-way analysis of variance (ANOVA) while the treatment group differences were analyzed with log-rank test.[7] PID and

SPID6 scores were analyzed using analysis of covariance with baseline PI scores.[7] The SPID6 scores for the experimental group was 83.3 (+/- 10.6) while the SPID6 scores for the placebo group was 37.2 (+/-12.9) with a difference of 46.1 (p=0.007).[7] Table 4 has data summarized below. Safety was assessed similarly to the study above through reported AE or change in clinical status. P-values used to determine differences in AE between the two groups were calculated with χ^2 test.[7] The IN ketorolac group had a AE frequency rate of 97.5% while the placebo group has a AE frequency rate of 98%.[7] Nasal irritation, throat irritation, and lacrimation were higher in the ketorolac group compared to placebo, but pyrexia/intermittent pyrexia and pruritis were reduced in the ketorolac group compared to placebo.[7] Most adverse events were either mild or moderate in nature. NNH was calculated with a result of -200. Table 5 has summary of results below.

Table 4: Mean Baseline VAS Scores and Difference in SPID6 Values

	Mean Baseline VAS Score (SEM)	SPID6 Values (SEM)	Difference between SPID6 Values	P-Value
Experimental Group	54.7 (+/- 0.6)	83.3 (+/- 10.6)	46.1	p=0.007
Control Group	54.1 (+/- 0.9)	37.2 (+/-12.9)		

Table 5: Comparison of Occurrences in Adverse Events between Ketorolac and Placebo

Control event rate (CER)	Experiment event rate (EER)	Relative risk increase (RRI)	Absolute risk increase (ARI)	Number needed to harm (NNH)
0.98	0.975	-0.005	-0.005	-200

In Singla et al.[8] study, a total of 321 patients were enrolled in the study and grouped in a 2:1 ratio (ketorolac to placebo, respectively).[8] 301 patients completed the 2-week follow up at the termination of the study; 203 patients in the experimental group (95%) and 98 patients in the placebo group (92%).[8] A last observation carried forward approach was taken for the subjects who withdrew early.[8] Demographic differences between the two groups were similar and most

patients were white, middle-age females undergoing partial or total hysterectomies.[8] The experimental drug contained 31.5 mg of ketorolac in a 15% solution.[8] The matched placebo was contained in an identical meter-pumped container and both groups were administered 100 µL of solution to each nostril. Subjects were given a kit containing five devices, each containing a month's supply of the study drug. All patients had access to a PCA morphine pump for the first 48 hours and then rescue opioid medications as needed. VAS and PID scores were assessed at multiple time intervals, but only those taken at 20,40, and 60 minutes, and 2,3,4,5, and 6 hours after the first dose will be used for this analysis.[8] PID and SPID scores were analyzed using the two-way analysis of covariance with the baseline PI score made prior to study as covariate.[8] The SPID6 scores for the experimental group was 117.4 (+/- 7.7) while the SPID6 scores for the control group was 89.9 (+/- 10.6).[8] The difference between the scores was 27.6 (p=0.032 with 95% CI 2.5-52.7).[8] Table 6 has a summary of the data below. Safety was also measured through AE and calculating NNH. The IN ketorolac group had a AE frequency rate of 93% while the placebo group has a AE frequency rate of 96%.[8] Nausea, constipation and vomiting were the most reported AE between both groups.[8] Nasal discomfort, rhinalgia and anemia occurred more frequently in the ketorolac group compared to placebo, however, there were less incidences of nausea, constipation, pyrexia and tachycardia in the ketorolac group compared to placebo.[8] The NNH was calculated at -33. Table 7 summarizes results for safety below.

Table 6: Mean Baseline VAS Scores and Difference in SPID6 Values

	Mean Baseline VAS Score (SEM)	SPID6 Values (SEM)	Difference between SPID6 Values	P-Value and CI
Experimental Group	62.5 (+/- 1.6)	117.4 (+/- 7.7)	27.6	p=0.032 with 95% CI 2.5-52.7
Control Group	60.8 (+/- 1.1)	89.9 (+/-10.6)		

Table 7: Comparison of Occurrences in Adverse Events between Ketorolac and Placebo

Control event rate (CER)	Experiment event rate (EER)	Relative risk increase (RRI)	Absolute risk increase (ARI)	Number needed to harm (NNH)
0.96	0.93	-0.031	-0.03	-33

DISCUSSION

Ketorolac is an accepted adjunctive therapy for acute post-surgical pain management in adults over 18 years of age. Although opioid medications continue to be first line as stated above, using multiple modalities of medication may better treat acute postoperative pain to reduce side effects and decreased quality of life. The IN route allows for easy and quick absorption which allows patients to administer the medication without the need for an IV catheter.[6,7,8] Although ketorolac is an effective analgesic component for post-surgical treatment, it is not indicated for all populations. All NSAIDs pose an additional risk to those who have current/past peptic ulcer disease or gastric bleeding, those at higher risk for cardiovascular thrombosis events, and those who have decreased or worsening kidney functions.[9] Ketorolac is only indicated for maximum 5 days of use in adults and should not be used in chronic pain management.[9]

All three studies showed a significant pain improvement between the experimental and control groups ($p < 0.05$). This could potentially mean that patients who are eligible for ketorolac could have a significant decrease in pain following a surgical procedure. Benefits of controlling pain more adequately after a procedure could include shorter hospital stays, decreased sequala, return to baseline more quickly and less incidences of chronic pain.[1,5] Although these studies focused on inpatient research, limited research is currently available on the use of IN ketorolac in the outpatient surgical setting. Upon original research for this analysis, only one RCT was found and this study demonstrated that IN ketorolac was effective in reducing postoperative pain in patients undergoing outpatient dental procedures.[10]

The main limitation to all studies, which may have affected the outcome or limited the applicability of the results, is the demographics of the study populations. All three studies used in this analysis primarily included white, middle-aged women undergoing hysterectomies. The sample size from each study was adequate but may have been too inclusive to a certain population for the results to be relevant for all surgical patients. Other surgical modalities and varying demographics were included in each study but not to the same proportion. Additionally, Moodie et al.[6] and Brown et al.[7] had a large loss to follow-up (>20%) which could also alter the impact of the results since the drug may have been given but the research team was unable to account for the effects and had to accept their last scores taken before withdrawing.

CONCLUSION

The clinical trials included in the analysis demonstrated that IN ketorolac is both relatively effective and safe in treating acute postoperative pain in a small group of patients over 18 years old. All three studies showed that pain was both better controlled and produced similar occurrences or even a reduction in AE with IN ketorolac compared to placebo. Further studies are needed in order to determine if the results carry over to a larger population size that includes a variety of demographics and/or more common surgical procedures. Further studies are also warranted to see if IN ketorolac could be applied to an outpatient surgical setting for acute postoperative pain. Initiating further research to address both limitations could help generalize the results and help normalize IN ketorolac in general practice so that practitioners could potentially reduce the massive burden of pain, both physically and financially, on the healthcare system.

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