Original Article

Effect of Preemptive Analgesia with Ketorolac on Intra and Post Operative Opioid Requirements in Patients Undergoing Total Abdominal Hysterectomy

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Objective: Pre-emptive analgesia may prevent or reduce hyper-analgesia, inhibit inflammation and reduce pain by blocking the synthesis of prostaglandins in response to tissue damage caused by surgery. NSAIDS are used frequently for treatment of post-surgical pain along with opioids. However, they may not be as effective as opioids. Ketorolac (one of the NSAIDS) used post-operatively can be used for pre-emptive analgesia to reduce opioid requirements in patients undergoing total abdominal hysterectomy (TAH).

Material and Methods: This was a double blind controlled trial with random allocation. After approval from hospital ethics committee, seventy ASA I and II patients between the ages of 40-60 years undergoing total abdominal hysterectomy (TAH) were included in the study after informed consent. They were divided into two equal groups (35 patients in each group). Each patient was shown the VAS (Visual Analogue Scale) preoperatively and explained how to rate her severity of pain on the scale. Thirty five patients, preemptive group (P group) received 30 mg of Ketorolac and 35 patients, control group (C group) received placebo (saline) intravenously (I.V) 30 minutes before induction of anesthesia. Intra-operatively, an increase in blood pressure and heart rate were taken as an indicator of pain during surgery and Injection Nalbuphine 0.05-mg/kg was administered as rescue analgesia. Postoperatively, for the initial 24 hours, pain was assessed on a VAS (VAS-score) of 1-3 considered as mild pain, 4-7 as moderate pain & 8-10 as severe pain). If score was more than 3 a top up dose of Inj. Nalbuphine 0.05 mg/kg was administered intravenously. Total Nalbuphine consumption during the intraoperative as well as initial 24 hours postoperative period was recorded for each patient.

Results: Thirty five patients in study group (P group) and 35 patients in the control group (C group) completed the study. Overall, there was no statistically significant difference in pain scores as well as opioid requirements in both these groups. ($P > 0.05$).

Conclusion: The results suggested that there was no decrease in opioid requirements in patients who received Inj. Ketorolac pre-emptively, therefore Ketorolac has little or no place as a preemptive analgesic.

Keywords: Ketorolac, NSAIDS, Nalbuphine, Pain Score and Total Abdominal Hysterectomy.

Introduction

Postoperative pain, a type of acute pain, is one of the disturbing conditions in surgical patients. A variety of drugs have been tried for this purpose. However, the basic drugs used for postoperative pain relief are still paracetamol, NSAIDS, local anesthetics and opioids. Opioids are used most frequently as an analgesic to treat surgical pain. Opioids also reduce the anesthetic requirements and result in smooth intra-operative course.[1] They are helpful in reducing the sympathoadrenal response to laryngoscopy and intubation especially in patients of hypertension and ischemic heart disease.[2] Opioids, however, are not free of side effects which are of concern to the anesthetist like respiratory depression, nausea and vomiting.[3] These side effects are dose related and by reducing the total dosage we can reduce the incidence of side effects.

Recent understanding of acute pain mechanisms particularly peripheral and central sensitization of dorsal horn neurons by surgical stimuli has led to the search for novel treatments.[4] Peripheral tissue injury provokes peripheral sensitization (a reduction in the threshold of nociceptor afferent peripheral terminals) and central sensitization (an activity dependent increase in the excitability of spinal neurons). These changes contribute to the post injury pain hypersensitivity state. The pre-emptive form of pain treatment (pain treatment before skin incision) prevents this state.

At the beginning of the last century, Crile was among the pioneers to introduce the concept of preemptive analgesia.[5,6] The preemptive analgesia reduces the intra and postoperative requirements of analgesics. It is achieved by modulation of central and peripheral sensitization processes, thereby attenuating or ideally preventing postoperative amplification of pain sensation.[7] Several drugs have been tried but the clinical utility has been limited by only moderate preemptive analgesic effect or significant side effects.[8]

Ketorolac (Trometamol) is a non-steroidal anti-inflammatory drug (NSAID) which can be given by IV route safely. NSAIDs unlike opioids do not cause adverse effects like respiratory depression, nausea and vomiting. Furthermore, they have been shown not to increase the risk of bleeding intra-operatively and post-operatively.[9] The idea of using Ketorolac preemptively was to reduce the total opioid dosage and thus minimizing the incidence of side effects while maintaining the quality of pain relief.

Material and Methods

This double blind, randomized controlled trial was done in anesthesia department of Fatima Memorial Hospital, Lahore and completed in 8 months (January 2006 to August 2006). After approval from the hospital ethics committee, seventy ASA I & II patients between the ages of 40-60 years undergoing TAH were included. The patients having history of allergy to any drug, acid peptic disease, hypertension, ischemic heart disease, asthma, renal or hepatic insufficiency and coagulation disorders were excluded from the study. These patients were randomly allocated to either of two groups after informed consent. Each of the patients was shown the visual analogue scale preoperatively and was explained how to rate their severity of pain on the scale. These seventy patients were divided into two groups. Group P (35 Patients) received pre-emptive dose of Ketorolac, 30 mg diluted in normal saline to make 3 ml, by IV route, 30 min before induction of anesthesia. Group C (35 Patients) received placebo, 3ml normal saline IV, 30 min before induction of anesthesia. The syringes containing ketorolac or normal saline (placebo) were prepared by another anesthetist having randomization list. He entered the name and medical record number of the patient on list and according to group allocation labelled the syringes inj-1 and inj-2. Thus for group P inj-1 contained ketorolac and inj-2 contained normal saline. For group C inj-1 contained normal saline and inj-2 contained ketorolac. These syringes were handed over to the anesthetist who was conducting the research. He did not know the information on the allocated groups or contents of the syringes.

Outcome Variables:

Pain assessment done intra-operatively, indirectly, if there is an increase in blood pressure and heart rate due to pain and postoperatively by visual analogue scale score (VAS score). These were noted/ recorded by a person who was blinded to the drug used. Intra-operative and postoperative additional Nalbuphine, if given, was also recorded. Ages of patients were also noted. Anesthetic technique was standardized for both groups. GA was maintained with O_2 40 %, N_2O 60% and Isoflurane 0.6% - 1% with flow rate of 3L/min. Muscle relaxation was maintained using reocuronium 0.1 mg/kg on appearance of one twitch on train of four (TOF). Ringer lactate (R/L) fluid was used for deficit and maintenance requirements of the patients. Blood loss initially replaced with three times of R/L and blood transfusion was given when estimated Hb % fell below 8 g/dl. If there was a drop in blood pressure by more than 20% of base line, R/L 3ml/kg was administered. In case of persistence of problem, isoflurane was reduced. When BP or HR increased by more than 20%, isoflurane was increased. If hypertension persisted, rescue analgesia was given. Reversal (Neostigmine 2.5 mg plus glycopyrrolate 0.5 mg) IV was given after skin sutures. All patients were monitored using ECG, Pulse Oximetry, Noninvasive blood pressure, $EtCO_2$ and Neuromuscular Function monitor. For postoperative analgesia in postanesthesia care unit (PACU)/ postoperative ward, all patients received Nalbuphne 0.05 mg/kg IV every two hours, first dose given two hours after surgery. All patients also received Ketorolac 30 mg IV 8 hourly, first dose given after 8 hours of induction. Assessment of pain was done using VAS score (VAS score of 1-3 considered as mild pain, 4-7as moderate pain and 8-10 as severe pain) on hourly basis for 8 hours and then 2 hourly until 24 hours. Patients with a VAS score of 3 or more were given a dose of Nalbuphine 0.05 mg/kg IV as rescue analgesia. Total dose of Nalbuphine used during 24 hours for each patient was recorded by a designated nurse who was blinded regarding the treatment groups.

Statistical Analysis:

The data was entered on pre-coded forms and processed using SPSS version 12. Statistical analysis was done by applying chi-square test for qualitative data and student's t test for quantitative data. A p-value of <0.05 was considered significant.

Results

Data forms were collected from all seventy patients included in the study (100% data collection) with 35 patients in each group, pre-emptive and control**.** The age of patients ranged between 40-60 years with a mean of 43.5 years. Intraoperatively, 27 patients (38.5%) out of total 70 received rescue analgesia. Among these 27 patients who received rescue analgesia, reason for giving the analgesia in 14 patients (20%) was a rise in BP, in 8 patients (11.4%)an increase in HR and in 5 patients (7.1%) a rise in both BP and HR. Intra-operatively out of 27 patients who received rescue analgesia, 12 patients were in pre-emptive group while 15 patients were in the control group.

In the post-operative period, rescue analgesia was prescribed if score was more than 3 cm (moderate pain) on VAS scale. In our study no pain was noted in 6 patients (8.6%), mild pain (0-3) noted in 21 patients (30%), moderate in 43 patients (61.1%) and severe pain in 0 patients (0%).

Post-operatively out of 43 patients who received rescue analgesia,18 patients were in the pre-emptive group and 25 patients in the control group. There was no significant difference between both groups regarding use of rescue analgesia (P>0.05).No significant difference was found in the average dose of Nalbuphine in both groups (Pre-emptive and control). (Table III, P>0.05)

Discussion

Pre-emptive analgesia works to prevent the process of central neuroplasticity due to the surgical nociception and the resultant hyper-algesic state, thereby ensuring a more positive overall surgical experience.[10] The definition of pre-emptive analgesia has varied and this has caused confusion, misunderstanding and controversy.[11,12] In our study we found that there was no significant difference in opioid requirements in both groups (Pre-emptive and control groups). An average dose of <4mg was given to only 2 patients in pre-emptive and 1 patient in control group, whereas an average dose of > 4 mg was given to 28 patients in pre-emptive and 34 patients in control group. There was not a significant association between average dose of Nalbuphine in

Table-I: Reasons for giving rescue analgesia intra-operatively.

Reason	Pre-emptive (n)	Control (n)	Total (n)
BP increase	5 (7.1%)	9 (12.8%)	14 (20%)
HR Increase	4 (5.7 %)	4 (5.7%)	8 (11.4%)
Both BP and HR increase	3 (4.3%)	2 (8.%)	5 (7.1%)
Total	12 (17.1%)	15 (21.4%)	27 (38.5%)

P- value is 0.600 that is greater than 0.05. So there is no association between reasons for giviing analgesia in both groups (preemptive and control).

Table-II Visual analogue scale (Post-operatively)

Visual Analogue Scale (cm)	GROUPS Pre-emtive (n)	Control (n)	Total (n)	Analgesia given
No Pain	05	01	6 (8.6%)	No
Mild Pain	11	10	21 (30%)	No
Moderate Pain	18	25	43 (61.4%)	Yes
Severe Pain	0	0	0 (0.0%)	No
Total	34	36	70 (100.0%)	

P- value is 0.052. It is greater than 0.05. So there is no siginificant difference between the mean pain score of preemptive and control groups.

Table-III: Nalbuphine given in both groups *Group Cross tabulationn.

Dose of Nalbuphine (mg)	Pre-emptive (n)	Control (n)	Total (n)
Average Dose< 4	02	01	03
Average Dose >4	28	34	62
Total (n)	30	35	65

Calculated P- value is 0.466, that is greater than 0.05. So there is no association between the average dose of nalbuphine in both groups (preemptive and control).

Pre-emptive and control groups. The opioid requirements were not significantly reduced in pre-emptive group. The pain score on the VAS scale showed that none of our patients felt severe pain. Forty three of these patients felt moderate pain (61.1%). Out of these 43 patients, 18 were from the pre-emptive group (52.9%) and 25 were from the placebo group (69.4%). Although rescue analgesia was permitted if the pain was unbearable within 24 hours of operation, yet there was no difference in this regard between pre-emptive group and placebo group. Like diclofenac, ketorolac is associated with decreased platelet function and increased bleeding time and may result in excessive blood loss[13,14]. This may exacerbate the bleeding in patients who have gastric ulceration. This is the reason the patents with gastric ulceration were excluded from the study. None of our patients who included in our study suffered from excessive blood loss. In this regard COX-2 inhibitors e.g. Parecoxib, are superior to conventional NSAIDs which are both COX-1 and COX-2 inhibitors. Almost twenty studies (from 1983 to 2000) were done to identify the pre-emptive effect with NSAIDs. Some aspects of post-operative pain control were improved by pre-emptive treatment in 4 of the 20 studies but no improvement was demonstrated in remaining16 trials. Overall, the meta-analysis demonstrated no analgesic benefit for pre-emptive compared with post-operative administration of NSAIDs.[15] From 2001 to 2004, at least 30 randomized studies of preversus post-operative administration of various analgesics were performed. Some reductions in post-operative pain and analgesic requirements with pre-emptive analgesia were observed in 13 studies[16-19] whereas no significant differences were observed in 17 other studies (20,21). In these studies the results were also inconclusive as far as NSAIDs are concerned for pre-emptive treatment. Our study results coincide with results of majority of the studies carried out as mentioned above. A number of other drugs have been demonstrated to interfere with the induction and maintenance of central hypersensitivity. Ketamine, dextromehorphan and gabapentin have demonstrated promising anti-hyperanalgesic potential in a number of clinical trials of post-operative pain.[22,23] The only way to prevent central sensitization might be to completely block any pain originating from the surgical wound from the time of incision until the final wound healing. Consequently, an 'idea' pre-emptive or post-emptive or protective analgesic clinical trial should investigate the effect of intense and prolonged multimodal interventions versus less aggressive conventional perioperative analgesia on immediate and late postoperative pain as well as on various psychosocial variables.

Conclusion

In this study, there was no significant difference in perioperative opioid requirements in the pre-emptive as well as in control groups in patients undergoing total abdominal hysterectomy. The treatment regimen used in this study was well tolerated by all patients.

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References

1. Aubin JP. Neural networks and qualitative physics. A viability approach, New York, Cambridge University Press, 1994
2. Tollison CD.Handbook of pain management. Baltimore, Williams and Wilkins Co., 1994.
3- Horlocker TT, Hebl JR, Kinney MA, Cabanela ME.Opioid free analgesia following total knee arthroplasty multimodal approach using continuous lumbar plexus block, acetaminophen and Ketorolac. RegAnesth Pain Med 2002; 27: 105-8.
4. Scholz J, Woolf CJ. Can we conquer pain? Nat Neurosci 2002; 5:1062-7.
5. Crile GW, Lower WE. Anoci-Association. Philadelphia: Saunders, 1914: 223-5.
6. Kehlet H. General vs. regional anesthesia. In: Rogers MC, Tinker JH, Covino BG, Longnecker DE (Eds.) Principles and Practice of Anesthesiology. St. Louis: Mosby, 1993:1218-34.
7. Moiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systemic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. Anesthesiology 2002; 96:725-41.
8. Mufti TMJ. Preemptive analgesia with local anaesthetics for caesarean section. Surg Pak 2002; 7:22-4.
9. Allen HW, Liu SS, Ware PD, Naim CS, Avens RD. Peripheral nerve blocks improve analgesia after total knee replacement surgery. AnesthAnalg 1998; 87:93-7 10.Frerichs JA, Janis LR. Pre-emptive analgesia in foot and ankle surgery. Clin Paediatr Med Surg 2003; 20: 237-38.
11. Kissin I. Pre-emptive analgesia. Anesthesiology 2000; 93: 1138-43.
12. Taylor BK, Brennan TJ. Pre-emptive analgesia: moving beyond conventional strategies and confusing terminology. J Pain 2000; 1: 77-84.
13. Dahl JB. The status of pre-

Anaesthsiol 1995; 8: 323-30.
14. Wilson YG, Rhodes M, Ahmed R. Intramuscular diclofenac sodium for postoperative analgesia after laparoscopic cholecystectomy.A randomized controlled trial. Surg Laparosc Endosc 1994; 4: 340-44.
15. Robinson PM, Ahmed I. Diclofenac & post-tonsillectomy haemorrhage. ClinOtolaryngol 1994; 19: 344-45.
16. Moiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systemic review of pre-emptive analgesia for postoperative pain relief the role of timing of analgesia. Anesthesiology 2002; 96: 725-41.
17. Kwok RF, Lim I, Chan MT, Gin T, Chiu WK. Preoperative ketamine improves postoperative analgesia after laparoscopic surgery. Anesth Analg 2004; 98: 1044-49.
18. Helmy SA, Bali A. The effect of pre-emptive use of the NMDA receptor against antagonist dextromethorphan on postoperative analgesic requirements. AnesthAnalg 2001; 92: 739-44.
19. Bernhardt MK, Southard KA, Batterson KD, Logan HL, Baker KA, Jakobsen JR. The effect of pre-emptive and/or postoperative ibuprofen therapy for orthodontic pain. Am J Orthod Dentofacial Orthop 2001; 120: 20-7.
20. Rosaeg OP, Krepski B, Cicutti N, Dennehy KC, Lui AC, Johnson DH. Effect of pre-emptive multimodal analgesia for arthroscopic knee ligament repair. RegAnesth Pain Med 2001; 26: 125-30.
21. Kokki H, Salonen A. Comparison of pre and post operative administrator of Ketoprofen for analgesia after tonsillectomy in children. PaediatrAnaesth 2002; 12: 162-67.
22. Katz J, Cohen L, Schmid R, Chan VW, Wowk A. post-operative morphine use and hyperanalgesia are reduced by preoperative but not intraoperative epidural analgesia. Implications for pre-emptive analgesia and prevention of central sensitization. Anesthesiology 1993; 98: 1449-60.
23. Power I, Barrot S. Analgesic agents for the post operative period. Non-opioids Surg Clin N Am 1999; 79: 275-95.
24. Dahl JB, Mathiesen O, Moiniche S. Protective premedication: an option with gabapentin and related drugs. Acta Anaesthesiol