Original Article

Comparison between paracetamol, piroxicam, their combination, and placebo in postoperative pain management of upper limb orthopedic surgery (a randomized double blind clinical trial)

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Abstract

Background: Therapeutic superiority of a combination of Paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) over either drug alone remains controversial. We evaluated the efficiency of a combination of Paracetamol and Piroxicam versus each drug alone and also placebo in the management of postoperative pain, in patients who had undergone elective upper limb orthopedic surgery under general anesthesia.

Materials and Methods: A total of 100 patients were randomly divided into four groups to receive either intravenous (IV) infusion of Paracetamol, 15 mg/kg., intramuscular (IM) injection of Piroxicam 0.4 mg/kg., their combination or placebo. The pain scores were recorded at the first; second, fourth, sixth, twelfth, and 24 hours after Post Anesthesia Care Unit (PACU) admission. After the operation 0.1 mg/kg of morphine was administered, if the patient needed.

Result: The means of the pain scores were 5.26 ± 1.53, 4.09 ± 0.88, 4.36 ± 1.48, and 4.11 ± 1.29, in groups A, B, C, and D, respectively, (Group A: received placebo; Group B: received both Paracetamol and Piroxicam; Group C received Piroxicam; Group D received Paracetamol). Except for differences between the mean pain scores in Groups B and D, the other differences were statistically significant (P value < 0.05). No adverse effect was reported in the four groups.

Conclusion: IV infusion of 15 mg/kg Paracetamol used as a preventive may provide effective analgesia in comparison with IM 0.4 mg/kg Piroxicam or placebo. Addition of Piroxicam to Paracetamol has not much more benefit than Paracetamol alone, in reducing pain after upper limb orthopedic surgery.

Key Words: Acetaminophen, orthopedic surgery, paracetamol, piroxicam, postoperative pain, preventive analgesia

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INTRODUCTION

Management of acute postoperative pain remains suboptimal. About 80% of the patients report moderate-to-severe pain after surgery.[1] On the other side, uncontrolled postoperative pain may produce a range of detrimental acute and chronic effects, so an appropriate dose of

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analgesia is important in postoperative pain management.[1-3]

The attenuation of perioperative pathophysiology that occurs during surgery, through the reduction of nociceptive input to the central nervous system and optimization of perioperative analgesia may decrease complications and facilitate recovery during the immediate postoperative period and after discharge from the hospital.[3]

Different classes of analgesics exert their effects through different mechanisms. Their side effects, for example, respiratory depression with opioids or enteropathy with nonsteroidal anti-inflammatory drugs (NSAIDs) tend to be different and may be dose-related.[4]

Opiates fail to produce adequate pain relief in more than 80% of the patients. A combination of opioids, NSAIDs,[1,2] and local anesthetic agents provides good pain relief. Although opioids provide effective pain relief, they are associated with known side effects. Apprehension concerning the potential adverse side effects of opioids, such as, emesis, excessive sedation, and risk of respiratory depression and addiction, has contributed to the underutilization of the prescribed opiates.[1-3]

The combination of analgesics with proven efficacy is an approach to achieving one or more therapeutic goals, such as, facilitating patient compliance, simplifying prescribing, and improving efficacy without increasing the adverse effects or decreasing adverse effects, without loss of efficacy.[5-9]

There has been a trend over the recent years of combining NSAIDs with Paracetamol (acetaminophen) for the management of acute postoperative pain,[4] but the therapeutic superiority of the combination over either drug alone remains controversial.[10,11]

Our aim was to determine whether the preventive administration of Paracetamol, Piroxicam, and their combination provided superior efficacy in the treatment of acute postoperative pain to either drug alone. Also, we wanted to determine whether Piroxicam, Paracetamol or their combination caused less opioid consumption and also less complication.

Preventive administration of drugs and use of Piroxicam are two specific features of this study.

MATERIALS AND METHODS

After approval of the Ethics Committee of the University, this randomized, double-blind, prospective clinical trial study was performed in 100 patients with American Society Anesthesia (ASA) I and II, aged 18-75 years, and who were candidates for elective surgery of the upper limb. The other inclusion criteria were patients without renal or hepatic disease, without a history of gastrointestinal bleeding, without allergy to the study drugs, and without history of drug abuse. We obtained a written informed consent from each patient.

This study was performed from June 2012 until June 2013, in the Al Zahra and Kashani teaching hospitals of the Isfahan University of Medical Sciences.

A formal sample size calculation was performed. The calculated sample size was 25 patients in each group. Hence, the total sample size required was 100.

We use two types of analgesics: Intramuscular injection of Piroxicam as an NSAID with Plasma half-life of 57 hours.[12] Paracetamol (intravenous Acetaminophen) with Plasma half-life of two to three hours.[12]

The patients were randomized according to a table of random numbers into one of the four groups; Group A included those who received intravenous and intramuscular normal saline (the same dose of the two above-mentioned drugs) as placebo; Group B included patients who received Intravenous Paracetamol 15 mg per kg and intramuscular Piroxicam 0.4 mg per kg; Group C included those who received intramuscular Piroxicam 0.4 mg per kg 2; and Group D included those who received intravenous Paracetamol 15 mg per kg.

All the mentioned drugs were administered when the surgeon started closure of the surgical incision.

We used an online random number generator to create a list of random numbers, based on our specification.

This specification was a generation of 100 random numbers in which the minimum value was 1 and the maximum value was 4, while we allowed duplicate entries without Seed. After pressing the calculate button, a rank of 100 random numbers according to the specification were produced. The first patient received treatment number 2, while the second patient received treatment number 3, and the randomization was continued till 100 patients received one of the four treatments. Sequence allocation and patient enrollment were carried out by a physician who was blinded to data collection. The participants were assigned to the intervention by a nurse, who was not involved in data collection.

We used closed packets with numbers from the randomization list written on them for each patient. The patients received study drugs before closure of the surgical incision in the Operation Room by a nurse who was not involved in data collection.

After patient arrival to the Operating Room, blood pressure, heart rate (HR), and oxygen saturation of arterial blood (SpO2) were recorded at 20 minute intervals during the operation. All patients received a standard general anesthesia and no premedication was administered. The patients were induced with the same dose of fentanyl (2 micg/kg), thiopental (5 mg/kg), and Atracurium (0.5 mg/kg).

Anesthesia was maintained with 50% nitrous oxide and oxygen, adding inhaling agent, 1.25% of Isoflurane. The patients also received intravenous morphine (0.1 mg/kg) before incision as an analgesic. After operation, the administration of the anesthetic gas was terminated and a muscle relaxant was reversed by using neostigmine 0.04 mg/kg and atropine 0.02 mg/kg, intravenously. After reversal of the muscle relaxant, if the patient's airway reflex was reversed, extubation was performed and the patient was transferred to the PACU.

The objective of the study was to measure the postoperative pain score based on the visual analog scale (VAS) and additional opioid analgesic consumption. An anesthesia nurse, who had no knowledge of the group to which the patient belonged, was responsible for the collection of data.

The pain score was assessed using the VAS (from 1 cm, no pain, to 10 cm, worst possible pain) at the first, second, fourth, sixth, twelfth, and twenty-fourth hours after entrance to the PACU (origin of time). An investigator, without any knowledge of the group to which the patient belonged, recorded the pain scores. If the patients had pain with VAS $\geq$ 4, we administered an additional dose of morphine 0.1 mg/kg.

Adverse effects include: Gastrointestinal bleeding, abdominal pain, and nausea and vomiting more than twice were recorded. Statistical analysis was performed using repeated measures ANOVA, Chi-square, Kruskal-Wallis, and *Post Hoc* tests. Significance was assumed at a 5% level.

RESULTS

One hundred patients were involved in the study from June 2012 to June 2013 [Figure 1].

There were no significant differences in the four groups among the age and sex of the patients, surgical zone, and operation time [Table 1]. One hour after PACU admission, the pain scores in groups B and D were less than in group A and also in groups B and D, in comparison with group C. Two hours after PACU admission, the pain score was significantly less in groups C and D in comparison with group A, and also in group D in comparison with groups B and C. There were no significant differences among the pain scores of the four groups at 4 hours and 6 hours. The pain score at 12 hours after PACU admission was significantly less in groups B and C in comparison with group A, and finally at the end of 24 hours, the pain score was significantly less in group A in comparison with group B. For better comparison, we calculated the mean of the pain scores over 24 hours in each group, where we obtained significant differences. The mean pain score in groups B and D were the same and also less than in group C. The mean pain score in group C was less than in group A. (Pain score: B = D < C < A) [Table 2].

The mean dosage of the additional analgesic (morphine) used for postoperative pain, had no significant difference in the four groups [Table 3].

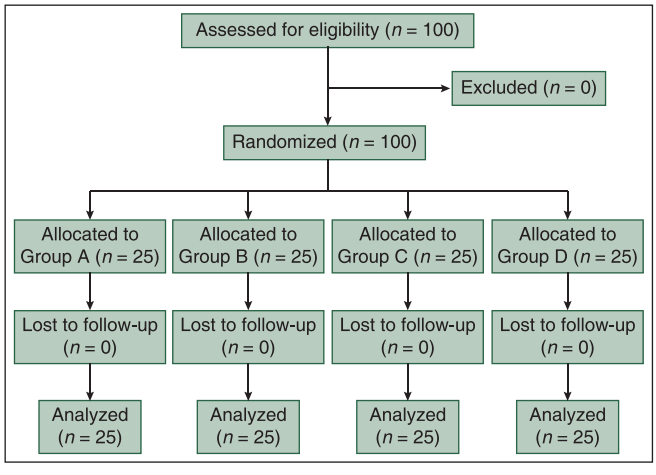

Figure 1: Flow diagram of randomized patients

Table 1: Demographic characteristics and duration of operation in four groups

Variable	Group A	Group B	Group C	Group D
Age (years)	35.92±14.30	39.12±14.47	34.04±11.89	35.72±13.78
Sex (male/female)	14/11	16/9	17/8	18/7
Surgical time (minutes)	77.92±18.58	76.40±26.67	65.20±16.48	84.00±40.00

Data are presented as mean ± SD or numbers, Group A = Received placebo, Group B = Received both Paracetamol and Piroxicam, Group C received Piroxicam, Group D received Paracetamol, There was no significant difference among the four groups ($P < 0.05$)

Table 2: The VAS scores at different time intervals after operation in four groups

Variables	Group A	Group B	Group C	Group D
Pain score: First hour	5.00±2.30	3.40±2.18	5.32±3.19	3.36±2.39
Pain score: Second hour	6.56±2.22	5.80±2.45	5.16±2.28	3.52±1.96
Pain score: Fourth hour	5.04±1.97	4.40±1.66	4.00±2.34	4.16±1.99
Pain score: Sixth hour	5.48±2.51	4.52±1.44	4.64±2.34	4.28±2.09
Pain score: Twelfth hour	5.40±2.70	3.88±1.30	3.76±2.10	5.64±2.44
Pain score: Twenty-fourth hour	4.12±2.33	2.56±1.19	3.28±2.01	3.72±1.77
Mean pain score	5.26±1.53	4.09±0.88	4.36±1.48	4.11±1.29

Data are presented as mean ± SD, Group A = Received placebo, Group B = Received both Paracetamol and Piroxicam, Group C received Piroxicam, Group D received Paracetamol, ($P < 0.05$)

Table 3: The mean dosage of rescue analgesic (Morphine) at different time intervals after operation in the four groups

Variable	Group A	Group B	Group C	Group D
Morphine dosage (mg)	5.80±5.33	4.80±4.44	3.96±3.29	4.40±3.62

Data are presented as mean ± SD, Group A = Received placebo, Group B = Received both Paracetamol and Piroxicam, Group C received Piroxicam, Group D received Paracetamol, There was no significant difference among the four groups ($P < 0.05$)

No adverse effect including gastrointestinal bleeding, abdominal pain, recurrent nausea, or vomiting was recorded in the four groups.

DISCUSSION

According to this study, a combination of Piroxicam and Paracetamol is more effective than Piroxicam alone. This conclusion is consistent with many previous expert reviews that recommend the use of combination analgesics.[6,13-20] In a qualitative systematic review article that was performed by Ong *et al.*[4] twenty-one human studies enrolling 1909 patients were analyzed. The NSAIDs used were Ibuprofen, Diclofenac, Ketoprofen, Ketorolac, Aspirin, Tenoxicam, and Rofecoxib. The findings showed that a combination of Paracetamol and an NSAID was more effective than NSAID alone in 64% of the relevant studies. In another study performed by Miranda *et al.*[21] the antinociception induced by the intraperitoneal coadministration of combinations of Paracetamol with NSAIDs that included Diclofenac, Ibuprofen, Ketoprofen, Meloxicam, Metamizol, naproxen, Nimesulide, Parecoxib and Piroxicam was studied by the isobolographic analysis in the acetic acid abdominal constriction test of mice. The effective dose that produced 50% antinociception (ED_{50}) was calculated from the log dose-response curves of fixed ratio combinations of Paracetamol with each NSAID. By the isobolographic analysis, this ED_{50} was compared with the theoretical additive ED_{50} calculated from the ED_{50} of Paracetamol and of each NSAID alone, obtained from ED_{50} dose-response curves. As shown by the isobolographic analysis, all the combinations were synergistic, the experimental ED_{50}s being significantly smaller than the theoretically calculated ED_{50}s. The results demonstrate potent interactions between Paracetamol and NSAIDs, and validate the clinical use of combinations of these drugs in the treatment of pain conditions.

In our study, we did not find significant differences between the combination of Paracetamol and Piroxicam and Paracetamol alone. In the review article that was performed by Ong *et al.*[4] it was noted that a combination of Paracetamol and NSAID was more effective than Paracetamol alone in 85% of the relevant studies. This conclusion was compatible with the results of others.[6,15,21]

The differences between the results of our study with these studies may be due to the low sample size of patients enrolled in our study. Moreover, it could have originated from the difference in the intensity and quality of the nociceptive stimulus. The type of NSAID may play a significant role in this regard. Control of some of these factors is difficult in clinical studies and may be a reason for the discrepancies between different researches in this regard.

According to this study preventive administration of IV infusion of Paracetamol 15 mg per kg confers additional analgesic efficacy over Piroxicam.

A quantitative review article performed by Hyllested *et al.*[6] demonstrated that the efficacy of NSAIDs and Paracetamol seemed without substantial differences in major and orthopedic surgeries, although firm conclusions could not be made because the number of studies was limited. Moreover, it was noted that Paracetamol was a viable alternative to NSAIDs, especially because of the low incidence of adverse effects, and should be the preferred choice in high-risk patients.

In another article performed by Gunsen *et al.*[22] the efficacy of Paracetamol versus Tenoxicam on postoperative pain, after abdominal hysterectomy, was evaluated, and it was found that Tenoxicam was associated with lower pain scores at the second, fourth, sixth, and twenty-fourth hour postoperatively.

In an article by Kashefi *et al.*[22] it was concluded that the use of oral Celecoxib 200 mg, two hours before

operation, was better than using oral acetaminophen 320 mg, two hours before the beginning of surgery, for control of postoperative pain in patients who had undergone lower extremity orthopedic surgery.

It clarified that different types of NSAIDs are used in these studies. There is limited data on the evaluated efficacy of Paracetamol versus NSAIDs like Piroxicam, and therefore, we cannot made a firm conclusion.

This point is notable that the maximum analgesic effect of Piroxicam is not mentioned, but its half-life is about 57 hours.[12] We gathered a pain score until 24 hours, so the next studies with longer follow up should be down for better comparison of Paracetamol versus Piroxicam.

In our study the mean dosage of the additional analgesic (morphine) used for postoperative pain has no significant difference in the four groups. It interferes with the conclusion made by Ong *et al*.[4] The analgesic supplementation was lesser in the combination versus the Paracetamol group or the NSAID group.

This difference may originate from the low sample size of our study.

The efficacy of preventive analgesia depends on many factors, including, the nature of the tissue injury, the degree of sensitivity of the nociceptors, the type of drugs used pre-emptively, the route and timing of drug administration, duration of its action, the degree of afferent nerve block, and finally the emotional, physiological, and psychological condition of the patients.[6-8,22]

Our study had some limitations:

1. We did not find any statistical difference in the postoperative pain scores or mean dosage of the rescue analgesic used, among the four groups. It could be due to the low sample size of the enrolled patients. We recommended performing studies with a larger sample size in the future;
2. We evaluated the efficacy of the preventive use of Piroxicam and Paracetamol for 24 hours.

According to the intramuscular administration and half-life of Piroxicam (about 57 hours[12]) versus intravenous infusion and half-life of Paracetamol (two to three hours[12]) increased duration of follow-up and use of additional doses of Paracetamol during follow-up will provide better comparison between Piroxicam and Paracetamol.

For the next studies we prefer increasing the sample size and matching of groups in aspects like: Type of operation and whether the operation is unilateral or bilateral. Increased duration of follow-up with regard to half-life and time of maximum efficacy of drugs is another important point for better comparison between analgesics.

CONCLUSION

This study showed that preventive administration of intravenous Paracetamol can control postoperative pain better than Piroxicam, and also a combination of these drugs is as effective as Paracetamol.

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REFERENCES

1. Brown ST, Kirkpatrick MK, Swanson MS, McKenzie IL. Pain experience of the elderly. Pain Manag Nurs 2011;12:190-6.
2. Battisti WP, Katz NP, Weaver AL, Matsumoto AK, Kivitz AJ, Polis AB, *et al*. Pain management in osteoarthritis: A focus on onset of efficacy – A comparison of rofecoxib, celecoxib, acetaminophen, and nabumetone across four clinical trials. J Pain 2004;5:511-20.
3. Miller RD, Robert W. Miller's Anesthesia.7th ed. Philadelphia: Churchill Livingstone; 2010. p. 1611-38.
4. Ong CK, Seymour RA, Lirk P, Merry AF. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: A qualitative systematic review of analgesic efficacy for acute postoperative pain. Anesth Analg 2010;110:1170-9.
5. Raffa RB. Pharmacology of oral combination analgesics: Rational therapy for pain. J Clin Pharm Ther 2001;26:257-64.
6. Hyllested M, Jones S, Pedersen JL, Kehlet H. Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: A qualitative review. Br J Anaesth 2002;88:199-214.
7. Maves TJ, Pechman PS, Meller ST, Gebhart GF. Ketorolac potentiates morphine antinociception during visceral nociception in the rat. Anesthesiology 1994;80:1094-101.
8. Salazar LA, Martínez RV, López-Muñoz FJ. Synergistic antinociceptive interaction between aspirin and tramadol, the atypical opioid analgesic, in the rat. Drug Dev Res 1995;36:119-24.
9. Fairbanks CA, Wilcox GL. Spinal antinociceptive synergism between morphine and clonidine persists in mice made acutely or chronically tolerant to morphine. J Pharmacol Exp Ther 1999;288:1107-16.
10. Merry AF, Power I. Perioperative NSAIDs: Towards greater safety. Pain Rev 1995;2:268-91.
11. Rømsing J, Møiniche S, Dahl JB. Rectal and parenteral paracetamol, and paracetamol in combination with NSAIDs, for postoperative analgesia. Br J Anaesth 2002;88:215-26.
12. Katzung B, Masters S, Trevor A. Basic and Clinical Pharmacology. 12th ed. New York: New York; 2012. p. 523-40.
13. Ong CK, Seymour RA. An evidence-based update of the use of analgesics in dentistry. Periodontol 2000 2008;46:143-64.
14. Ong CK, Lirk P, Tan CH, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. Clin Med Res 2007;5:19-34.
15. Seideman P. Additive effect of combined naproxen and paracetamol in rheumatoid arthritis. Br J Rheumatol 1993;32:1077-82.

16. Curatolo M, Sveticic G. Drug combinations in pain treatment: A review of the published evidence and a method for finding the optimal combination. Best Pract Res Clin Anaesthesiol 2002;16:507-19.
17. Mehlisch DR. The efficacy of combination analgesic therapy in relieving dental pain. J Am Dent Assoc 2002;133:861-71.
18. Lange H, Kranke P, Steffen P, Steinfeldt T, Wulf H, Eberhart LH. Combined analgesics for postoperative pain therapy. Review of effectivity and side-effects. Anaesthesist 2007;56:1001-16.
19. Desmeules J, Rollason V, Piguet V, Dayer P. Clinical pharmacology and rationale of analgesic combinations. Eur J Anaesthesiol Suppl 2003;28:7-11.
20. World Health Organization. Cancer Pain Relief and Palliative Care: Report of a WHO Expert Committee. Geneva: World Health Organization; 1990. p. 7-21.
21. Gunusen I, Karaman S, Acar A, Sargin A, Firat V. The efficacy of paracetamol versus tenoxicam on postoperative pain and morphin consumption after abdominal hysterectomy: A placebo-controlled, randomized study. Clin Exp Obstet Gynecol 2012;39:49-52.
22. Kashefi P, Honarmand A, Safavi M. Effects of preemptive analgesia with celecoxib or acetaminophen on postoperative pain relief following lower extremity orthopedic surgery. Adv Biomed Res 2012;1:66.

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