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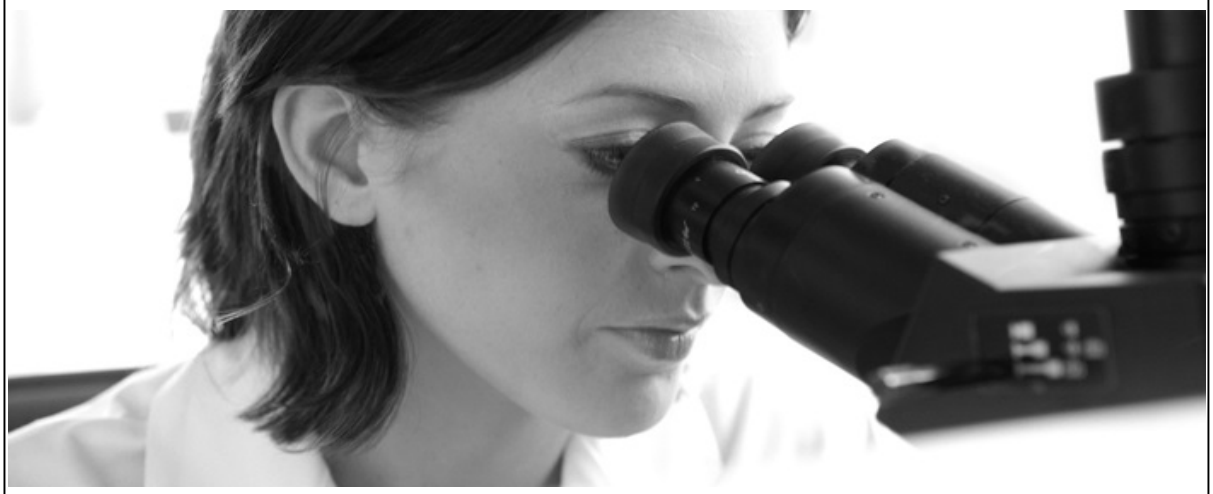

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RESEARCH ARTICLE

A RANDOMISED DOUBLE BLIND STUDY COMPARING PREEMPTIVE ANALGESIC EFFICACY OF ORAL ACETAMINOPHEN, DICLOFENAC AND COMBINATION OF ACETAMINOPHEN AND DICLOFENAC IN MODIFIED RADICAL MASTECTOMY SURGERY

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ABSTRACT

This randomised double- blind study was designed to compare preemptive analgesic efficacy of acetaminophen, diclofenac and combination of both, administered orally in patients undergoing elective modified radical mastectomy. One hundred and twenty female patients of American Society of Anaesthesiologists physical status I-III scheduled for modified radical mastectomy surgery under general anesthesia were randomized according to a computer generated randomization schedule into four groups of 30 each to receive orally either acetaminophen 10mg/kg (Group I), diclofenac 1mg/kg (Group II), combination of acetaminophen 10mg/kg and diclofenac 1mg/kg(Group III) or placebo (Group IV) 1 hr before surgery. The rescue analgesia was provided with morphine postoperatively. In the first 24 hours of postoperative period, intensity of pain, time and dose to first rescue analgesia and total analgesic requirement were recorded. Dose of first rescue analgesic, mean VAS, mean morphine and total morphine requirements were lowest in combination group. Time to first rescue analgesic was prolonged in diclofenac and combination group as compared with acetaminophen and placebo. Global satisfaction score as regard to postoperative pain at 12 hours and 24 hours were significantly better in combination and diclofenac group as compared to acetaminophen and placebo. In conclusion, combination of acetaminophen and diclofenac sodium forms a superior analgesic for postoperative pain management as compared to individual drugs. Diclofenac and acetaminophen have a definitive opioid sparing effect but diclofenac possesses better pre-emptive analgesic efficacy than acetaminophen.

INTRODUCTION

Surgical trauma induces profound changes in both peripheral and central nervous system that together amplify postoperative pain[1]. Preemptive analgesia is fundamentally an antinociceptive therapy with the aim to prevent both peripheral and central sensitisation thereby attenuating postoperative amplification of pain sensation[2].The common interventions performed for preemptive analgesia are epidural analgesia, local wound infiltration, use of systemic NMDA (N-methyl-D-aspartate) receptor antagonist, non steroidal anti-inflammatory drugs (NSAIDs) and systemic opioids[3]. Acetaminophen and diclofenac are nonopioid analgesics with analgesic and anti-inflammatory effects through inhibition of COX enzyme mediated prostaglandin (PG) biosynthesis both in spinal cord and at periphery[4, 5]. Diclofenac sodium is an effective NSAID which inhibits peripheral sensitisation and is also a potent inhibitor of cyclooygenase pathway, hence prostaglandin production[6]. Acetaminophen acts predominantly by central mechanism at spinal and supraspinal levels by interference with prostaglandin function, nitric oxide pathways [7], modulation of descending pain pathways[8], opioidergic systems inhibit central sensitisation[6, 8, and 9]. Both drugs have opioid sparing effects[10, 11].

Hence present study was conducted to analyse the hypothesis that combination of diclofenac sodium which acts peripherally and acetaminophen which acts centrally by multimodal mechanism provide more effective preemptive analgesia than these drugs used individually.

MATERIAL AND METHODS

This double blind, controlled, randomised and prospective study was conducted at Rajiv Gandhi Cancer Institute and Research Centre. After obtaining approval from the ethical committee, informed written consent was taken from each patient. The trial was registered with number PR/ANAE S/206/05 and conducted from May 2005 to May 2007. The study included 120 female patients, age group 20-70 years, ASA I-III, weight less than 80kg scheduled for modified

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radical mastectomy surgery with the surgical duration of 60-120 minutes. Exclusion criteria included patient refusal, known drug allergy, bleeding disorders, coagulopathy, pregnancy, family history of bleeding, gastric and duodenal ulcers, bronchial asthma, treatment with NSAIDs or acetylsalicylic acid taken till 10 days prior to study or concomitant treatment with hypoglycaemics, lithium, carbamazepine, diphenylhydantoin, liver and renal dysfunction.

Randomisation was done according to a computer generated numbers into four groups of 30 each. The groups were as follows: Group I received acetaminophen 10mg/kg, Group II received diclofenac sodium 1mg/kg, Group III received acetaminophen 10mg/kg and diclofenac sodium 1mg/kg and Group IV received a placebo. All medications including placebo were dissolved in 5ml of water and administered orally one hour prior to surgery. The study drugs, all identical looking, were prepared and given by qualified anaesthesiologist not involved in the study.

After a detailed pre-anaesthetic evaluation, all patients were premedicated with tablet diazepam 5mg and tablet rantidine 150mg night before surgery and tab granisetron hydrochloride 2mg on the morning of surgery. After recording baseline parameters including non invasive blood pressure, ECG, heart rate and SpO2, all patients were administered midazolam 1mg and fentanyl 1.5µg/kg intravenously in the operation theatre. General anaesthesia was induced with propofol 1.5mg/kg bodyweight and tracheal intubation was facilitated by non depolarising muscle relaxant. Anaesthesia was maintained with nitrous oxide 60%in oxygen and isoflurane. Supplements of fentanyl (0.5µg/kg) were administered when required. Muscle relaxation was monitored using a peripheral nerve stimulator to assess train of four (TOF). At the end of surgery, trachea was extubated after reversing neuromuscular blockade with neostigmine (0.05mg/kg) and glycopyrrolate (0.02mg/kg). Intraoperatively, blood loss was determined by combining the blood in the suction canister as well as by weighing the blood soaked surgical sponges and gauzes that were used during surgery (surgical sponges and gauzes of standard weight were used in all). The monitoring was continued in the postoperative period for all the patients by using Datex Ohmeda Aestiva 5. Postoperatively, analgesia was measured using VAS (visual analogue scale) score on arrival to recovery room at 0, 1, 2, 6, 8, 12 and 24hours. Depending upon the VAS score at above intervals rescue analgesia was administered with intravenous morphine.VAS <3 was considered adequate analgesia and if patients were asleep during scheduled time for pain assessment, they were not awakened and VAS score was taken as <3.

Bleeding episodes, postoperative nausea vomiting, respiratory rate, sedation were recorded postoperatively till 24hours. First bolus dose of morphine, time for first morphine demand and total dose of morphine administered were recorded for first 24hours. Global satisfaction score was assessed at 12 and 24hours using four point satisfaction scale where the score of 1 was poor, 2 was fair, 3 was good and 4 was considered excellent.

Statistical analysis

At the end, results were compiled and subjected to analysis by a trained research assistant otherwise not involved in the study. Demographic data (age, weight), blood loss and clinical data were analysed with ANOVA-F test whereas frequencies were compared with chi-square test. Intergroup differences between variables recorded throughout first 24hours period was analysed with students t-test and paired t-test. A p-value of <0.05 was considered significant. Mean VAS was derived using multivariate repeated measurement analysis.

RESULTS

In the present study, there was no statistical significant difference among four groups with respect to age, weight, duration of surgery and mean blood loss during surgery (Table1)

Table1 Demographic profile

	Gp I	Gp II	GpIII	Gp IV
	Acetaminophen	Diclofenac	Acetaminophen+ Diclofenac	Placebo
Age (years)	51.53(9.69)	47.71(11.6)	48.83(10.3)	48.79(10.7)
Weight	62.5(7.88)	60.20(10.8)	58.40(10.3)	61.47(10.5)
Duration of Surgery (min)	135(44.3)	118(43.5)	127(55.2)	115(38.6)
Mean Blood loss (ml)	85(52.77)	100(74.68)	83(42.88)	75.5(35.82)

The time for first rescue analgesic was 29.93(14.2) minutes in placebo group and 45.83(35.65) minutes in acetaminophen group. Diclofenac sodium alone and in combination with acetaminophen prolonged time for first analgesic request significantly. Five out of thirty patients in combination group and one out of thirty patients in diclofenac group did not require analgesia (p<0.001). Total morphine required within 24hours was maximum in placebo and least in combination group .Total morphine dose required in diclofenac was lower compared with acetaminophen, p value <0.001. Global satisfaction score was assessed at 12 and 24 hours as shown in Table (2). At 12hours, global satisfaction score was significantly higher in combination and diclofenac group as compared to placebo and acetaminophen group (p<0.001). Similarly at 24hours after surgery, global satisfaction score was higher in combination and diclofenac group compared to placebo and acetaminophen group.

Table 2 Observations of post-operative period

	Gp I	Gp II	Gp III	Gp IV
Time for first rescue request (min)	45.83(35.65)	89.17(61.76)	65.67(49.32)	29.93(14.2)
Amount of first morphine request (mg)	2.75(1.04)	1.9(0.95)	1.35(0.72)	2.95(1.47)
Number of opioid free patients	0	1	5	0
Mean VAS	4.2(0.12)	3.47(0.12)	2.84(0.12)	4.46(0.12)
Total morphine consumed (mg)	5.75(1.82)	3.95(1.90)	2.3(1.74)	7.35(1.82)
Global satisfaction score at 12 hours	1.93(0.52)	2.17(0.46)	2.7(0.65)	1.37(0.55)
Global satisfaction score at 24 hours	2.43(0.56)	2.73(0.58)	3.47(0.73)	2.07(0.58)

VAS (visual analogue scale) among four groups was recorded at 0, 1, 2, 6, 8, 12 and 24 hours. VAS score at all intervals was

maximum in placebo and minimum in combination as in figure (1).

Patients in placebo and acetaminophen group had significantly higher pain score than other two groups. Maximum VAS score were observed during first 6hours of surgery in all groups. Maximum VAS was observed at 1hour in placebo group (5.5±1.81) and minimum VAS was in combination group (1.67± 1.34).

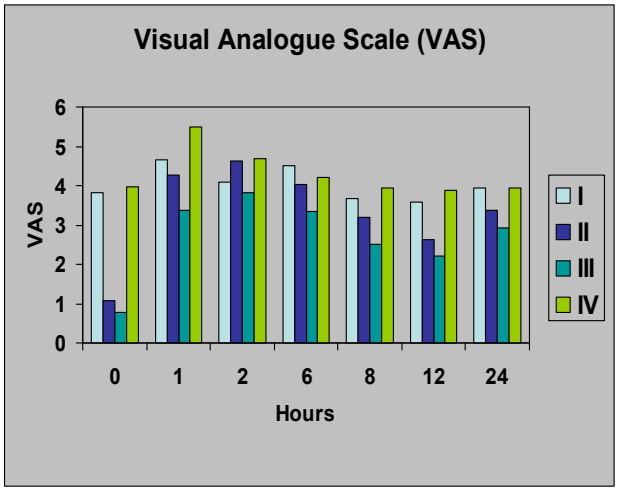

Figure1 VAS of different groups in post-operative period

We recorded adverse effects throughout 24hours postoperative period.

Table 3 Adverse events observed post-operatively

	Gp I	Gp II	Gp III	Gp IV
Nausea/vomiting	6	10	11	1
Respiratory depression	-	-	-	-
Sedation	-	-	-	-

DISCUSSION

Diclofenac alone and when combined with acetaminophen decreased post-operative pain score and morphine consumption in first 24 hours. Additionally time to first rescue analgesic was prolonged in combination group. Hence, diclofenac alone and when combined with acetaminophen proved to possess better analgesic efficacy as compared with acetaminophen alone. Preemptive analgesia is a treatment that is initiated before the surgical incision in order to reduce the sensitisation of pain pathways and subsequent postoperative pain.[12] As bradykinins and prostaglandins are currently regarded as the primary mediators of pain, premedication with anti-inflammatory drugs seems logical. Diclofenac sodium and acetaminophen are non opioid analgesics with different mechanism and site of action. Acetaminophen has central analgesic effect and diclofenac is peripherally acting analgesic, hence their actions may be synergistic or additive. A recent review by Cliff *et al* suggested that combining paracetamol and NSAID confers additional analgesic efficacy over either drug alone [13]but it did not study its preemptive analgesic effect, hence, this study was undertaken to compare and investigate preemptive analgesic efficacy of quite commonly used analgesics that is oral acetaminophen and diclofenac in modified radical mastectomy surgery. Raid *et al* studied preemptive analgesia with rectal diclofenac 100mg and paracetamol 40mg/kg and their combination 1 hour prior to inguinal hernia repair in children. They concluded preoperative combined administration of rectal diclofenac 1mg/kg – paracetamol 40mg/kg is superior to either drug alone with respect to postoperative pain scale and decreased need for morphine consumption in postoperative period.[14] Fayaz *et al* concluded that diclofenac (100mg) alone or with combination with rectal paracetamol (1g) has significant opioid-sparing effect after CABG in adults leading to more rapid extubation and better oxygenation.[15]

Total analgesic consumption is perhaps one of the best outcomes for predicting a true preemptive analgesic effect. The total morphine consumption in combination group (2.3) was significantly less than control group (7.35) and also individual acetaminophen (5.75) and diclofenac (3.95). About 16% of patients in the combination group showed no demand for rescue medication throughout postoperative period. In this respect, our results are compatible with Montgomery *et al*, who demonstrated 30% decrease in morphine consumption after administration of rectal diclofenac (100)mg combined with acetaminophen(20mg/kg) in women undergoing elective abdominal gynaecological procedures.[16]Fletcher *et al* compared propacetamol and ketoprofen monotherapy with combined therapy after lumbar disc surgery, showing that drug combination reduced pain scores.[17]

Diclofenac sodium administered prior to induction has marked and definitive opiod sparing effect. Similarly, Tuzuner and Ucok *et al* have also shown that preoperative administration of diclofenac or tramadol in orthognatic surgery, effectively decreases postoperative opioid consumption.[18] Literature search revealed preemptive analgesic effect of diclofenac for postoperative pain.[15,19,20,21,22] Cochrane review also demonstrated preemptive efficacy of single dose of paracetamol.[23]The dose dependent morphine sparing effect of acetaminophen has also been demonstrated by Reijo Korpela *et al*.[10]Remy *et al* concluded that morphine requirements decreased by 37% in patients with moderate pain , but only 18% in patients with severe pain.[24] Our study reveals acetaminophen has opioid sparing effect though there was no significant reduction in pain scores. It may be attributed to inadequate dose of acetaminophen administered to the patient. Low plasma levels of acetaminophen do not prevent central nociceptive sensation and henceforth contributes to inadequate reduction in pain scores. [25] Hence, commonly used dosages of acetaminophen (10-15 mg/kg) have not confirmed its antinociceptive efficacy. Diclofenac sodium is superior in its results when used as a preemptive analgesic drug. Morton and O'Brien demonstrated that concurrent administration of diclofenac in children receiving patient-controlled analgesia (PCA) with morphine has a highly significant morphine sparing effect.[26]

Further it was observed as in table 3, nausea and vomiting was observed in 20% patients in acetaminophen group, around 30% in diclofenac sodium group and combination group where as only 3% patients suffered from nausea/vomiting in control group. This difference is statistically significant, indicating NSAIDs do predispose to nausea and vomiting. Hyllested *et al* have reported acetaminophen as a viable alternative to

the NSAIDs in view of the low incidence of adverse effects and according to them, should be preferred in high-risk patients.[27] This was also observed by Afhami *et al* in their study to evaluate efficacy and safety of preoperative paracetamol for postoperative pain relief.[28]

There was no significant difference in blood loss between all the groups in the present study. The mean blood loss in all the groups was statistically insignificant (0.352). Although, NSAIDs have a role to play in increased blood loss by reducing platelet aggregation and prolonging capillary time. Earlier studies by Tarkkila P and Saarnivaara L have shown that Ketoprofen, Diclofenac or Ketorolac administered, does not increase bleeding.[29]This is supported by study done by Wuolijoli E, Oikarinen who have found out that diclofenac did not increase wound bleeding when compared to placebo.[30] Respiratory depression was not observed in any group. Intergroup comparison in terms of VAS score, mean time to first rescue analgesic, and total morphine requirement in accordance to this study revealed that diclofenac is a superior preemptive analgesic as compared to acetaminophen.

CONCLUSIONS AND RECOMMENDATIONS

Diclofenac alone as well as when combined with acetaminophen, provides adequate pre-emptive analgesia. The postoperative morphine consumption is reduced and patients have better satisfaction scores. Thus this is a simple, economic and effective way for alleviating post-operative pain. This technique of pre-emptive analgesia can be adopted for various surgeries in order to decrease the incidence of post-operative pain.

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