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COMPARISON OF PROPACETAMOL WITH PETHIDINE FOR POSTOPERATIVE PAIN RELIEF

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The purpose of this study was to evaluate the analgesic effect of a single bolus I.V dose of propacetamol given before induction of anaesthesia and compare this effect with that of I.V pethidine also given before induction. Another objective was to study the opioid sparing effect of cetamol by using in combination with pethidine, after surgical incision had been made. Sixty adult patients of ASA I or II status were included and divided into three groups. Group A received propacetamol 2gm intravenously just before induction , in group B IV bolus dose of pethidine 0.75 mg/kg was given just before induction and group C received combination of pethidine 0.4mg/kg and propacetamol 2gm intravenously 10 minutes after the incision. After awakening from anaesthesia patients were observed for sixty minutes in recovery for pain assessment by the pain scales and the pain scores by VAS & NRS were analysed statistically by using student's t test and Mann-Whitney test. Pain scores by verbal response scale were analysed by Chi square test. $p<0.05$ was considered significant. No statistical difference was seen among the groups regarding their post-operative pain scores (p-VAS>0.3, NRS>0.2). The patients who received combination of pethidine and propacetamol required longer time ($p<0.05$) for supplementary analgesia than the patients who were given propacetamol alone. Propacetamol 2 gm given IV before induction had no advantage over pethidine. Significant benefit of pre-emptive analgesia was not evident in first 60 min after recovery from anaesthesia.

***Keywords**: Propacetamol, postoperative pain, opioid*

INTRODUCTION

Acute postoperative pain is a complex physiologic reaction to tissue injury, visceral distension or disease. It is a manifestation of autonomic, psychological and behaviour responses that result in unpleasant, unwanted sensory and emotional experience. Effective pain relief after surgery is an essential element of good anaesthetic practice. In addition to improving patient comfort, relief of pain reduces sympathetic system response and helps to control postoperative hypertension and tachycardia.

Though opioids remain the most commonly used drugs for management of postoperative pain, NSAIDs are being increasingly used. They are used both as sole analgesics or as an adjunct to opioid medication. The main benefits of NSAIDs in postoperative pain derive from an opioid sparing effect with subsequent reduction of opioid induced side effects and also a multimodal approach to enhance the quality of analgesia by combining drugs with central and peripheral effects.

Propacetamol is a diethylglycidylester of paracetamol. After parentral administration the ester is quickly and quantitatively hydrolysed by non-specific esterases into paracetamol. Propacetamol HCL 1 gm generates 500 mg of paracetamol. It has been shown to improve analgesia after orthopaedic, gynaecologic or abdominal surgery[1].

SUBJECTS AND METHODS

The study was carried out on 60 adult patients of ASA I or II Status scheduled for elective surgery under general anaesthesia. All patients were aged between 18 and 65 years and weighed between 55 and 80 kg. After informed consent and explanation about pain assessment scales, three groups of 20 patients each were made by random allocation. Group A received propacetamol 2gm intravenously just before induction, Group B was given pethidine 0.75 mg/kg I.V just before induction of anaesthesia and Group C received combination of pethidine 0.4mg/kg and propacetamol 2gm I.V 10 minutes after the incision. Patients with significant concomitant disease, who were ASA III or IV, had pain before surgery, were already taking strong or weak analgesic medication, obese, with history of

allergy to NSAIDs and with history or biochemical evidence of hepatic disease were not recruited.

All patients received a standard general anaesthesia. ECG monitor, automatic blood pressure, pulse rate and pulse oximeter were applied. The duration of anaesthesia was noted. Induction of anaesthesia was done with thiopentone sodium 4-5mg/kg and suxamethonium 1mg/kg. Following tracheal intubation, anaesthesia was maintained with 0.5% halothane and 60% N_2O in O_2 after atracurium 0.5mg/kg. After surgical procedure neuromuscular block was antagonized with neostigmine and atropine. After awakening from anaesthesia patients were observed for sixty minutes in recovery for pain assessment by the following pain scales:

1. *5-point verbal response scale:* 0- no pain, 1-mild pain, 2- moderate pain, 3- severe pain, 4- unbearable pain.
2. *A 10cm visual analogue scale.*
3. *A numerical rating scale.* '0'- no pain and '100' meant unbearable pain.

Besides pain, nausea and vomiting, and sedation were also noted.

Rescue analgesia was given in the form of pentazocine to patients who demanded such analgesia. The time since awakening from anaesthesia to the first demand of analgesia was recorded. Assessment of pain scores were made at the time of first demand of analgesia and after sixty minutes of recovery. Pulse rate, blood pressure and heart rate were also noted at the time of pain assessment.

Statistical Analysis

Patient's age, height, weight, duration of surgery, time of rescue analgesia requested by the patient and the pain scores by VAS & NRS were analysed using student's t test and Mann-Whitney test. Pain scores by verbal response scale were analysed by Chi square test. $p<0.05$ was considered significant.

RESULTS

The groups were comparable as regard their age, sex, weight, height and duration of surgery (table 1). Heart rate(HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and respiratory rate were within normal range and no statistical difference was seen between groups (table 2). The mean pain scores for propacetamol group were higher than for pethidine or the combination of two drugs. In no case the difference was statistically significant ($p>0.7$).

Table 1: *Demographic Data expressed as number or mean [sd].*

Groups	A	B	C
Age (yr)	42.8 (10.48)	41.9 (9.41)	41.65 (10.66)
Sex (m/f)	11/9	8/12	10/10
Height (cm)	162.55 (4.7)	161.15 (5.14)	162.95 (5.15)
Weight(kg)	68.15 (5.83)	66 (5.4)	66.5 (4.66)
Time of surgery (min) mean	69	78	74

Table 2: *Mean pulse rate, blood pressure(BP) and respiratory rate at the time of pain assessment scores [sd].*

Groups	A	B	C
Pulse Rate (min^{-1})	82.9 (9.5)	84.2 (7.22)	87.1 (8.35)
BP (mmHg)	128/81 (19.2/11.3)	133.9/79.8 (18.5/11.2)	134.8/83 (17.1/7.38)
Respiratory Rate (min^{-1})	17.9(1.94)	16.3 (4.28)	18 (1.66)

The pain scores were noticed when patient requested for pain relief in recovery. Fifteen patients in Group A, 15 in Group B and 17 patients in Group C required analgesia before 60 minutes. Five patients in Group A, 5 in Group B and 3 in Group C did not breakthrough analgesia. Their mean pain scores at the end of 60 minutes are shown in table 3.

Table 3: *Number of patients who did not breakthrough analgesia and their mean pain scores.*

Groups	Total	Patients	VRS	VAS	NRS
A	20	5	mild	1.88 (0.43)	17 (10.37)
B	20	5	mild	2.32 (1.34)	22 (6.71)
C	20	3	mild	2.5 (0.56)	2.17 (2.89)

The mean time before supplement analgesia was 23.92 in group A, 29.73 in Group B and 36.06 in Group BC (Table IV) This was insignificant statistically between Groups A vs B and B vs C. But it did assume statistical significance between Groups A and C. The time to first demand for analgesia after awakening from anaesthesia was significantly longer ($p<0.05$) in Group C than in Group A.

Table 4: *Mean pain scores at the time of first request for analgesia and its mean time from the time of awakening of anaesthesia [sd].*

Groups	A	B	C
VAS	5.28(2.48)	5.06(2.39)	4.61(1.99)
NRS	55.25(27.98)	52.25(25.16)	45 (23.79)
Time (min)	23.93(13.82)	29.73(20.35)	36.06(17.56)

The two scales (VAS or NRS) correspond with each other in the same patient (table 5).

Table 5: *Correspondence of three scales used (values in range).*

VRS	VAS	NRS
Mild	1.5-4.2	0-40
Moderate	3.8-6.7	40-70
Severe	7.2-9.0	70-100

The difference between Group C and the other two groups did not assume statistical significance ($p>0.2$). Verbal response scale was analyzed using Chi-square test (table 6).

Table 6: *Verbal response scale.(Chi square test) ($p>0.5$).*

Groups	A	B	C
Mild pain	5	8	8
Moderate pain	8	6	8
Severe pain	6	6	4

Nausea and vomiting was seen in 6 patients in Group A, 8 patients in Group B and 7 in Group C. One patient in Group B could not complete VAS because of sedation at the end of 60 minutes, although she was able to respond to VRS and NRS. In the rest sedation was not a problem.

DISCUSSION

To avoid opioid related side effects, the use of NSAIDs in the postoperative period is increasing as studies indicate injectible agents such as ketorolac, diclofenac, indomethacin etc, to have useful analgesic properties especially for mild to moderate pain[2-4]. Many of these drugs have well known side effects such as gastric ulceration, impaired coagulation and alteration of renal function. Propacetamol is a non-opioid analgesic devoid of any major contraindication.

This study was designed to assess & compare the analgesic efficacy of dosing with propacetamol and pethidine given before surgery in an attempt to reduce excitability of neurons in the periphery and in the spinal cord during nociceptive input—thereby to reduce central and peripheral sensitization. A comparison of their effects was also made with a combination of these drugs given after the incision had been made in the patients.

The nervous system does not modulate all pain in a fixed manner. It responds to some stimuli by dynamic modification or 'plasticity' and once induced this neuroplasticity may sustain and magnify the experience of pain. Noxious stimulation may generate hyperexcitability in the dorsal horn of the spinal cord. This central sensitization prolongs and increases sensitivity to noxious stimuli over an expanded receptive field (hyperalgesia) and results in pain from previously innocuous stimuli (allodynia). Repetition of noxious stimulus evokes a progressively escalating response in the cord, which further magnifies the pain—a phenomenon termed "wind up". Allodynia, hyperalgesia and reflex hyperexcitability caused by sensitization of the nervous system also occur in surgical patients suggesting a potential for preemptive analgesia in humans[5].

Peripheral sensitization to injury has also been suggested causing hyperalgesia at the site of injury and in the surrounding non-traumatized tissue. The hyperalgesic effect of various prostanoids varies considerably. After a rapid onset, the effect of prostacyclin(PGI_2) only lasts for approximately 30 minutes whereas PGE_1 and PGE_2 cause hyperalgesia for up to 3 hours after a slow onset. Thus several hours may pass before the maximum effect on pain threshold is reached when using inhibitions of prostaglandin synthesis.

The measurements obtained in this study were noticed immediately in the first hour postoperatively. It is possible that benefits of preemptive treatment might be produced in considerable time after operation. Time is critical problem. Is the preemptive effect short, medium, or long-term phenomenon? Is the preemptive effect equally relevant for acute postoperative pain (nociceptive) and for the development of long term sequelae such as phantom limb pain (neuropathic)[6].

First dose of analgesia was not required for many hours in patients who received local or opioid analgesics. Simple analgesics like codeine-paracetamol or NSAIDs like tenoxicam when administered preoperatively, produced residual

analgesia in recovery period and reduced parentral opioid requirement[3]. Results of this study have shown that the mean pain scores were higher and time for the first demand for analgesia were lower in propacetamol group as compared to pethidine group. Hans P et al found that propacetamol had minor analgesic properties and did not improve analgesia in the immediate postoperative period. Given 2gm six hourly, it provided pain relief 12 hours after the end of lumbar disc surgery[1]. In the present study, the effect of only one dose of propacetamol was studied. Further doses could have produced better results. In other studies satisfactory analgesic efficiency of propacetamol has been established after minor or moderate surgery[7,8].

In a study comparing propacetamol with ketorolac in orthopaedic surgery, Zhou found faster onset of action for propacetamol (8 min) than for ketorolac (14 min). However propacetamol had shorter duration of action (3.5 vs 6 hrs), found similar analgesic properties during a 6 hour assessment period in patients undergoing orthopaedic surgery[9]. In our study the average duration of surgery was 77 min. At the end of study period (1 hr postop) propacetamol was expected to last by the end of study period. In a randomized double-blind placebo controlled study, Sinatra et al found a median time to morphine rescue analgesia of 2-6 hrs after propacetamol as compared to 3 hrs in IV acetaminophen group. They found significantly reduced morphine consumption over 24 hr period[10].

Results of this study failed to show a clinically obvious advantage of pre-induction dose of propacetamol as judged by the first demand for analgesia in the immediate postoperative period (60 min). The mean time for first demand for analgesia was significantly longer in patients who received a combination of drugs after the incision (group C) than in the patients receiving propacetamol alone prior to incision ($p<0.05$). Though this time was also longer than in the group B patients but it did not differ significantly ($p>0.3$). The statistical difference between pain scores of all three groups was insignificant (VAS > 0.3 & NRS > 0.2). Present study shows that propacetamol is inadequate for severe postoperative pain.

Both drugs i.e pethidine and propacetamol when combined and administered after incision produced better results when compared with other studies on the opioid sparing effect of NSAIDs[11,12]. Monrigal and colleagues showed that propacetamol and nalbuphine 10 mg combination provided greater decrease in pain scores in two hours postoperatively than a single dose of nalbuphine 20 mg in patients undergoing obstetric and gynaecological surgery[12].

The incidence of nausea and vomiting was similar in the three groups regardless of the type of analgesic used. This may be because many other factors have been shown to influence the incidence of postoperative nausea and vomiting in addition to analgesic agents.

Aubrun et al showed that propacetamol was not able to decrease significantly the occurrence of morphine related side effects (nausea, vomiting and urinary retention), though they demonstrated a morphine sparing effect (31%) in moderate postoperative pain. They failed to demonstrate any benefit from propacetamol in patients with severe postoperative pain[13].

The complexity of pain production and the number of mechanism involved make it difficult to block the nociceptive input. It is unlikely that one single analgesic method will be sufficient and we should look towards to a multimodal approach to pain relief. A relatively effective analgesic regimen is equally effective whether initiated before or after operation.

In **conclusion** this study, does not allow significant conclusion to be drawn regarding the pre-emptive or opioid sparing effect of propacetamol by using in combination with pethidine in the immediate postoperative 60 minutes.

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