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A comparison of the analgesic effect of intravenous nalbuphine and tramadol in patients with post-operative pain - a double blind prospective randomised study

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ABSTRACT

This study was designed to compare the analgesic effects of intravenous Nalbuphine 0.2mg/kg with intravenous tramadol 1mg/kg in the post-operative period as bolus dose, keeping in account the onset of action, duration of analgesia, hemodynamic changes and side effects like respiratory depression, nausea, vomiting, pruritis and sedation. Eighty patients scheduled for elective surgery under general anaesthesia are randomly selected with forty patients in each group. Randomization was done by block randomization technique. Percentage of pain relief was highly significant ($p<0.001$) mean VAS score 0.72±0.64 in nalbuphine group as compared with mean VAS score 1.72±0.75 in tramadol group at 30 minutes.Nalbuphine appears to be a safe and effective analgesic for the relief of moderate to severe postoperative pain than tramadol in equianalgesic doses with minimum circulatory effects, providing good sedation and significantly lower incidence of nausea and vomiting.

INTRODUCTION

The effective relief of pain is of paramount importance to any patients undergoing surgery. This should be achieved for humanitarian reasons, but there is now evidence that pain relief has significant physiological benefit. Not only does effective pain relief mean a smoother postoperative course with earlier discharge from hospital, but also reduce the onset of chronic pain syndromes [1].

Postoperative pain is something in particular which at times we treat or at times have to endure. In modern postoperative care, this means effective relief from pain, suffering, anxiety and sleeplessness. The outcome of the postoperative recovery may be greatly influenced by effective pain management .Thus avoiding consequences of inadequate postoperative pain relief [2].

The expression of gratitude from patients free from this acute pain contributes to feeling of self-esteem and job satisfaction. Additionally, contact with patients, nurses, other physicians and administrators in the postoperative period helps to define anaesthesiologists as valued ´perioperative physicians´.The aim of this study was to compare the analgesic effects of intravenous nalbuphine 0.2mg/kg with intravenous tramadol 1mg/kg in the post-operative period as bolus dose, keeping in account the onset of action, duration of analgesia, hemodynamic changes and side effects like respiratory depression, nausea, vomiting, pruritis and sedation.

METHODOLOGY

This study was conducted to compare the analgesic effects of intravenous nalbuphine with intravenous tramadol in the post-operative period as bolus doses. This was a double blind prospective randomized clinical study. The protocol of the trial was submitted and presented in the institutional ethics committee and approval was taken. Prior to inclusion in the study, a written informed consent from patients was obtained. Eighty patients presented for elective surgery under general anaesthesia were randomly selected with forty patients in each group. Patients who were given nalbuphine 0.2mg/kg were in group A and those who were given tramadol 1mg/kg were in group B. Randomization was done by block randomization technique.

All those patients belonging to either sex between the ages of 20-60 years, ASA physical status I or II; posted for general surgical, orthopaedic, ENT and gynaecological procedures were included in this study. Patients belonging to ASA physical status III and above, patients with demonstrable or suspected renal, liver or haematological disease were excluded from the study.

Patients with history of tolerance, dependence or allergy to opioids, patients with history of chronic consumption of alcohol, patients with diminished mental competence, deafness and visual disturbances which would prevent them to comprehend and use visual analogue scale, patients on psychotropic drugs or with seizure disorders, pregnant or Lactating patients, patients with respiratory or cardiac disease were also excluded from the study.

Detailed clinical examination and routine investigations including laboratory tests (complete blood count, haemoglobin, and serum chemistry profile and urine analysis) electrocardiogram and chest x-ray were taken if indicated or in patients above 40yrs.

All the patients were informed about the nature of the study and anaesthetic technique. They were introduced to the concept of visual analogue scale to record pain. Adequate nil per oral status was maintained. Premedication used was diazepam 0.15mg/kg. orally on the night before and in the morning two hours prior to surgery. After shifting the patient to operating room, base line values were measured. Midazolam 0.02mg/kg and Fentanyl 2mcg/kg were given before induction of anaesthesia. Induction was done with propofol 2-2.5mg/kg after adequate pre-oxygenation. After checking for ventilation muscle relaxation was attained by vecuronium 0.1mg/kg .After endotracheal intubation, confirmation of the tube placement by auscultation of bilateral equal air entry. Standard general anaesthesia technique consisting of O_2:N_2O and isoflurane 0.8-1% to achieve the MAC of 1 and muscle relaxation by vecuronium 0.02mg/kg bolus intermittently. Intraoperative monitoring included electrocardiogram, non invasive blood pressure, pulse-oximeter, end- tidal CO2 and peripheral nerve stimulator. After the procedure, neuromuscular block was antagonized by using neostigmine 0.05mg/kg and glycopyrolate 0.01mg/kg. Extubation was done after complete recovery. Postoperatively after shifting the patient to post operative care unit the vital signs was measured. The level of pain was enquired, as they were asked to point out the intensity of pain on a scale of 0-10cm.When a score of 3 or more was recorded the patients were randomly allocated to the study groups and analgesics administered as per following.

Group A Inj. Nalbuphine 0.2 mg/Kg and Group B Inj. Tramadol 1mg/Kg The volume of study drug and the capacity of loading syringe used were identical in both the groups. The drug was administered intravenously slowly. The observer, patient and staff nurse were unaware of the nature of drug received by the patient. The onset and duration of analgesia was noted, vitals are monitored at intervals of 1,5,10,15,30min and 1, 2, 3, 4, 5, 6, 8, 10, 12,24th hours and so on till the patient have VAS score equal to or more than 3. Side effects, complaints and concomitant medications were recorded. The respondents are those patients who had a drop of VAS score by 2 within 30min's.The subsequent dose of study drug was repeated when the patient complained of pain again (VAS score more than 3) or after 6 hrs of drug administration. Patient who didn't have pain relief and recorded VAS score more than 3 after 30min and within 6 hrs of drug administration were considered as 'failure of analgesia'.

Table 1 : Pain score in patients post operatively

PAIN SCORE

	GROUP	N	Mean	Std. Deviation	t	
PSBASE	Group A	40	7.5500	.59700		1.01500
	Group B	40	7.4250	.50064	p=0.313 ns	
PS1	Group A	40	7.5500	.59700		1.01500
	Group B	40	7.4250	.50064	p=0.313 ns	
PS5	Group A	40	7.4000	.63246		.19600
	Group B	40	7.4250	.50064	p=0.845 ns	
PS10	Group A	40	6.7750	.61966		2.99700
	Group B	40	7.2000	.64847	p=0.004 hs	
PS15	Group A	40	6.1500	.97534		.37600
	Group B	40	6.2250	.80024	p=0.708ns	
PS30	Group A	40	.7250	.64001		6.41100
	Group B	40	1.7250	.75064	p<0.001 vhs	
PS4HR	Group A	40	.0000	.00000		2.11100
	Group B	39	.1026	.30735	p=0.038 sig	
PS5HR	Group A	40	.0750	.26675		3.39800
	Group B	40	.4250	.59431	p<0.001 vhs	
PS6HR	Group A	40	.4250	.59431		4.73100
	Group B	40	1.1250	.72280	p<0.001 vhs	
PS8HR	Group A	40	1.2500	.74248		5.57900
	Group B	40	2.1500	.69982	p<0.001 vhs	

Table 2 : Side effects

SIDEEFFECTS * GROUP

			GROUP		
			Group A	Group B	Total
SIDEEFFE	0	Count	32	27	59
		%	80.0%	67.5%	73.8%
	D	Count	5	2	7
		%	12.5%	5.0%	8.8%
	H	Count	1	1	2
		%	2.5%	2.5%	2.5%
	N	Count	2	5	7
		%	5.0%	12.5%	8.8%
	NV	Count	0	1	1
		%	.0%	2.5%	1.3%
	V	Count	0	4	4
		%	.0%	10.0%	5.0%
Total		Count	40	40	80
		%	100.0%	100.0%	100.0%

a. X2=7.995 P=.157 NS

Diclofenac sodium 75mg intramuscularly was used as rescue analgesic.

RESULTS

There were 40 patients in each group. All observations were recorded in the proforma. Statistical analysis of all the quantitative data was done by using the student´s unpaired t test (e.g. mean age, body weight ,VAS score, HR, RR, SBP, DBP, SPO2). Statistical analysis of all the qualitative data was done by using the chi (X2) square test (e.g. gender, surgeries, side effects). A statistical package SPSS version 17.0 was used to do the analysis, $p<0.05$ was considered as significant.

Selected patients underwent various general surgical, orthopaedic, ENT and gynaecological procedures in both the groups, there was no statistical difference in the mean age, body weight, and gender in both the groups. ($p>0.05$).All the patients were respondents (VAS drop>2 after medication within 30 minutes) as shown (Table 1 and Graph). Mean VAS at the time of administration of drug was 7.55±0.59 in nalbuphine group and 7.42±0.50 in tramadol group, which was not statistically significant.

At 10 minutes after the drug administration, percentage of pain relief was significant ($p=0.04$) mean VASscore6.77±0.61 in nalbuphine group as compared with mean VAS score7.20±0.64 in tramadol group. At 30 minutes, percentage of pain relief was highly significant ($p<0.001$) mean VAS score0.72±0.64 in nalbuphine group as compared with mean VAS score1.72±0.75 in tramadol. Pain relief was significant at the end of 4, 5,6and 8 hours also.

There was 100% pain relief between 60 to 240 minutes intervals indicating the peak effect (i.e. the time duration when mean VAS reached 0 and pain relief in VAS was 100%) in nalbuphine group, and peak effect was between 60 to 180 minutes in tramadol group. There was no case of failure of analgesia in either groups as evidenced by the fact that no patient requested the rescue analgesic at any point of time during the study.

The cardiovascular parameters monitored were heart rate (HR), systolic and diastolic blood pressure (SBP and DBP).There was no statistically significant difference in Systolic and diastolic blood pressure in both groups. There was no statistically significant difference in pulse rate in both groups. The respiratory parameters monitored were respiratory rate (RR) and oxygen saturation (SpO2).The mean changes in RR and SpO2 showed no statistically significant difference in two groups. The side effects seen were drowsiness, headache, nausea alone and both nausea and vomiting. Nalbuphine group showed a significant incidence of drowsiness (12.5%) as compared to tramadol (5%) group. However tramadol group showed a highly significant incidence of nausea (12.5%) both nausea and vomiting (10%) as compared to nalbuphine group which had nausea (5%) and none of them had vomiting (Table 2)

DISCUSSION

Postoperative pain is undertreated for a number of reasons. These include lack of knowledge regarding effective dose ranges, duration of action of opioids, unfounded fear of respiratory depression and addiction in hospitalized patients experiencing pain. Through the use of currently available knowledge, drugs techniques well known to anaesthesiologists, effective analgesia for most patients with postoperative pain are possible[1].Our study was done to find out a good analgesic agent to alleviate postoperative pain, which is one of the very severe types of acute pain. Keeping in mind the various side effects associated with

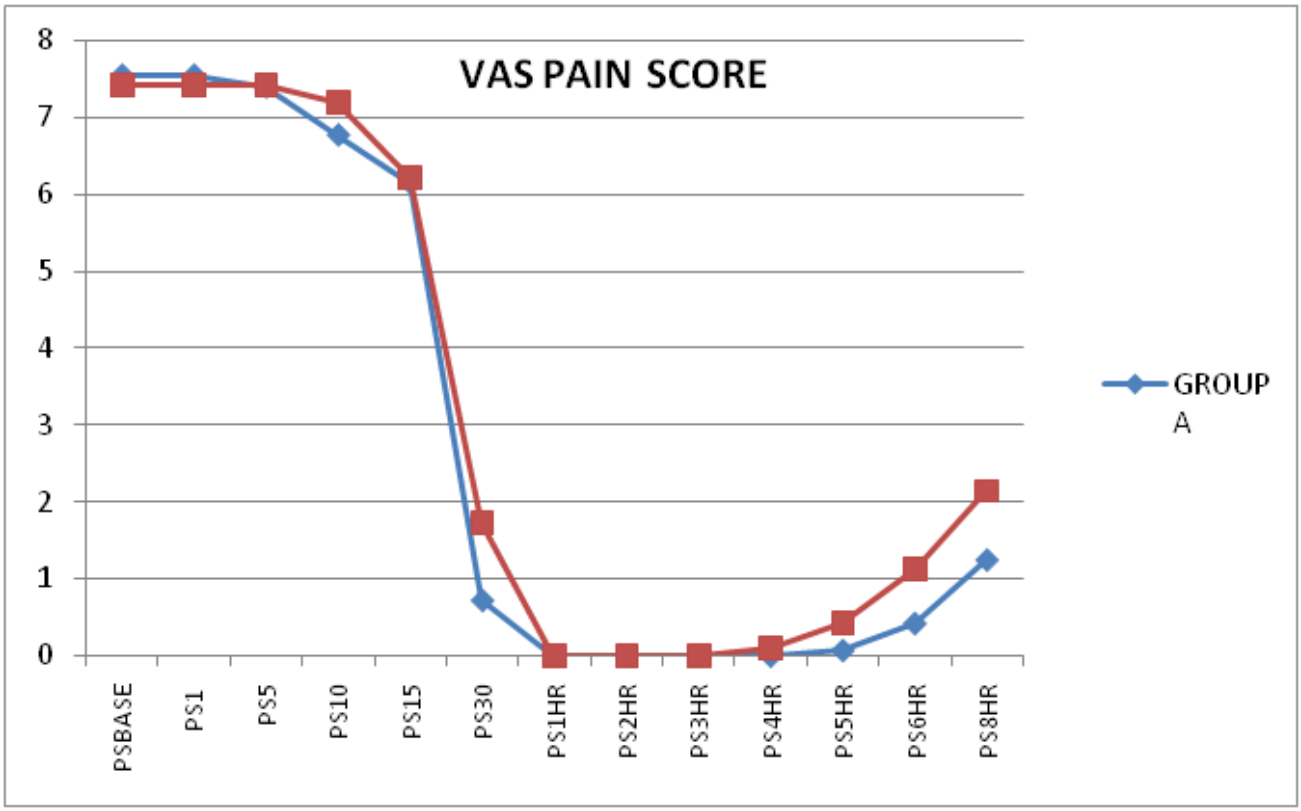

Figure 1 : Pain score in patients post operatively

opioid agents against the unparalleled excellent pain relief, we sought out to compare an opioid agonist- antagonist nalbuphine with one of the most common agent used in clinical practice for postoperative pain relief, tramadol. The study was a double blind prospective randomised clinical study. There was no significant difference in the demographic profile of patients in the study. The nature of surgical procedure too did not have much of an impact on the study as they were equally divided into two groups.The difficulty of evaluating pain is well known. Extensive reviews have appeared in literature recognizing and evaluating the subjective responsiveness to pain and analgesics. Unlike experimental pain studies in normal volunteers who serve as their own controls, all variables cannot be eliminated when studying analgesic in the post operative period. For instance, the quality of postoperative pain varies considerably from patient to patient due to several factors; such as age, sex, surgical procedure, the physician-patient relationship and the psychological makeup of the patient. With regard to this last factor, the patient's reaction to illness or injury or impact that it has on his life situation is additional contributing factors.

For these reasons, an attempt was made to eliminate at least one variable by having all pain evaluations recorded by the same trained observer. In addition, the premedication and the anaesthetic techniques were similar. The dosages used were equianalgesic as determined by previews and studies thus the dosages used were 0.2mg/kg nalbuphine and 1mg/kg of tramadol as intravenous bolus doses.

In the comparison of analgesia, both the drugs doses used were equianalgesic, after recording a VAS >3 the designated drug was administered. Mean VAS at the time of administration of drug was 7.55±0.59 in nalbuphine group and 7.42±0.50 in tramadol group, which was not statistically significant. All patients were respondents (VAS drop>2 after medication within 30 minutes). There was no case of failure of analgesia in either group as evidenced by the fact that no patient requested the rescue analgesic, diclofenac sodium at any point of study. Time of onset of analgesia was determined to be after 15 minutes in both the groups as mean VAS score was 6.15±0.97 and 6.22±0.80 in nalbuphine and tramadol group which was not significant. Percentage of pain relief was highly significant ($p<0.001$) mean VAS score0.72±0.64 in nalbuphine group as compared with mean VAS score 1.72±0.75 in tramadol group at 30 minutes. There was 100% pain relief between 60 to 240 minutes intervals indicating the peak effect (i.e. the time duration when mean VAS reached 0 and pain relief in VAS was 100%) in nalbuphine group, and peak effect was between 60 to 180 minutes in tramadol group. The duration of action of both the drugs was 8 hours.

Pain relief was significant with nalbuphine group till 8 hours of drug administration as compared with tramadol group. But, no re-medication was given till 8 hours as mean VAS score was1.25±0.74 in nalbuphine group and 2.15±0.69 in tramadol group which was statistically significant, but there was no rise of mean VAS scores from 0 to 3 or more and no fall of percentage of pain relief in VAS scores more than 50% or more. Thus the duration of the analgesic effects was between 240 to 480 minutes in nalbuphine group and 180 to 480 minutes in tramadol group.

The analgesic profile of nalbuphine was compared to that of tramadol by Alon E. et. Al[3] they demonstrated that there was no significant differences between the two groups. But patient control administration was 21.7 in the General well being of the patients on a 4 point scale was significantly better in the nalbuphine group after 45, 60 and 90 minutes. Similar analgesic

profile was seen in other study as well.The cardiovascular parameters monitored were heart rate (HR), systolic and diastolic blood pressure (SBP and DBP). The mean changes in HR, SBP and DBP showed no statistically significant difference in two groups.

However another study demonstrated that haemodynamic response to intubation and skin incision was stable as compared to other opioids and mixed opioid analgesics.

The respiratory parameters monitored were respiratory rate (RR) and oxygen saturation (SpO2).The mean changes in RR and SpO2 showed no statistically significant difference in two groups. All patients were receiving supplemental oxygen via face mask for first four hours. Study by Thomas J Gal et. al [4] ,they demonstrated as compare to morphine, nalbuphine exhibits a ceiling effect for respiratory depression for more than 30mg. Many other studies also have supported that tramadol is a good analgesic without respiratory depression[5,6,7].The side effects seen were drowsiness, headache, nausea alone and both nausea and vomiting. Nalbuphine group showed a significant incidence of drowsiness (12.5%) as compared to tramadol (5%) group. However tramadol group showed a highly significant incidence of nausea (12.5%) both nausea and vomiting (10%) as compared to nalbuphine group which had nausea (5%) and none of them had vomiting. The nausea was respondent to ondansetron. The safety profile of nalbuphine has been widely accepted by many trials [8,9,10.]

CONCLUSION

In conclusion, Nalbuphine appears to be a safe and effective analgesic for the relief of moderate to severe postoperative pain than tramadol in equianalgesic doses with minimum circulatory effects, providing good sedation and significantly lower incidence of nausea and vomiting. Its use in the postoperative period can also attenuate the mu-opioid receptor related adverse events, a ceiling respiratory depression.

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