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COMPARATIVE STUDY OF NALBUPHINE AND MORPHINE FOR PAIN RELIEF IN SPINE SURGERIES

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ABSTRACT

BACKGROUND AND AIM: The aim was to compare the analgesic efficacy of the two drugs nalbuphine and morphine administered intravenously in equi-analgesic doses in patients undergoing open spine surgeries. The primary outcome was the duration of analgesia and the requirement of rescue analgesic. Other than this, the post-operative VAS (visual analogue scale) score and the intraoperative haemodynamic parameters were compared.

METHODS: Eighty patients were selected and were randomly allocated into two groups with forty patients in each. Group M received intravenous morphine 0.15mg per kg of body weight. Group N received nalbuphine 0.15mg per kg of body weight. At the end of operation the VAS score was assessed at regular intervals and when VAS score was more than 4, a rescue analgesic was given. This period between extubation and administration of rescue analgesic was the duration of analgesia.

RESULTS: Nalbuphine was found to provide a longer duration of analgesia than morphine and it was statistically significant. The VAS scores measured at 30 minutes and 60 minutes showed statistically significant greater value in the morphine group than the nalbuphine group. This meant better post-operative analgesia in patients who received nalbuphine than those who received morphine. Haemodynamic parameters like heart rate, mean arterial pressure were compared and did not show any significant difference in the two groups. No significant side effects like respiratory depression, pruritus, nausea and vomiting were seen during the study.

CONCLUSION: The study showed that nalbuphine is a good analgesic and can be used as alternative to morphine in spine surgeries. It is safe and does not cause any significant side effects.

KEYWORDS : Spine Surgery, Analgesia, Nalbuphine, Morphine, Vas.

INTRODUCTION

Addressing intraoperative and postoperative pain is an integral part of anaesthesia practice. Multimodal approaches that target multiple sites along the pain pathway is necessary to combat pain adequately[1]. Pre-emptive analgesia is the process by which analgesics are given prior to the surgical stimulus.

Spinal fusion surgeries cause severe pain, hampering recovery[2]. Adequate analgesia results in early ambulation and discharge as well as lesser chance of developing chronic post-surgical pain. Thus, anaesthesia for spine surgeries is not only concerned with relieving pain during operation but also during the post-operative period[3].

Now, there has been a radical improvement in the quality of pain relief both during and after anaesthesia and there is still a lot of scope to make analgesia not only more effective but also less hazardous[4]. It is accepted that the most effective treatment for post-operative pain is opioid therapy and morphine is the most commonly used drug[5]. This is a fact despite decades of advancement in pain management. However morphine is associated with side effects including respiratory depression, sedation, post-operative nausea and vomiting and pruritus. Nalbuphine on the other hand is known to cause less respiratory depression. It is an opioid agonist antagonist of the phenanthrene series which was synthesized in an attempt to provide analgesia without the undesirable side effects of the pure agonists[6]. It attenuates the mu-opioid effects and enhances the kappa-opioid effects[7]. The agonist-antagonist opioid analgesics are a heterogeneous group of drugs with moderate to strong analgesic activity comparable to that of the pure opioid agonists like codeine and morphine but with a limited effective dose range. The group includes drugs which act as an agonist or partial agonist at one receptor and an antagonist at another. These include pentazocine, butorphenol, nalbuphine, dezocine and drugs acting as a partial agonist at a single receptor like buprenorphine.[8]

Now, pain can be measured both intra and post operatively. It has been seen that during anaesthesia with controlled ventilation, changes in heart rate and blood pressure may occur in response to pain and an increase in airway pressure may reflect an increase in broncho motor tone[9]. In the post-operative period, the duration of analgesia is a measure of analgesic efficacy.[10]

The equi-analgesic doses of morphine and nalbuphine have been determined after studying various literatures about the pharmacology of different opioid and non-opioid drugs and then 0.15mg/kg of both have been used to provide pre-emptive analgesia to the patients [9,11-13].

MATERIAL AND METHODS

This prospective, randomized, comparative, double blind study was conducted at a tertiary care hospital in Eastern India over a period of one year (January 2017-December 2017) after approval of the Ethical cum Screening Committee. We included randomly selected 80 patients (determined by power analysis study) in between the age of 20-60 years with American Society of Anaesthesiologists (ASA) physical status (PS) I and II, of either sex, weighing between 45 and 75 kg posted for elective open spine surgeries under general anaesthesia in prone position. Each patient received a written and verbal description of the research protocol and written informed consent was taken from all the patients in their language for inclusion in the study. Exclusion criteria for the study were patients with known cardiovascular, respiratory, renal or hepatic disease, patients with history chronic opioid use, emergency surgery, known allergy to study drug, patients with anticipated difficult airway. Eligible patients were randomly allocated using computer generated -randomized test to one of two equal (n=40) groups:

Group M: - Received intravenous Morphine 0.15mg/kg before induction of anaesthesia

Group N: - Received intravenous Nalbuphine 0.15mg/kg before induction of anaesthesia

PARAMETERS TO BE STUDIED

The parameters which were considered for this study were demographic variables like age (in years),sex male/female),body weight (in kg), hemodynamic parameters (heart rate, mean arterial pressure by non-invasive technique), and visual analogue scale (VAS) score.

STUDY TECHNIQUE

After approval of the Hospital Ethical cum Screening committee, 80

patients with the above mentioned criteria were selected for the study. On the preceding day of operation, relevant history, preanaesthetic check-up and informed consent of the patients were taken. Patients were also taught to interpret the VAS (graded from 0 = no pain to 10 = maximum pain) for the assessment of the severity of pain. Patients were premedicated with diazepam 10 mg tablets and ranitidine 150mg tablets on the night before surgery and ASA fasting guidelines were maintained.

On the day of surgery patients were randomly allocated into two groups, Group M and Group N. After arrival in the operating room, patient's identity and informed consent form were checked and all requisite monitors were attached. Blinding were done by using two separate persons doing the required work. Study drugs were supplied in sealed envelope with number codes. Anaesthesiologists were chosen to conduct the procedures randomly. Later on all the data were collected from them and tabulation was done. After preoxygenation, group M received intravenous morphine 0.15mg/kg and group N received intravenous nalbuphine 0.15mg/kg.

All patients received a standardized anesthetic as described-preoxygenation for 3 minutes with gas flow @ 5 liters/minute, followed by induction of anesthesia with inj. Propofol (2mg/kg I.V). Laryngoscopy (using Macintosh Laryngoscope) and intubation with appropriate sized flexometallic armored endotracheal tube were facilitated with Inj. Vecuronium bromide (0.1mg/kg). Maintenance of anesthesia was done with 40% of O_2 -60% of N_2O, and Isoflurane inhalation 0.6 % MAC. Muscle relaxation was achieved with vecuronium, which was repeated at 25%-30% of the initial dose as per requirement. Ventilation was mechanically controlled and adjusted to control end tidal CO_2 concentration at 30-35 mmHg. Hemodynamic parameters were monitored every 5 minutes and recorded by an independent observer. At the end of operation residual neuromuscular blockage was antagonized with neostigmine (40 mcg/kg I.V) and glycopyrrolate (0.01mg/kg I.V). Extubation was done only after adequate reversal from general anesthesia judged on clinical basis. After oxygenation for about 5 minutes postoperatively patients were sent to the ward.

After shifting the patients to the post-operative ward, the intensity of the pain was assessed using the visual analogue scale. Haemodynamic monitoring was continued every half an hour till the patients express a VAS>4. This duration between extubation and expression of VAS>4 was taken as the duration of analgesia. Further analgesia was managed with intramuscular diclofenac sodium 75mg which can be considered as rescue analgesic. Side effects and complications like nausea, vomiting, hypotension, dizziness, oxygen desaturation and sedation were noted and managed accordingly.

STATISTICALANALYSIS:

The sample size was calculated based on the previous study taking the significant level as 0.05, power as 80% & difference between mean as 10 & standard deviation 15, the required sample size was calculated as 35 in each group making the total sample size 70 which was converted to a round figure & the total sample size taken were 80 with 40 in each group (n=40). Randomization was done with the help of computer generated random number table.

Categorical variables were expressed as Number of patients and percentage of patients and compared across the groups using Pearson's Chi Square test for Independence of Attributes/ Fisher's Exact Test as appropriate. Continuous variables were expressed as Mean, Median and Standard Deviation and compared across groups using Levenes test and t- test. The statistical software SPSS version 20 was used for the analysis. A p value < 0.05 was considered as statistically significant and < 0.01 was considered as highly significant.

RESULTS:-

DEMOGRAPHIC VARIABLES

The groups were statistically comparable with respect to sex, age, body weight and ASA grading. [Table 1] No significant differences were observed between the groups (*p value* > 0.05)

Table 1. Comparison of demographic variables between the study groups

DEMOGRAPHIC VARIABLES	GROUP M	GROUP N	P value
Sex(M:F)	27:13	28:12	>0.05
Mean Age(yrs)	47.40±9.65	46.93±9.51	>0.05
Mean Weight(kg)	61.70±8.77	61.53±9.22	>0.05
ASA Grade (I:II)	22:18	25:15	>0.05

Table 2. Duration of analgesia (DOA) among the groups

	Group	n	mean	Std.dev.	Std.error of mean
DOA	M	40	96.75	28.410	4.492
	N	40	137.25	21.362	3.378

Statistical Analysis of Table 2.

		Levenes test		t-test						
		F	sig	t	df	Sig (2 tailed)	Mean diff	Std.error of diff	95%confidence limit	
DOA	Equal variances assumed	0.779	0.380	7.206	78	0.000	-40.500	5.620	-51.689	-29.311
	Equal variances not assumed			7.206	72.418	0.000	-40.500	5.620	-51.703	-29.297

Table 2 shows that the duration of post-operative analgesia was significantly more in the nalbuphine group when compared to the morphine group.

Table 3. Analysis of VAS score at 30 minutes post-extubation

	Group	n	mean	Std.dev	Std.error of mean
VAS at 30 min post extubation	M	40	1.88	0.791	0.125
	N	40	1.28	0.452	0.071

Statistical Analysis of Table 3.

		Levenes test		t-test						
		F	sig	t	df	Sig (2 tailed)	Mean diff	Std.error of diff	95%confidence limit	
									lower	upper
VAS at 30 mins post extubation	Equal variances assumed	6.489	0.013	4.167	78	0.000	0.600	0.144	0.313	0.887
	Equal variances not assumed			4.167	62.052	0.000	0.600	0.144	0.312	0.888

Table 4. Analysis of VAS score at 60 minutes post-extubation

	Group	n	mean	Std.dev	Std.error of mean
VAS at 60 min post extubation	M	40	3.15	1.099	0.174
	N	40	1.83	0.874	0.138

Statistical Analysis of Table 4.

		Levenes test		t-test						
		F	sig	t	df	Sig (2 tailed)	Mean diff	Std.error of diff	95%confidence limit	
									lower	upper
VAS at 60 mins post extubation	Equal variances assumed	0.385	0.537	5.969	78	0.000	1.325	0.222	0.883	1.767

	Equal variances not assumed			5.969	74.230	0.000	1.325	0.222	0.883	1.767

Table 3, 4 show that the VAS score at 30 minutes and 60 minutes following extubation were significantly more in the morphine group compared to the nalbuphine group. VAS scores were not compared after that because rescue analgesics were given to the patients when VAS exceeded 4.

Table 5:-Mean heart rate (HR) and standard deviation

HR	Group	n	mean	Std.dev	Std.error of mean
After Intubation	M	40	93.25	5.651	0.894
	N	40	94.15	6.331	1.001
At 1 hour	M	40	85.15	5.357	0.847
	N	40	85.90	6.717	1.062
At 2 hour	M	40	80.90	6.209	0.982
	N	40	82.45	7.282	1.151
After Extubation	M	40	90.20	6.223	0.984
	N	40	91.40	6.598	1.043

Table 6: Mean arterial pressure (MAP) and standard deviation

MAP	Group	n	mean	Std.dev	Std.error of mean
After Intubation	M	40	95.58	6.946	1.098
	N	40	97.60	7.348	1.162
At 1 hour	M	40	92.68	6.216	0.983
	N	40	93.45	5.491	0.868
At 2 hour	M	40	90.03	5.650	0.893
	N	40	91.50	5.561	0.879
After Extubation	M	40	95.53	6.733	1.065
	N	40	96.80	5.488	0.868

Table 5 and 6 show no significant difference between the mean values of HR and MAP of the two groups recorded and documented at four different times, during and after operation.

DISCUSSION

In the study, nalbuphine had a significantly longer duration of action than morphine and a significantly lower VAS score than morphine when measured at 30 minutes and 60 minutes postoperatively.

Nalbuphine is a drug with low abuse potential and proven safety in clinical practice[14]. This fact is also shown in the study where there is no significant difference between the heart rate and mean arterial pressure of the two drugs when observed intraoperatively and just after operation. The study demonstrated that it was a good analgesic and can be used as an alternative to morphine. This was true when both the drugs were given in equi-analgesic doses, 0.15 mg./kg .

The findings were almost similar to those of Anton A Van den Berg and collegues [9], where, a significant residual analgesic effect in the recovery was provided by nalbuphine.

Further, it also stated that morphine could not match this residual analgesic effect of nalbuphine. The reason behind this longer duration of analgesic action may be attributed to the different target of action compared to morphine. Nalbuphine is a central kappa receptor agonist[15]. A similar class of drug is buprenorhine and like nalbuphine, it also results in longer duration of analgesic action compared to morphine. Due to this central action, these two drugs have also been found to have longer sedative action compared to morphine.

In their study, Anton A Van den Berg and collegues[9] opined that nalbuphine given individually at a dose of 0.13 mg/kg as a single i.v. bolus for induction of anaesthesia is one of the most efficacious analgesics.

Longer duration of action of nalbuphine has also been reported in a study of Pallasch T J et al[16] that compared it with butorphanol. This study also opined that parenterally nalbuphine, butorphanol and morphine were equi-analgesic.

The analgesic effect of nalbuphine and its duration of action has always been a topic of interest of researchers. In their study Chen KT and collegues[17] opined that, the analgesic duration of nalbuphine HCl was 2 h while that of nalbuphine pivalate was 30 h. They concluded that nalbuphine pivalate, a pro drug, has a very long duration of analgesic action.

Workers like K S Liu et al[18] in their article had said that a long acting analgesic was necessary in combating long lasting pain and in order to synthesize a long acting analgesic they used a novel preparation of nalbuphine. They concluded that nalbuphine hydrochloride 10 mg. i.m provided analgesia for 3 to 5 hrs.

This finding is similar to the present study where the mean duration of action of post-operative analgesia has been shown to be 137.25 minutes. This means the intra and post-operative duration of analgesia would be about 4- 5 hrs. Other studies have also mentioned that the half-life of nalbuphine is approximately 4 hrs.[19,20]

So far as the haemodynamic parameters were concerned, neither morphine nor nalbuphine showed any significant alteration of heart rate and mean arterial pressure. No significant side effects like sedation, respiratory depression, pruritus and nausea and vomiting were recorded.

Previous studies have shown that nalbuphine does not cause respiratory depression.[9] Even if it causes, respiratory depression at higher doses has a ceiling effect[5]. Nalbuphine did cause somewhat prolonged sedation in some cases but that was not statistically significant. This prolonged sedation can be attributed to the central kappa mediated action of nalbuphine.

This finding is almost similar to the study of S T Ho et al[21] who compared patient controlled analgesia with nalbuphine and morphine with a bolus dose of 1 mg and a lock out time of 10 minutes.

In the study of Shiv Akshat and collegues[5] side effects like pruritus, nausea and vomiting in either of the groups did not reach statistically significant value.

The findings of the present study is similar to that of Zachy JP et al[22] who showed that 10mg of nalbuphine produces a profile of subjective, psychomotor and physiological effects similar to that of an equi-analgesic dose of morphine i.e.10mg.

Conclusion

The present study showed that nalbuphine is a good analgesic and can be used as an alternative to morphine in spine surgeries. It is safe and does not cause any significant side effects like sedation, respiratory depression, pruritus or nausea and vomiting. The duration of post-operative analgesia was significantly more when nalbuphine was used as an analgesic than when morphine was used. This was further shown by low VAS scores postoperatively in case of nalbuphine treated patients compared to morphine treated patients.

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Nil.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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