8-14-2010

Preemptive Non-Steroidal Anti-Inflammatory Drugs for Orthopedic Surgery

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Abstract
Background: Pain and infection are two of the major unwanted outcomes of surgery that physician have long been trying to control. There has been a great deal of advancement to limit pain caused by surgery, from the anesthesia during surgery to the commonly used opioids after surgery. Preemptive analgesia is defined as an anti-nociceptive treatment that prevents establishment of altered processing of afferent input, which can increase postoperative pain. By reducing the level of prostaglandins in your body, NSAIDs help relieve pain any condition causing inflammation, fever, and also prevent clotting. For these reasons it is felt that the use of NSAIDS preemptively could be helpful in decreasing the sensation of pain before it starts. With the discomfort of surgery kept to a minimum, pain medications could be decreased. With the decrease of analgesic medication also comes the decrease of unwanted side effects the worst of these being, opioid addiction or dependancy. Methods: This systematic review examines original research that looks at the preemptive use of NSAIDS in orthopedic surgery and the effects on postoperative pain. There were many articles excluded for their use of vioxx, some that were older and all those that had Dr. Scott Reuben as an author due to fabricated data. Results: Three studies published in the last ten years comparing the use of NSAIDs to placebo and one observationally blinded study during orthopedic surgery where included. These four studies looked at the preemptive use of NSAIDs in orthopedic surgery and either compared it to placebo or no intervention. The articles found did look at postoperative pain and analgesic usage. Conclusion: Non-Steroidal Anti-Inflammatory Drugs have been shown to have a greater postoperative effect on pain relief when given preemptively to those undergoing orthopedic surgery, than currently used postoperative practices. Opioid sparing is possible with preemptive use of NSAIDs, but were NSAIDs to be used every 12 hours after surgery further opioid sparing could be possible as discussed in the Haung et al study.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

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Keywords
preemptive NSAIDs, opioid sparing, orthopedic surgery, pain relief

Subject Categories
Medicine and Health Sciences

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A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 14 2010

Faculty Advisor: Annjanette Sommers MS, PAC
Clinical Graduate Project Coordinators: Annjanette Sommers MS, PAC & Rob Rosenow PharmD, OD

Biography

Jesse Mumm grew up in Rexburg, ID where he also graduated with his bachelors in Health Science. Jesse had always wanted to be a doctor but did not want to put all that time into school, so when he heard of the Physician Assistant profession he new it would be a perfect fit. Jesse has always wanted to be able to have a family of his own with whom to have fun, and to spend a lot of time, and being a PA would allow him that life style. While going to college Jesse worked full-time as a construction worker, small engine mechanic, and phlebotomist. After graduating with a bachelors he was employed at a surgery center that offered him a wide range of experience. While at the surgery center Jesse was the x-ray technician, phlebotomist, did laundry, building maintenance, purchased medical supplies, was able scrub in on a number of surgeries, performed EKGs and cleared all patients for surgery. During all this Jesse has been able to start his family, he currently has a 7, 4 and 3 year old boys and a little girl that is one and is expecting baby number five soon after graduating PA school.

ABSTRACT

Background: Pain and infection are two of the major unwanted outcomes of surgery that physician have long been trying to control. There has been a great deal of advancement to limit pain caused by surgery, from the anesthesia during surgery to the commonly used opioids after surgery. Preemptive analgesia is defined as an anti-nociceptive treatment that prevents establishment of altered processing of afferent input, which can increase postoperative pain. By reducing the level of prostaglandins in your body, NSAIDs help relieve pain any condition causing inflammation, fever, and also prevent clotting. For these reasons it is felt that the use of NSAIDS preemptively could be helpful in decreasing the sensation of pain before it starts. With the discomfort of surgery kept to a minimum, pain medications could be decreased. With the decrease of analgesic medication also comes the decrease of unwanted side effects the worst of these being, opioid addiction or dependancy.

Methods: This systematic review examines original research that looks at the preemptive use of NSAIDS in orthopedic surgery and the effects on postoperative pain. There were many articles excluded for their use of vioxx, some that were older and all those that had Dr. Scott Reuben as an author due to fabricated data.

Results: Three studies published in the last ten years comparing the use of NSAIDs to placebo and one observationally blinded study during orthopedic surgery where included. These four studies looked at the preemptive use of NSAIDs in orthopedic surgery and either compared it to placebo or no intervention. The articles found did look at postoperative pain and analgesic usage.

Conclusion: Non-Steroidal Anti-Inflammatory Drugs have been shown to have a greater postoperative effect on pain relief when given preemptively to those undergoing orthopedic surgery, than currently used postoperative practices. Opioid sparing is possible with preemptive use of NSAIDs, but were NSAIDs to be used every 12 hours after surgery further opioid sparing could be possible as discussed in the Haung et al study.

Keywords: preemptive NSAIDs, opioid sparing, orthopedic surgery and pain relief

ACKNOWLEDGEMENTS

To the love of my life, my wife Heather Mumm, who has gone through this whole experience while taking care of for children and being pregnant. She has been there to pick me up and push me forward through all the trials of PA school. She has always believed in me and has been by my side even as others put me down. My wife has given up all that she wants for a time so that she can be there to support our children and give them stability.

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ABBREVIATIONS

NSAIDS.....	Non-steroidal anti-inflammatory drugs
VAS.....	Visual Analog Score
COX.....	Cyclooxygenase
PGE2.....	Prostaglandin E2
IV.....	Intravenous
PCA.....	Patient-Controlled Analgesia
TKA.....	Total Knee Arthroplasty
ROM.....	Range of Motin

Preemptive Non-Steroidal Anti-Inflammatory Drugs for Orthopedic Surgery

BACKGROUND

Pain and infection are two of the major unwanted outcomes of surgery that physicians have long been trying to control. There has been a great deal of advancement to limit pain caused by surgery, from the anesthesia during surgery to the commonly used opioids after surgery. Medications have also been given before surgery to decrease discomfort this is termed preemptive analgesia. Preemptive analgesia is defined as an antinociceptive treatment that prevents establishment of altered processing of afferent input, which can increase postoperative pain. The concept of preemptive analgesia has been around since the last century, when Crile advocated the use of regional blocks in combination with general anesthesia to prevent intraoperative nociception and the formation of painful scars resulting from surgery.[1] Whether preemptive analgesic interventions are more effective than current method of controlling acute postoperative pain remains controversial. A meta-analysis reviewed several studies that addressed this question and have drawn fundamentally different conclusions.[2] Some of the studies looked at concluded that preemptive analgesia is effective as such, but some have concluded it to be effective only for certain analgesic drugs and surgeries.[2] Some analyses have attributed no beneficial effect to any drug, whereas some have postulated dependence on a range of factors, and some reviews have been unable to draw a final conclusion regarding efficacy.[2] This systematic review will look at the preemptive use of non-steroidal anti-inflammatory drugs (NSAIDs) in orthopedic surgery to decrease postoperative pain and the use of opioids.

Non-steroidal anti-inflammatory drugs (NSAIDs) stop cyclooxygenase enzymes (COX enzymes) in our bodies from working. COX enzymes increase production of hormone-like substances called prostaglandins, which can cause the feeling of pain by irritating nerve endings.[3] When nociceptors are activated by the noxious stimuli caused by tissue damage or infection, chemical substances and enzymes are released from the damaged tissues, increase the transduction of painful stimuli. Prostaglandins and leukotrienes cause sensitization of the peripheral receptors, reducing their activation threshold and increasing their responsiveness to stimuli.[4] By reducing the level of prostaglandins in your body, NSAIDs help relieve pain any condition causing inflammation, fever, and also prevent clotting.[3] For these reasons it is felt that the use of NSAIDS preemptively could be helpful in decreasing the sensation of pain before it starts. With the discomfort of surgery kept to a minimum, pain medications could be decreased. With the decrease of analgesic medication also comes the decrease of unwanted side effects the worst of these being, opioid addiction or dependency.

METHODS

This systematic review examines original research that looks at the preemptive use of NSAIDS in orthopedic surgery and the effects on postoperative pain. Meta-analyses and narrative reports are only used for background information. A search of the literature published in the previous ten years was conducted on the MEDLINE, CINAHL, and Web of Science databases using the following search terms: Preoperative, preemptive, postoperative pain, NSAIDs, orthopedic surgery and surgery. Subsequent examination of

bibliographic entries in retrieved works yielded additional studies for consideration. All studies were reviewed and scored as shown in Table 1.

The search was then limited to the English publications and adult subjects. All studies used, had a focus on preemptive use of current FDA approved non-steroidal anti-inflammatory drugs in orthopedic surgery. This was done to eliminate those studies that used Vioxx (rofecoxib) and other cycloxygenase-2 (COX-2) that are not approved due to the COX-2 adverse drug reactions. Also excluded several articles with Dr. Scott Reuben as an author as the journal of Anesthesia and Analgesia states that Dr. Scott Reuben fabricated data reported, and that all fabricated data were created under the sole control of Dr. Reuben.[5]

RESULTS

Three studies published in the last ten years comparing the use of NSAIDs to placebo and one observationally blinded study during orthopedic surgery where included.[6-9] These four studies looked at the preemptive use of NSAIDs in orthopedic surgery and either compared it to placebo or no intervention.

Takada et al, 2007

Takada et al[6] set a goal to clarify the effects of pre-administration of flurbiprofen, a nonselective cycloxygenase (COX) inhibitor, on plasma concentrations of prostaglandin E2 (PGE2) in patients undergoing open knee surgery using a tourniquet. Nonsteroidal

anti-inflammatory drugs (NSAIDs) inhibit the synthesis of PGs both in the spinal cord and at the periphery. This study also looks at the preemptive effects of flurbiprofen on post operative pain and opioid use.[6]

The study was performed in a prospective, randomized, controlled, and double-blind fashion. All solutions were prepared in a 100-mL bag of saline by the first investigator who was also responsible for subject grouping. The second investigator that performed IV injections was blinded as to type of test solution. The outcomes were measured by a third investigator who was blinded as to the type of solution.[6]

The study states that subjects were randomly divided, by sealed envelope assignment, into two groups. Group A (n = 16) received one mLd kg1 intralipid as a placebo, and group B (n = 16) received one mgd kg1 (1 mLd kg1) flurbiprofen IV 6 minutes before tourniquet inflation.[6] Placebo and flurbiprofen were administered over 16 minutes, and completed 6 minutes before the tourniquet inflated. Both solutions were made to be similar in appearance.[6]

Six mL of blood was taken from the femoral vein and cubital vein to measure plasma concentrations of PGE2. Blood samples were taken before tourniquet inflation (T1; before the administration of IV drugs), before tourniquet deflation (T2), and immediately after tourniquet deflation (T3).[6](Table 2)

Postoperative analgesia was supplied by IV 0.1 mg buprenorphine according to patient demand. The postoperative pain was assessed at 0.5, one, two, 4, 6, 12 and 24 hours after surgery, using a Visual Analog Scale (VAS), by trained nurses that were blinded as to which patients had received preemptive NSAIDs. All side effects were recorded as reported by patients or by nurse observation.[6]

The visual analog scale (VAS) in the experimental group B was significantly lower than group A at 0.6(P = 0.0033), one (P = 0.0018), two (P = 0.0038), and 4 (P = 0.0424) hours after surgery. By 6 hours post surgery, the differences in VAS scores were no longer significant. Buprenorphine consumption in group B was also significantly lower than that in group A during the first 4 post operative hours(P<.01 vs. group A). In group A, plasma concentrations of PGE2 in the femoral vein increased significantly at T2 and returned to control values (T1 level) at T3, whereas PGE2 in the cubital vein showed little change throughout the time course.(Table 2) In group B, plasma concentrations of PGE2 in either the femoral or cubital vein showed no change through time.(Table 2) There were no adverse effects associated with flurbiprofen in this study.[6]

Norman et al

Norman et al[7] performed a randomized, double-blind, controlled trial, set out to examine the effect of ketorolac as a preemptive analgesic for limited orthopedic surgery of the lower extremity, performed with a tourniquet. The preemptive dose was administered shortly before the tourniquet was inflated, and the postoperative dose was administered immediately after tourniquet inflation. Because ketorolac exerts its analgesic effects primarily at the peripheral level, the second dose functions as a poststimulus dose, because it does not reach the surgery site until after the tourniquet is deflated at the end of surgery. This study has a unique model for exploring the potential effects of preemptive analgesia by NSAIDs without having the problem of a time delay between the administration of the poststimulus doses of analgesia.[7]

Patients were randomly assigned by a computer generated table of random numbers to receive ketorolac before (PRE group), or after (POST group), tourniquet inflation. Each subject received one 50-ml bag of 0.9% NaCl intravenously after induction, while the leg was being prepared, and a second 50-ml bag of 0.9% NaCl intravenously immediately after tourniquet inflation. The time interval between administration of these bags was less than 16 minutes. Patients in the PRE group received ketorolac before tourniquet inflation and placebo after tourniquet inflation, and the POST group received its placebo first, and ketoralac after tourniquet inflation. Double-blinding was achieved by having the hospital pharmacy prepare the 50-ml bags for each patient and label them with only the patient's identification number. The pharmacy retained the codes which indicated to what group the patients were assigned, until the conclusion of the study.[7]

Norman et al[7] reported that postoperative analgesia was supplied by intravenous morphine using patient-controlled analgesia (PCA) with a 2-mg bolus dose, lockout period of 10 minutes, 4-hour maximum dose of 28 mg, and no basal infusion rate.[7]

Patients' visual analog scale (VAS) pain scores were documented thirty minutes preoperatively by each subject as a base. The VAS was a 100-mm scale, were patients were instructed that a 100 signified the "worst possible pain" and 0 represented "no pain". VAS scores, cumulative PCA morphine usage and presence or absence of bleeding at the surgical site was recorded postoperatively at 2,4,6,8,10,12 and 24 hours after tourniquet inflation. The study calculated the sample size by assuming that a 30% reduction in pain scores or postoperative morphine usage would be clinically useful.[7]

Furthermore, the study reported that the demographic data for both groups were similar. Of the 54 subjects enrolled in the study, 6 were eliminated from the study: 2 in

the PRE group (one because of malfunction of the tourniquet, and one because of an inadvertent booking of a midfoot fracture as an ankle fracture) and 4 in the POST group (one because of conversion of the surgical procedure to a closed reduction, one because of administration of intravenous fentanyl in the postoperative anesthesia care unit, one because of incorrect timing of study drug administration, and one because of an administrative error). The final PRE group consisted of 23 subjects, and the POST group was composed of 26 subjects. Graphic analysis of VAS scores revealed that any postoperative differences were present from 2– 4 hours only. Norman et al[7] stated that "VAS pain scores were significant for PRE versus POST at P = 0.0226 and were significant for change over time at P = 0.00158. The PRE group had significantly lower VAS pain scores than the POST group at hour 2 (P = 0.0203) and hour 4 (P= 0.00549). By hour 6, the intergroup differences were not significant (P = 0.388)."[7] Although VAS scores were lower in the PRE group morphine usage was similar for both groups.[7]

Takada et al, 2009

Takada et al[8] looked at the preemptive effects of flurbiprofen in arthroscopic rotator cuff repair. The study hypothesized that the combination of intravenous flurbiprofen and the currently used intraarticular ropivacaine could produce better postoperative analgesia than intraarticular ropivacaine alone, because the two drugs have different sites of action.[8]

Each patient was preoperatively instructed in the use of a 100-mm horizontal visual analog scale (VAS) for the evaluation of postoperative pain. The study was performed in a prospective, randomized, placebo controlled and double-blind fashion by three investigators. The first investigator prepared the 100-ml bag of saline, and was responsible for subject grouping. The second investigator who performed the intravenous injection, did not know the type of test solution being used. The postoperative VAS scores were recorded by the third investigator, who was blinded to the type of test solution used.[8]

Patients were placed randomly in to two equally sized groups by the use of a table of random numbers. Group A (n = 22) received 0.1 ml/kg lipid emulsion, in which the ingredients are the same as those of the flurbiprofen solvent, as a placebo, given intravenously 6 minutes before surgery. This was done to keep the two solutions similar in appearance. Group B (n = 22) received 1 mg/kg flurbiprofen, given intravenously 6 minutes before surgery. The placebo and flurbiprofen were mixed with 100 ml saline and given over a period of 16 minutes.[8]

VAS scores were assessed and recorded at 0.5, 1, 2, 4, 6, 12 and 24 hours after surgery. Postoperative analgesia was provided with intravenous 0.1 mg buprenorphine was given according to patient demand. The time was also measured from directly after surgery to the time when first dose of buprenorpine was given.[8]

This study reported that the demographic data for both groups were similar . VAS scores in group B were significantly lower than those in group A within the first 6 hours postoperatively (Table 5), but no significant difference was found in VAS scores at 12 hours or later. Buprenorphine consumption in group B was also significantly lower than

that in group A within the first 2 hours postoperatively , but from 4 hours and later no difference was measured.(Table 4) The time to the first analgesic was given in group B (368 ± 296 min) was significantly longer (P = 0.0027) than that in group A (110 ± 167 min).

Huang et al

The purpose of the Huang et al study[9] was to show the effectiveness of preoperative celecoxib for postoperative pain management after a total knee arthroplasty (TKA). Rofecoxib had previously been studied in coxib studies, but in September 2004, it was withdrawn from the market due to its thromboembolic effects, particularly myocardial infarction.[9]

This study showed that a preemptive dose of oral celecoxib can be used to achieve less postoperative pain and better rehabilitation after TKA surgery, especially in the first week. Although there have been previous studies which have evaluated the analgesic efficacy of rofecoxib, few studies have evaluated the efficacy of celecoxib for TKA. This study hypothesized that celecoxib provides better efficacy than the use of patient-controlled analgesic (PCA) morphine, which is currently the standard therapy. Huang et al[9] aimed to compare the difference in the pain scores at rest, pain during ambulation, range of motion (ROM) and morphine-sparing effects of celecoxib.[9]

In this study all TKA surgeries were performed by one surgeon (Ching-Chuan Jiang). This study was a randomized, prospective, observer-blind study design. Subjects were sorted by random numbers into two groups. This study used the diagnosis of primary osteoarthritis and over the age of sixty as it inclusion criteria. Exclusion criteria

for this study were the diagnosis of rheumatoid arthritis, end-stage renal disease, previous cerebral vascular accident history, history of peptic ulcers, recent myocardial infarction (within 1 year), and allergy to sulfa, NSAIDs, or morphine.[9]

According to the study, group A (n = 40) received 400 mg oral celecoxib at about 1 hour prior to surgery, and 200 mg every 12 hours, along with PCA morphine, over the first five post-operative days. Group B (n = 40) received only the PCA morphine over the same postoperative period.[9]

The celecoxib group had lower postoperative VAS pain at rest than group B at 48 hours ($p = 0.03$) and 72 hours ($p = 0.02$) after TKA surgery. Group A had reduced postoperative pain at ambulation, but did not reach significant difference when compared with group B. Repeated measures showed that the celecoxib group had significant VAS pain score reduction when compared to the control group at rest ($p = 0.023$) but not during ambulation ($p = 0.51$).[9]

The study report that celecoxib significantly improved postoperative knee ROM, especially during the first three days (Day1: $p = 0.01$; Day 2: $p = 0.004$; Day 3: $p = 0.004$). This group also had increased active ROM of 12–16 degrees in comparison with the control group. Repeated measures showed that the celecoxib group also had significantly better postoperative ROM than the control group ($p = 0.0009$).[9]

PCA morphine usage was notably lower in group A. PCA usage during the first 24 hours was significantly lower (15.1 ± 8.7 mg vs 19.7 ± 9.6 mg; $p = 0.03$). Norman et al[9] reported that the total PCA morphine usages in the celecoxib group and controls were 17.6 ± 11.9 and 24.6 ± 14.6 mg, respectively ($p = 0.03$). The celecoxib group used about 40% less morphine.[9]

DISCUSSION

In Takada et al,[6] 2007, Norman et al[7] and Takada et al,[8] 2009, which were double blinded studies, it was found that the VAS scores were significantly lower during the first four to six hours post surgery. While the VAS scores were down in all the studies, opioid sparing was found to only be significant in two [6,7] out of the three studies.[6,7,8] and it was only significant for two to four hours. The Huang et al[9] study was only blinded to the observer and did not have a placebo group and it continued NSAID usage after surgery. However it did have more pain relief and greater opioid sparing than the other studies reviewed.

Moreover, the Takada et al,[6] 2007, Norman et al[7] and Takada et al,[8] 2009, studies where very thoroughly done (Table 1) and even though the Huang et al[9] study could have had a lot of biases, it still made very valid observations that the other three studies ignored. Takada et al,[6] 2007, Norman et al[7] and Takada et al,[8] 2009, studies were double blind with placebos given to reduce the prejudice in the study. The Huang et al[9] study used was different in that it was only blinded to the observer. The way this study was conducted left it open to possible bias but it does make several observation not included in the other studies.

The biggest omission from all the studies [6-9] was a record of the instructions that were given to patients on the usage of PCA pumps and when the patient should take other postoperative analgesics. It is often explained to patients that they should stay on top of their pain by pushing the PCA button every 15 minutes or so before they feel the pain. These instructions are to help patients not reach a hyperalgesic state. The instructions for

postoperative analgesics could easily skew the amount of analgesics used after surgery, and could explain why, in many of the studies, little to no difference in the amount of pain medication used to control postoperative pain was found, whereas VAS scores remained lower in experimental groups. Another omission from Norman et al was followup on all the patients instead of just dropping them out of a study because exact protocol was not followed.

One of the focuses of the observational study by Haung et al,[9] although it could of had the most bias, was that all the surgeries performed by one surgeon, Ching-Chuan Jiang. The Huang et al[9] study, unlike the other studies, eliminated the variable of different surgeons' techniques. This study also continued the use of NSAIDS after surgery to further decrease opioid usage and increase pain control. It was also the only study that used a COX-2 that is approved by the FDA. Finally, it also looked at improved range of motion and had a study length of one week post surgery, making it the longest study by several days.

In the Takada et al,[6] 2007, and Norman et al[7] studies the surgeries were done with cuffs to reduce bleeding. The fact that these surgeries were performed while using an inflated cuff also helped decrease bias of pain killers taking too long a time to get to the site post surgery. The control groups were given analgesics shortly after the cuff was inflated which would ensure the immediate delivery of analgesics when the cuff was deflated.

PGE2 plasma concentrations were also found to be decreased in the experimental group in the Takada et al,[6] 2007, study. This helped validate the lower VAS scores,

which are subjective, that were reported in the experimental group by using a blood test, which is objective.

CONCLUSION

Non-steroidal anti-inflammatory drugs have been shown to have a greater postoperative effect on pain relief when given preemptively to those undergoing orthopedic surgery, than currently used postoperative practices. Opioid sparing is possible with preemptive use of NSAIDs, but where they to be used every 12 hours after surgery further opioid sparing could be possible as discussed in the Haung et al[6] study. Future studies, examining the use of NSAIDs preemptively in orthopedic surgery, should be to relieve postoperative pain and increase opioid spearing should be double blind prospective study, uses a 100-mm VAS scale, a single surgeon, using the NSAIDs post operatively, make sure placebo and control solution look the same, making sure to explain when and how to use postoperative analgesics, take care to look at the overall total of opioid usage over longer period of time and the measuring plasma concentration of PGE2. It is also important to follow up and analyze all patients in there assigned group. Future studies observing preemptive NSAID use verses of opioid use in patients need to be completed carefully as each drug does have its own adverse effects. These studies do need to be done so physicians can, when possible, treat patients with fewer opioids and help minimize the problems with addiction and dependency.

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TABLES

Table 1 Summary Matrix

Study	Yr. published	Patients/ Population	Intervention	Comparison	Outcome(s)	Study type	Validity (Jadad score)	Comments
Takada et al	2007	32 ASA physical status I-II patients scheduled for total knee arthroplasty or open anterior cruciate	Flubuprofrin one mg/kg IV 6min before surgery	Placebo	VAS scores and consumption of Buprenorphine was lower in intervention group and also PGE2 showed no increase. The placebo group	Randomized double blind controlled study	4 lost point for randomization by sealed envelope	They measured the PGE2 which stimulates neurons directly.
Norman et al	2001	54 Adults with ankle fractures having open orthopedic surgery	Ketoralac 30 mg IV 16min before surgery	Placebo	VAS scores were down in intervention group, opioid use was the same, blood loss was the same	Randomized double blind controlled study	5	This was a well done randomized trial presentation of results. Could be better. Although the Ketoralac group had less pain initially but used about the same opioids as placebo group.
Takada et al	2009	44 patients undergoing elective	flubuprofrin one mg/kg IV 6min before surgery	Placebo	Opioid use, Vas scores where all down	Randomized double blind controlled study	3	Here it was able to show decrease in opioids but there discussion is week and used randomly quotes from other studies some of which did not pertain.
Huang et al	2008	80 patients underwent total knee arthroplasty	400 mg dose clecoxib, one hour before surgery, and 2oomg celecoxib every 12 hours for five days	control group no placebo	Postoperative pain at rest 48h and 72 hours out and opioid consumption was decreased	Randomized observer blind control study	3	This study was not very well done although it still scored a Jadad score of three mainly just cause it was randomized. There is a lot of chances for bias to enter this paper and some of its references where taken out of context.

I.

Table 2 Plasma concentration of PGE2 Takada et al, 2007[6]

	T1	T2	T3
Group A			
Cubital pg/mL	212 ± 82	237 ± 82	258 ± 103
Femoral pg/mL	211 ± 61	359 ± 105[abc]	252 ± 77
Group B			
Cubital pg/mL	176 ± 39	191 ± 49	206 ± 61
Femoral pg/mL	201 ± 49	237 ± 63	239 ± 85

Data are presented as means ± SD

[a] P < .01 vs T1

[b] P < .01 vs group B (at T2)

[c] P < .o1 vs cubital vein (at T2)

Table 3 Postoperative pain Takada et al, 2009[8]

	Postoperative Time (hours)						
	0.5	1	2	4	6	12	24
Group A	70(30-100)	60(40-100)	60(20-80)	50(10-90)	38(20-80)	30(0-90)	30(0-80)
Group B	35(0-70)	25(0-70)	15(0-70)	12(0-70)	20(0-70)	25(0-80)	30(0-75)
P Value	<.0001*	<.0001*	<.0001*	<.0001*	<.0008*	0.4146	0.9528

*P< .01 was regarded as significant

Data are presented as median ranges

Table 4 Analgesic Consumption Takada et al, 2009[8]

	Postoperative time (hour)		
	Within 2	2-6	6-24
Group A (mg)	0.1 (0-0.2)	0 (0-0.1)	0 (0-0.1)
Group B (mg)	0 (0-0.1)	0 (0-0.1)	0.1 (0-0.2)
P value	.0002*	0.2216	0.2865

*P< 0.01 was regarded as significant

Data are presented as median ranges