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Comparison of Nalbuphine with 0.125% Bupivacaine and Plain 0.125% Bupivacaine in Thoracic Epidural for Post Operative Analgesia in Upper Abdominal Surgery: A Retrospective Study

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Abstract
Acute uncontrolled post-operative pain and the pathophysiological response to surgery by stimulation of autonomic nervous system leads to stress responses causing significant adverse effects and complications to multi organ systems. In this study, we attempted to define the hemodynamic, analgesic profile and efficacy of Nalbuphine as an additive to Bupivacaine in thoracic epidural for postoperative analgesia in upper abdominal surgeries. The term extra dural, peridural and epidural are synonymous, with a greek and latin origin. The study was conducted at mookambika medical college between 2023-2024. After obtaining Ethical Committee approval, 50 ASA I-II patients undergoing infraumblical surgeries were randomly allotted into two groups. Statistical analysis was done using the statistical package for social sciences (SPSS). Different statistical methods were used as appropriate. This study is a prospective, randomised double blind controlled comparative study done to assess the hemodynamic, analgesic profile and efficacy of Nalbuphine as an adjuvant in providing postoperative analgesia in thoracic epidural for upper abdominal surgeries. The discovery of opioid receptors in brain and spinal cord, action of narcotics through opioid receptor have become an eye opener in achieving satisfactory postoperative analgesia with narcotic administration in regional techniques. The study concludes that epidural nalbuphine in a dose of 0.2 mg/kg with 0.125% bupivacaine, provides faster onset and longer duration of analgesia with better quality and patient satisfaction.

INTRODUCTION

Acute uncontrolled post-operative pain and the pathophysiological response to surgery by stimulation of autonomic nervous system leads to stress responses causing significant adverse effects and complications to multi organ systems. The important goal is to reduce the postoperative pain and discomfort Controlling pain is a multi modal approach with the use of various pharmacological agents (opioids and non-opioids), by different routes (intravenous vs regional techniques) with minimal incidence of adverse effects. In the above setting, Thoracic Epidural Analgesia (TEA) remains the mainstay of treatment in the management of perioperative pain in upper abdominal surgeries[1-5]. Advantages of epidural analgesia being the ability to provide prolonged duration of analgesia, minimal adverse effects than with systemic opioids, less haemodynamic changes, improved lung function, minimal gastrointestinal complications (paralytic ileus), early mobilisation and better patient satisfaction[6]. Nalbuphine is an agonist antagonist opioid related chemically to oxymorphone and naloxone. Acts as μ(mu) antagonist and kappa agonist with analgesic potency equal to that of morphine. Its rapid onset and longer duration of action and less cardiovascular and respiratory side effects makes it a better choice in postoperative analgesia. In this study, we attempted to define the haemodynamic, analgesic profile and efficacy of Nalbuphine as an additive to Bupivacaine in thoracic epidural for postoperative analgesia in upper abdominal surgeries. The term extradural, peridural and epidural are synonymous, with a greek and latin origin[7-9]. The epidural space, consisting of fat and blood vessels lies between the dural envelope of the spinal cord and bony walls of spinal canal and is approached either between the two lamina of adjacent vertebral arches-the “spinal” epidural route, or through sacral hiatus-the “caudal” approach. Corning in 1885 was the first to use epidural analgesia. He hypothesised that, “medications injected within the spinal canal will be taken up by the rich plexus of blood vessels around the spinal cord and carried into the substance of spinal cord, allowing direct medication of the cord, that is used for treatment of neurological disease and provide surgical analgesia”. However, from the descriptions of his two experiments, it is evident that he did not achieve a genuine epidural injection. In 1901, jean athanase sicard[2,3] and fern and cathelin of France popularized caudal/peridural approach. Marin the odors tougher 4 in the same year, attempted epidural analgesia by use of lumbar approach but lacked success. In 1911, lawen[5], emphasized caudal route to be the only safe approach to the epidural space, which limited the spread of drug to the area supplied by cauda equina[10]. Only in 1912, fildes pages[6] renewed the mid lumbar approach, because of its easy access and wide applicability. He invented the “pages method” of identifying epidural space-a “tactile feel” of the needle obtained on piercing ligamentum flavum. In 1913 heile[7], revived the idea of epidural block by entering the spinal canal laterally through the intervertebral foramina instead of midline puncture.in 1930’s, archile mario dogliotti[8-10], with the evidence from jansen’s, “discovery of negative pressure in the epidural space”, described a practical technique for administering lumbar segmental anaesthesia.with dogliotti’s work as foundation, in 1932, gutierrez[11] described the “hanging drop technique” to identify the epidural space. All these works were poorly understood and with the advent of neuromuscular blocking agents in 1946 and much satisfactory muscle relaxation with general anaesthesia alone, there was a rapid decline in use of regional techniques for anaesthesia and analgesia. Epidural analgesia managed to escape this crisis by the introduction of tuohy needles and indwelling epidural catheters. With technical refinements it was made possible to maintain analgesia intermittently or continuously for long periods of time[11,12]. Eugene aburel[13] placed a silk ureteral catheter in the epidural space and used for analgesia for women in labor. During world war ii in america in 1941, robert hingson 13 was assigned to care for the pregnant wives of united states coast guard seamen. Hingson used lemmon’s malleable needle and placed it sacrally, deep to the peridural ligament and administered drugs continuously. This safe and effective method of producing painless childbirth became popularly known as “continuous caudal anaesthesia”. In 1949, manuel martinez[14] modified a silkcatheter for continuous spinal anaesthesia and inserted it into the lumbar epidural space, producing the first continuous epidural block. By 1962, the first polyvinyl catheter[15] with a closed tip was introduced, making the continuous epidural block much more accurate and easier to perform. The first use of epidural morphine for analgesia was reported by behar[16] in 1979. This technique had given advantage over muscle relaxants in producing analgesia and maintaining voluntary function of the patient. And then the debate between de-efferentation (endotracheal intubation with muscle relaxants-artificial ventilation-awakening the patient to a period of post operative pain, with return of patients protective reflexes, normal movement and respiratory function) and de-afferentation (normal respiratory function that could be preserved even during surgery -pain free ambulation soon after leaving the operating room) was complete. The ideas from clinical observations had brought epidural analgesia out of its, “former state of empirism to a new level of versatility and clinical safety”. However certain complications were encountered and reported as in woolley and roe

case explaining paraplegia after spinal anaesthesia in 1954. In 1980's with spinal chloroprocaine, there was incidence of neurologic deficits and adhesive arachnoiditis and with continuous spinal lidocaine anaesthesia in 1990, patients had developed cauda equina syndrome. Currently, epidural analgesia has been combined with subarachanoid narcotics to ease the pain of labor. Combined spinal- epidural anaesthesia is one of the leading techniques in obstetric anaesthesia and analgesia. With recent advances, epidural has widely and safely been used in areas of surgery, obstetrics (walking epidurals, pain free labour) and in areas of chronic pain relief.

Aims of the Study: The aim of the present study is to evaluate the effects of addition of 1 mcg/kg of preservative free clonidine to the maximum of 75 mcg, 1 mcg/kg of preservative free fentanyl to the maximum of 50mcg and 50mcg/kg of preservative free midazolam to 30ml of 0.25%.

MATERIALS AND METHODS

The study was conducted at mookambika medical college between 2023-2024. After obtaining Ethical Committee approval, 50 ASA I-II patients undergoing infraumblical surgeries were randomly allotted into two groups. Statistical analysis was done using the statistical package for social sciences (SPSS). Different statistical methods were used as appropriate. Mean± SD was determined for quantitative data and frequency for categorical variables. The independent t-test was performed on all continuous variables. The normal distribution data was checked before any t-test. The Chi-Square test was used to analyze group difference for categorical variables. A p-value <0.05 was considered significant.

RESULTS AND DISCUSSIONS

Table 1: Age Distribution of the Study Groups (N=60)

Age group	Group A n (%)	Group B n (%)	Total n (%)
<25 years	3 (10)	1 (3.3)	4 (6.7)
26 - 40 years	9 (30)	4 (13.3)	13 (21.7)
41 - 55 years	18 (60)	25 (83.3)	43 (71.7)
Total	30 (100)	30 (100)	60 (100)

Mean (±S.D.) Age: 44.88±9.80. Age distribution of subjects in both the groups was comparable with minor difference.

Table 2: Distribution of the Study Groups According to Mean Age (N=60)

Group	N	Mean Age (years)	Std. Deviation	Mean difference	Student 't'test p value
A	30	42.43	10.852	-4.90	0.052
B	30	47.33	8.083		

The difference in mean age between subjects in the two groups was not statistically significant and hence the groups were comparable.

Table 3: Gender Distribution of the Study Groups (N=60)

Group	Female n (%)	Male n (%)	Total n (%)
Group A	11 (55)	19 (47.5)	30 (50)
Group B	9 (45)	21 (52.5)	30 (50)
Total	20 (100)	40 (100)	60 (100)
Chi-square value: 0.300		p value:0.584	

The difference in gender distribution of subjects between the 2 groups was not statistically significant.

Table 4: Distribution of the Study Groups According to Body Weight (N=60)

Group	N	Mean weight (Kg)	Std. Deviation	Mean difference	Student 't'test p value
A	30	55.80	9.901	-0.200	0.939
B	30	56.00	10.222		

The difference in mean weight between subjects in the two groups was not statistically significant and hence the groups were comparable.

Table 5: Distribution of the Study Groups According to Body Height (N=60)

Group	N	Mean weight (Kg)	Std. Deviation	Mean height (cms)	Student 't'test p value
A	30	158.73	5.330	-0.367	0.781
B	30	159.10	4.816		

The difference in mean height between subjects in the two groups was not statistically significant and hence the groups were comparable.

Table 6: Distribution of the Subjects According to Indication of Surgery (N=60)

Surgery indication	Group A n (%)	Group B n (%)	Total n (%)
Elective	22 (73.3)	21 (70)	43 (71.7)
Emergency	8 (26.7)	9 (30)	17 (28.3)
Total	30 (100)	30 (100)	60 (100)
Chi-square value: 0.082		p value:0.774	

The difference in distribution of elective and emergency surgeries done between the groups was not statistically significant.

Table 7: Distribution of the Subjects According to Type of Surgery (N=60)

Surgery type	Group A n (%)	Group B n (%)	Total n (%)
Supraumbilical hernia surgery (umbilical, paraumbilical, epigastric)	6 (20)	5 (16.7)	11 (18.3)
Gastrointestinal surgeries (gastric outlet obstruction, duodenal ulcers, growth - stomach, small bowel)	7 (23.3)	9 (30)	16 (26.7)
Hepatobiliary surgery (obstructive jaundice, cholecystitis)	8 (26.7)	6 (20)	14 (23.3)
Emergency laparotomies (perforative peritonitis, hollow viscous perforation)	8 (26.7)	9 (30)	17 (28.3)
Renal surgery (nephrectomy)	1 (3.3)	1 (3.3)	2 (3.3)
Total	30 (100)	30 (100)	60 (100)
Chi-square value: 0.685	p value:0.953		

The difference in distribution of type of surgeries done between the groups was not statistically significant.

Table 8: Distribution of the Study Groups According to Time of Onset of Sensory Blockade (N=60)

Group	N	Mean onset time (mins)	Std. Deviation	Mean difference	Student 't'test p value
A	30	7.07	1.081	-10.767	<0.001
B	30	17.83	2.984		

The difference in mean time of onset of sensory blockade between subjects in the two groups was statistically significant with group A having shorter and quicker onset of action (sensory blockade) by approximately 10mins than group B.

Table 9: Group-Wise Comparison of Heart Rate at Various Time Periods (N=60)

	Group	Mean PR	Std. Deviation	N
Heart rate Baseline	A	99.67	15.196	30
	B	95.70	14.346	30
	Total	97.68	14.787	60
Heart rate 15 min	A	87.53	10.670	30
	B	90.47	13.148	30
	Total	89.00	11.963	60
Heart rate 30 min	A	86.17	10.498	30
	B	82.83	11.489	30
	Total	84.50	11.040	60
Heart rate 60 min	A	85.57	9.797	30
	B	79.43	10.285	30
	Total	82.50	10.427	60
Heart rate 2 hours	A	86.00	9.385	30
	B	80.37	9.084	30
	Total	83.18	9.587	60

Factorial-Repeated measures ANOVA was applied to test the difference in mean heart rate at various time intervals between the two groups.

Model	mean heart rate	mean heart rate * Group
Wilks's Lambda F	58.60	17.217
Df	4,55	4,55
p value	**<0.001**	**<0.001**

There was statistically significant difference in the heart rate over time as suggested above but as there was statistically significant interaction between heart rate and the Group variable, heart rate at various time periods was analyzed in each group individually to report the simple effects.

Table 10: Comparison of Heart Rate at Various Time Periods in Group A (N=30)

	Group A		
Time	Mean	Std. Deviation	N
Baseline	99.67	15.196	30
15 min	87.53	10.670	30
30 min	86.17	10.498	30
60 min	85.57	9.797	30
2 hour	86.00	9.385	30
Group			A
Wilks's Lambda F			24.156
p value			<0.001
Partial Eta square			0.788

Table 11: Post-Hoc Test For Mean Arterial Pressure in Group B (N=30)*

Comparison Group (1 vs 2)	Mean difference (1-2)	p-value
Baseline vs 15 min	11.933	**<0.001**
Baseline vs 30 min	17.567	**<0.001**
Baseline vs 60 min	16.367	**<0.001**
Baseline vs 120 min	8.667	**<0.001**
15 min vs 30 min	5.633	**<0.001**
15 min vs 60 min	4.433	**0.017**
30 min vs 120 min	-8.900	**<0.001**
60 min vs 120 min	-7.700	**<0.001**

*Only statistically significant pair-wise comparisons mentioned. All other comparisons not significant. There was statistically significant drop in mean arterial pressure from baseline till 30mins and then it raises again marginally by 60mins and then raises significantly by 120 minutes and both the drop and rise in MAP was statistically significant in the Group B as observed in post-hoc tests.

This study is a prospective, randomised double blind controlled comparative study done to assess the hemodynamic, analgesic profile and efficacy of Nalbuphine as an adjuvant in providing postoperative analgesia in thoracic epidural for upper abdominal surgeries. The discovery of opioid receptors in brain and spinal cord, action of narcotics through opioid receptor have become an eye opener in achieving satisfactory postoperative analgesia with narcotic administration in regional techniques. The use of wide variety of additives along with local anaesthetics with epidural has increased patient comfort and satisfaction and has become a popular technique for management of acute postoperative pain. However there are some disadvantages associated with narcotics like nausea, vomiting, pruritus, sedation, respiratory depression and urinary retention[17-22]. Opioids have anti nociceptive effects on central or spinal cord levels. Stimulation of opioid receptors on the central nervous system leads to inhibition of neuronal serotonin uptake which leads to augmentation of spinal inhibitory pain pathways[23]. The role of opioids in spinal inhibition of nociceptive transmission is evident. The dorsal horn nociceptive neuron exhibit "windup" phenomenon-a frequency dependent potentiation of response to repeated C fibre stimulation. Opioids reduce the release of primary afferent transmitters via inhibitory presynaptic opioid receptor terminals thus reducing or blocking C fibre stimulation of the dorsal horn nociceptive neurons and delaying the onset of windup[24-26]. Nalbuphine is a synthetic opioid with mixed kappa agonist and mu antagonist activity. Because of its affinity to kappa receptors it results in analgesia, sedation, cardiovascular stability and

minimal respiratory depression and low abuse potential. Because of its mu receptor antagonism it is devoid of pruritus, nausea vomiting and respiratory depression and also antagonizes the respiratory depression activity of other narcotics. Nalbuphine exhibits the ceiling effects for respiratory depression and is a safety feature of this drug[27-30]. Demographic data comparing Age, Gender, Weight, Height and BMI distribution were comparable in both groups and not statistically significant by students "t" test. ASA grading and Type of surgeries done under elective and emergency of subjects in both the groups were comparable with minor differences and are not statistically significant by "chi square test". The difference in mean time of onset of analgesia between subjects in the two groups was statistically significant ($p<0.001$) by chi square test with group A having shorter and quicker onset of action by approximately 10mins than group B (7.07min Vs 17.83min). This faster onset of action of Nalbuphine may be attributed to its lipophilicity. The difference in mean duration of analgesia between subjects in the two groups was statistically significant ($p<0.001$) by student "t "test with group A having longer duration of analgesia by approximately 4 hours and 45mins than group B (8.4 hrs Vs 3.6 hrs). The synergistic action of nalbuphine on bupivacaine may have prolonged the duration of analgesia[31]. There was statistically significant difference in the heart rate and mean arterial pressure over time in both groups but as there was statistically significant interaction between heart rate and the Group variable, heart rate at various time periods was analyzed in each group individually. In group A, a statistically significant drop in heart rate from baseline till 15mins and then it stabilizes at the lower rate after 15mins as observed in post-hoc tests. And in group B statistically significant drop in heart rate from baseline till 60mins (as against 15mins in Group A) and then it stabilizes at the lower rate at 2 hours as observed in post-hoc tests[32-34]. In group A, drop in mean arterial pressure from baseline till 30mins and then it raises again significantly to reach near-baseline levels by 120 minutes and both the drop and rise in MAP was statistically significant as observed in post-hoc tests. In group B, drop in mean arterial pressure from baseline till 30mins and then it raises again marginally by 60mins and then raises significantly by 120 minutes and both the drop and rise in MAP was statistically significant in the Group B as observed in post-hoc tests. These hemodynamic changes may be attributed to the Sanjay P Gadre *et al* studied that the mean onset of sensory block (6.8±1.13 min vs 11.03±1.33min), motor block (9.87±1.22min vs 15.3±0.88min), duration of analgesia (414.6±37.7min vs 255.67±26.6 min) was statistically significant in Nalbuphine with Bupivacaine group. Sateesh *et al,* suggested that epidural Nalbuphine 0.2 mg/kg with 0.5% Bupivacaine produces early onset of sensory blockade (3.23±0.97 min vs 15.30±2.97 min) and prolongs the duration of analgesia(449±67 min vs 185.93±32.43 min) in comparison to 0.5% Bupivacaine with normal saline. Ramakrishna CD *et al*, suggesting the mean onset of sensory blockade (5.22 min vs 9.52 min) and mean onset of motor blockade(7.8 min vs 12.84 min) and duration of analgesia (287.40±29 min) was significant in Nalbuphine group compared to plain Bupivacaine group. Mohamed *et al*, suggested that with Nalbuphine (0.1 mg/kg), there was significant difference in postoperative pain and sedation scores and prolonged duration of analgesia and sedation and time to first rescue analgesia (10.1±1.5 hrs). M.S. Mok *et al* studied that with nalbuphine onset of pain relief appeared at 15minutes, peak at 30-60 minutes and lasted for 13.6±4.2 hours and no incidence of adverse effects.

CONCLUSION

The study concludes that epidural nalbuphine in a dose of 0.2 mg /kg with 0.125% bupivacaine, provides faster onset and longer duration of analgesia with better quality and patient satisfaction. Although there were significant hemodynamic changes over time which correlated with peak plasma action of the two drugs involved in the study, there was no incidence of any adverse effects and complications reported in both groups.

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