ORIGINAL RESEARCH

Intrathecal buprenorphine as adjuvant for postoperative analgesia in lower limb orthopedic surgery

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ABSTRACT

Background: Buprenorphine is a partial agonist-antagonist opioid, and is thirty times more potent than morphine, having both spinal and supra-spinal components of analgesia. It has high lipid solubility, high affinity for narcotic receptors, and prolong duration of action. Literature on the anesthetic potency of intrathecally administered bupivacaine with buprenorphine is less, which prompted us to conduct this study**. Method:** This was a prospective randomized case control study. 100 patients of ASA GRADE I AND II were equally divided in two groups. Control group (A) received 2.8 ml hyperbaric (0.5 %) bupivacaine(14mg) + 0.2 ml normal saline and study group (B) received hyperbaric (0.5 %) bupivacaine(14mg) + 0.2 ml buprenorphine (60mcg) in subarachnoid space in patients undergoing lower limb orthopaedic surgeries. Patients was evaluated for post-operative analgesia by Magills score, number of hypotensive episodes, bradycardia, respiratory depression intra-operatively and post operatively. Any side effects intra-operatively and postoperatively were monitored. **Result:** Hemodynamic stability was significant in study group(B). Duration of postoperative analgesia was significantly longer in the study group (B) with mean value of 14.69+/- 3.83 hours than in control group which was 4.92 +/-0.82 hours (p value <0.0001) without having any side effects. **Conclusion:** It can be concluded from our study that buprenorphine reduces dose of local anaaesthetic to achieve good quality of sensory block and postoperative analgesia

Keywords: Buprenorphine, spinal anaesthesia, bupivacaine, postoperative analgesia

INTRODUCTION

Anesthesia refers to the practice of administering medications that block the pain and other sensations, allowing medical and surgical procedures to be performed without causing any undue discomfort to the patient[1.] In 1885 James Leonard Corning (1855-1923), a neurologist in New York, first used spinal analgesia .[2] He accidentally pierced the dura mater during his experiment on spinal nerves of a dog. The first planned spinal anesthesia for surgery in man was administered by August Bier (1861–1949) on 16 August 1898, in Kiel, when he injected 3 ml of 0.5% cocaine solution into a 34-year-old labourer.[3] After using it on 6 patients, he and his assistant each injected cocaine into each other's spine. They used it for surgeries of lower limb, but stopped practicing it due cocaine toxicity.

Spinal anesthesia also called subarachnoid block, spinal block, intradural block and intrathecal block,[4] is a form of neuraxial regional anesthesia involving the injection of a local anesthetic or opioid into the subarachnoid space, generally through a fine needle, which measures 9 cm (3.5 inch) in length. It is an easier, safer and effective form of anesthesia, performed by anesthesiologists which can be used as an alternative safe technique to general anesthesia commonly for surgeries involving the lower limbs and infraumbilical region.

Pain is perceived to be a multidimensional and subjective experience. Its subjectivity influenced by behavioral, psychological, sensory, cognitive and cultural factor. Trauma due to surgical interventions causes tissue damage and result in pain. It is the fact that inadequate analgesia adversely affect the patient‘s

cardiovascular, pulmonary and emotional status and has provoked development of new and highly effective and safe methods of controlling pain.

The postoperative analgesia helps in speedy recovery, decreasing physical and mental stress, improvement in pulmonary function (by allowing the patient to cough, breathe and move more easily), reducing stress response to cardiovascular function, reducing incidence of thromboembolic events as well. Demonstration and localization of various receptors that play role in nociception and anti-nociception in spinal cord have made possible introduction of concept of intrathecal (subarachnoid) analgesia. The intrathecal route prove advantageous mainly in fact that they provide prolonged duration of analgesia relatively in lesser doses and thus less likely to be cause undesirable systemic effects of these drugs. The discovery of opioid receptors in early 70‘s has changed the concepts of pain relief [5]. It is proposed that by administering a low dose of opioid as an adjuvant to local anesthetic solution, the duration of postoperative analgesia can be significantly prolonged without increasing side effects. Intrathecal narcotics enhance the sensory blockade of local anesthetics without affecting the sympathetic activity. Adding opioid to local anesthetics reduces pain severity during and after surgery and curtails the dose of anesthetic required.[6] Buprenorphine is a partial agonist-antagonist opioid, and is thirty times more potent than morphine. It is a centrally acting lipid soluble analog of the alkaloid the baine having both spinal and supra spinal components of analgesia. In addition, it demonstrates ceiling effect on respiratory depression but not on analgesia. Central sensitization is prevented by the anti hyperalgesic property of buprenorphine. Its high lipid solubility, high affinity for narcotic receptors, and prolong duration of action makes buprenorphine a better choice as an adjuvant to intrathecal local anesthetic for managing moderate to severe postoperative pain. Buprenorphine, in preservative-free preparation, is compatible with the cerebrospinal fluid (CSF). Intrathecal doses (30 microgram–150 microgram) are much lower than parenteral doses and are known to augment analgesia without affecting motor blockade. Being more lipophilic than morphine, Buprenorphine has low modularly bioavailability after subarachnoid administration so that the occurrence of side effects is less, making it an attractive alternative. Several studies have demonstrated efficacy of Buprenorphine as an adjuvant to local anesthetics in subarachnoid block.[7]However, literature on the anesthetic potency of intrathecally administered bupivacaine with Buprenorphine is less, which prompted us to conduct this study. Therefore, we designed a randomized clinical trial to compare the anesthetic efficacy and hemodynamic effects of hyperbaric bupivacaine (14 mg) and hyperbaric bupivacaine (14 mg) with Buprenorphine (60mcg) for spinal anesthesia.

AIMS & OBJECTIVE

The aim of the study was to compare postoperative analgesia using intrathecal hyperbaric Bupivacaine (0.5%) (14mg) and Buprenorphine (60mcg) with hyperbaric Bupivacaine (0.5%) (14mg) in lower limb orthopedic surgery

PRIMARY

- To compare the duration of post-op analgesia.
- To compare the onset time of sensory block.
- To compare the onset time of motor block.
- To compare the duration of sensory block.
- To compare the duration of motor block.

SECONDARY

- To compare the hemodynamic changes
- To evaluate the incidence of Buprenorphine side effects

MATERIAL AND METHODS

Place of work

- Department of Anesthesiology, N.S.C.B. Medical College & Hospital, Jabalpur (M.P.)

Duration

- From 1st march 2020 to 31st august 2021

Design of study

- This was a prospective randomized case control study.

After getting permission from Institutional Ethics Committee, the study was conducted on 50 patients in each group

Inclusion criteria

Patients undergoing lower limb orthopedic surgeries

- Age group 18- 65 yrs.
- ASA grade I –II.
- Weighing 50 -90 kg.
- Height 140 -180 cm.
- Hemodynamically stable.

Study protocol

100 patients of ASA class I and II were equally divided in two groups.

The study was done after the approval obtained by ethical committee of the institution and written informed consent from the patient involved in the study. Simple randomization technique was used to divide the study subjects into 2 groups using table of random number. A list of random number for both groups would be prepared before the start of study. Subjects who satisfy the criteria would be given consecutive numbers and treatment allocation would be done as per as list prepared. Demographic variables like weight, height, age were recorded. Patients were instructed for non per os according to ASA guideline prior to surgery. Technique of neuraxial anesthesia and Magills‘classification for pain evaluation was discussed and explained to patients. Before shifting the patient to the operating table, the table was made horizontal to ground by using a fluid filled leveling device. Routine monitoring devices was attached.

Preinduction vitals noted. Two peripheral intravenous access secured (18G and20 G) and preloading with Ringer Lactate was done with 8-10 ml /kg body weight . Urinary catheterization was done. Subarachnoid block was performed at L3-L4 intervertebral space using 26 G Quinckes'spinal needle by midline approach. After confirming free flow clear cerebrospinal fluid tap, drug was administered into subarachnoid space; Control Group (A) received hyperbaric bupivacaine (0.5%) 2.8 ml (14mg) +0.2 ml normal saline and Study Group (B) received hyperbaric bupivacaine (0.5%) 2.8 ml (14mg) +0.2 ml buprenorphine (60 microgram) respectively in sitting position in patients undergoing lower limb orthopedic surgeries .Precaution was taken to administer precise dose of buprenorphine by using tuberculin syringe. Immediately after injection the patients were placed in supine position. They were given supplemental oxygen immediately after administration of spinal anesthesia. Variables like heart rate, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure and respiratory rate were monitored every 15 minutes for first two hours and then every 30 minutes till completion of surgery. Oxygen saturation monitoring was continuously done intraoperatively. Onset time of sensory block was checked by loss of cold sensation by using alcohol swab at T 12 level. Motor block was assessed by modified Bromage scale (0: No motor block, 1: Inability to raise extended leg but able to move knees and feet, 2: Inability to raise extended leg and move knee but able to move feet, 3: Complete block of motor limb) and onset of motor block considered by achieving grade 3 on modified Bromage scale. Intraoperative fluid maintenance was done with ringer lactate. Use of sedatives or any analgesic drug was avoided intraoperatively. Hypotension intraoperatively was treated when MAP decreased to <30% of baseline with intravenous mephentermine 6 mg. Bradycardia is considered when heart rate < 60/min and treated by intravenous atropine 0.2mg. Postoperative pain assessment was done using MAGILL'S classification and rescue analgesia was provided by intramuscular diclofenac sodium 75 mg when the score is >2.

Postoperatively, variables like heart rate, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, respiratory rate and oxygen saturation were monitored continuously and data noted every thirty minutes for first two hours and then every two hours for up to twenty four hours. We kept strict vigilance in order to avoid administration of any dose of rescue analgesia in pain free interval to avoid bias in result of study. Patient were strictly evaluated for duration of postoperative analgesia in ward by Magills' classification was noted every thirty minutes for first two hours and then every 2 hours for upto 24 hours.

MAGILLS' CLASSIFICATION

0 NO PAIN,
1 SLIGHT PAIN,
2 DISCOMFORT,
3 UNBEARABLE PAIN,
4 EXCRUCIATING PAIN

Rescue analgesia with intramuscular diclofenac 75mg was considered when Magills' classification achieved a value of 3, means patient complains of unbearable pain and time duration up to this point is considered as the duration of postoperative analgesia. Patients were also monitored every thirty minutes for the appearance of respiratory depression which was taken as respiratory rate of less than 10/min. Patients were also looked upon post operatively for other side effects like hypotension,bradycardia ,nausea and vomiting, shivering, drowsiness etc. Urinary retention was not assessed as bladder was catheterized in each patient

RESULTS

Table 1: Demographic variables (Mean and standard deviation)

Variables	Study Group	N	Mean	SD	SE	t test	p value
Age (years)	Bupivacaine+NS	50	37.64	13.169	1.862	0.166	0.868
	Bupivacaine +Buprenorphine	50	38.1	14.492	2.049		
Height (cm)	Bupivacaine+NS	50	172.14	3.886	0.55	1.278	0.204
	Bupivacaine +Buprenorphine	50	173.18	4.246	0.6		
Weight (kg)	Bupivacaine+NS	50	66.14	6.652	0.941	0.331	0.742
	Bupivacaine +Buprenorphine	50	65.68	7.243	1.024		

- Analysis of variants showed that the difference between various demographic variables were in significant ($p>0.05$).

Table 2: Demographic variables (median & range)

	Group					
	Bupivacaine+ NS			Bupivacaine +Buprenorphine		
	Median	Minimum	Maximum	Median	Minimum	Maximum
Age	36.00	20.00	64.00	39.00	18.00	65.00
Height (CM)	172.00	165.00	181.00	173.00	167.00	180.00
Weight (KG)	66.50	52.00	82.00	66.00	51.00	80.00

Table 3: Duration of surgery (mean and standard deviation)

Variables	Study Group	N	Mean	SD	SE	t test	p value
Duration of surgery (min)	Bupivacaine+NS	50	205.2	38.505	5.445	1.306	0.195
	Bupivacaine+Buprenorphine	50	217.2	52.335	7.401		

- Analysis of mean value and standa deviation showed that the difference in duration of surgery was found to be insignificant in two groups (p>0.05).

Table 4: Duration of surgery (median and range)

	Group					
	Bupivacaine+NS			Bupivacaine+Buprenorphine		
	Median	Minimum	Maximum	Median	Minimum	Maximum
Duration of Surgery in min	210.00	120.00	300.00	210.00	120.00	300.00

Table-5: Onset time of sensory and motor block

	Study Group	N	Mean	SD	SE	t test	p value
Onset of Sensory Block (Mts)	Bupivacaine+NS	50	6.86	1.906	0.27	8.785	<0.0001
	Bupivacaine+Buprenorphine	50	3.82	1.535	0.217		
Onset of Motor Block (Mts)	Bupivacaine+NS	50	10.26	2.891	0.409	7.418	<0.0001
	Bupivacaine+Buprenorphine	50	6.3	2.426	0.343		

- Analysis of data showed that there was early onset of sensory block and motor block in study group (p<0.0001).

Table 6: Duration of sensory and motor block

Variables	Study Group	N	Mean	SD	SE	t test	p value
Duration of Sensory Block (Mts)	Bupivacaine+NS	50	191.72	22.997	3.252	7.794	<0.0001
	Bupivacaine+Buprenorphine	50	227.82	23.317	3.298		
Duration of Motor Block (Mts)	Bupivacaine+NS	50	169.44	20.667	2.923	1.056	0.294
	Bupivacaine+Buprenorphine	50	173.94	21.937	3.102		

Table 7: Variation inpulserate betweentwo groups

Pulse Rate (min)	Study Group	N	Mean	SD	SE	t test	p value
0 min	Bupivacaine+NS	50	77.82	9.454	1.337	3.475	0.001
	Bupivacaine+Buprenorphine	50	84.44	9.594	1.357		
15 min	Bupivacaine+NS	50	70.24	8.623	1.219	4.773	<0.0001
	Bupivacaine+Buprenorphine	50	79.10	9.896	1.399		
30 min	Bupivacaine+NS	50	67.56	6.122	0.866	4.626	<0.0001
	Bupivacaine+Buprenorphine	50	75.82	11.041	1.561		
60 min	Bupivacaine+NS	50	73.66	9.866	1.395	2.232	0.028
	Bupivacaine+Buprenorphine	50	78.24	10.636	1.504		
90 min	Bupivacaine+NS	50	76.34	8.38	1.185	1.87	0.064
	Bupivacaine+Buprenorphine	50	79.34	7.644	1.081		
120 min	Bupivacaine+NS	50	79.00	7.521	1.064	0.284	0.777
	Bupivacaine+Buprenorphine	50	79.46	8.662	1.225		
150 min	Bupivacaine+NS	49	80.04	9.294	1.328	0.489	0.626
	Bupivacaine+Buprenorphine	48	80.94	8.743	1.262		
180 min	Bupivacaine+NS	44	80.25	8.37	1.262	0.102	0.919
	Bupivacaine+Buprenorphine	42	80.05	10.058	1.552		
210 min	Bupivacaine+NS	30	82.57	7.842	1.432	0.574	0.568
	Bupivacaine+Buprenorphine	29	83.97	10.709	1.989		
240 min	Bupivacaine+NS	14	80.21	9.472	2.532	1.369	0.18
	Bupivacaine+Buprenorphine	22	83.86	6.549	1.396		
270 min	Bupivacaine+NS	5	80.6	10.237	4.578	0.717	0.483
	Bupivacaine+Buprenorphine	14	84.07	8.974	2.398		
300 min	Bupivacaine+NS	2	75.0	18.385	13.0	1.064	0.323
	Bupivacaine+Buprenorphine	7	85.0	10.198	3.854		

- Variation in pulse rate between two groups was comparable and significant difference was observed up to 30 min. (p<0.0001) during the intraoperative period.

Table 8: Variation in systolic blood pressure between two groups

SBP (min)	Study Group	N	Mean	SD	SE	t test	p value
0 min	Bupivacaine+NS	50	120.98	8.385	1.186	2.499	0.014
	Bupivacaine+Buprenorphine	50	125.72	10.471	1.481		
15 min	Bupivacaine+NS	50	107.86	10.142	1.434	2.98	0.004
	Bupivacaine+Buprenorphine	50	114.58	12.304	1.74		
30 min	Bupivacaine+NS	50	106.36	8.831	1.249	3.898	<0.0001
	Bupivacaine+Buprenorphine	50	114.46	11.742	1.661		
60 min	Bupivacaine+NS	50	106.64	9.174	1.297	4.723	<0.0001
	Bupivacaine+Buprenorphine	50	115.36	9.288	1.314		
90 min	Bupivacaine+NS	50	109.04	8.533	1.207	3.846	<0.0001
	Bupivacaine+Buprenorphine	50	116.00	9.536	1.349		
120 min	Bupivacaine+NS	50	110.82	9.151	1.294	3.821	<0.0001
	Bupivacaine+Buprenorphine	50	117.46	8.2	1.16		
150 min	Bupivacaine+NS	49	111.04	8.753	1.25	3.716	<0.0001
	Bupivacaine+Buprenorphine	49	116.88	6.651	0.95		
180 min	Bupivacaine+NS	44	113.41	8.306	1.252	3.694	<0.0001
	Bupivacaine+Buprenorphine	42	119.88	7.924	1.223		
210 min	Bupivacaine+NS	29	112.93	8.097	1.504	2.523	0.014
	Bupivacaine+Buprenorphine	29	118.62	9.049	1.68		
240 min	Bupivacaine+NS	13	114.15	7.946	2.204	1.056	0.299
	Bupivacaine+Buprenorphine	22	117.18	8.342	1.778		
270 min	Bupivacaine+NS	5	121.00	10.794	4.827	0.639	0.531
	Bupivacaine+Buprenorphine	14	117.86	8.977	2.399		
300 min	Bupivacaine+NS	1	123.00	.	.	0.111	0.915
	Bupivacaine+Buprenorphine	7	123.71	6.02	2.275		

- Variation in systolic blood pressure between two groups was comparable but significant difference was observed for up to 180 min. ($p<0.0001$) and there after became insignificant.

Table 9: Variation in diastolic blood pressure between two groups

DBP (min)	Study Group	N	Mean	SD	SE	t test	p value
0 min	Bupivacaine+NS	50	70.44	6.634	0.938	4.231	<0.0001
	Bupivacaine+Buprenorphine	50	76.52	7.696	1.088		
15 min	Bupivacaine+NS	50	63.1	7.56	1.069	3.477	0.001
	Bupivacaine+Buprenorphine	50	69.18	9.783	1.383		
30 min	Bupivacaine+NS	50	62.46	6.303	0.891	4.074	<0.0001
	Bupivacaine+Buprenorphine	50	68.98	9.399	1.329		
60 min	Bupivacaine+NS	50	62.74	6.194	0.876	4.883	<0.0001
	Bupivacaine+Buprenorphine	50	69.4	7.393	1.045		
90 min	Bupivacaine+NS	50	64.02	6.554	0.927	3.639	<0.0001
	Bupivacaine+Buprenorphine	50	69.6	8.638	1.222		
120 min	Bupivacaine+NS	50	65.44	6.603	0.934	4.506	<0.0001
	Bupivacaine+Buprenorphine	50	71.62	7.102	1.004		
150 min	Bupivacaine+NS	49	64.92	6.788	0.97	4.431	<0.0001
	Bupivacaine+Buprenorphine	49	71.18	7.204	1.029		
180 min	Bupivacaine+ NS	44	66.23	6.799	1.025	3.135	0.002
	Bupivacaine+Buprenorphine	42	71.33	8.263	1.275		
210 min	Bupivacaine+NS	29	67.07	7.221	1.341	2.421	0.019
	Bupivacaine+Buprenorphine	29	71.97	8.152	1.514		
240 min	Bupivacaine+NS	13	71.31	9.295	2.578	0.695	0.492
	Bupivacaine+Buprenorphine	22	73.41	8.25	1.759		
270 min	Bupivacaine+NS	5	74	10.025	4.483	0.389	0.702
	Bupivacaine+Buprenorphine	14	72.07	9.36	2.502		
300 min	Bupivacaine+NS	1	67	.	.	0.844	0.431
	Bupivacaine+Buprenorphine	7	75.57	9.502	3.591		

- Variation in diastolic blood pressure between two groups showed highly significant difference for up to 150 min. ($p<0.0001$).

Table 10: Variation in mean arterial blood pressure between two groups

MAP (min)	Study Group	N	Mean	SD	SE	t test	p value
0 min	Bupivacaine+NS	50	87.38	6.282	0.888	3.128	0.002
	Bupivacaine+Buprenorphine	50	92.22	8.956	1.267		
15 min	Bupivacaine+NS	50	78.04	7.516	1.063	3.044	0.003
	Bupivacaine+Buprenorphine	50	83.6	10.504	1.485		
30 min	Bupivacaine+NS	50	77.44	6.289	0.889	4.019	<0.0001
	Bupivacaine+Buprenorphine	50	84.2	10.093	1.427		
60 min	Bupivacaine+NS	50	77.32	6.377	0.902	5.158	<0.0001
	Bupivacaine+Buprenorphine	50	84.38	7.281	1.03		
90 min	Bupivacaine+NS	50	79.1	6.412	0.907	3.878	<0.0001
	Bupivacaine+Buprenorphine	50	84.6	7.712	1.091		
120 min	Bupivacaine+NS	50	80.7	6.192	0.876	4.876	<0.0001
	Bupivacaine+Buprenorphine	50	86.56	5.821	0.823		
150 min	Bupivacaine+NS	49	80.29	6.529	0.933	4.754	<0.0001
	Bupivacaine+Buprenorphine	49	86.37	6.129	0.876		
180 min	Bupivacaine+NS	44	81.86	6.529	0.984	3.828	<0.0001
	Bupivacaine+Buprenorphine	41	87.63	7.365	1.15		
210 min	Bupivacaine+NS	29	82.38	6.646	1.234	3.118	0.003
	Bupivacaine+Buprenorphine	29	89.14	9.598	1.782		
240 min	Bupivacaine+NS	13	85.69	8.38	2.324	1.321	0.196
	Bupivacaine+Buprenorphine	20	89.15	6.612	1.478		
270 min	Bupivacaine+NS	5	89.6	10.015	4.479	0.46	0.652
	Bupivacaine+Buprenorphine	14	87.57	7.939	2.122		
300 min	Bupivacaine+NS	1	86	.	.	0.495	0.642
	Bupivacaine+Buprenorphine	6	90	7.483	3.055		

- Variation in mean arterial blood pressure between two groups was highly significant for up to180 min. ($p<0.0001$).

Table 11: Variation in respiratory rate between two groups

RR (min)	StudyGroup	N	Mean	SD	SE	t test	p value
0 min	Bupivacaine+NS	50	16.06	1.889	0.267	0.164	0.87
	Bupivacaine+Buprenorphine	50	16.12	1.769	0.25		
15 min	Bupivacaine+NS	50	15.36	1.871	0.265	0.607	0.545
	Bupivacaine+Buprenorphine	50	15.58	1.751	0.248		
30 min	Bupivacaine+NS	50	15.1	1.705	0.241	0.917	0.361
	Bupivacaine+Buprenorphine	50	15.44	1.991	0.282		
60 min	Bupivacaine+NS	50	15.38	1.883	0.266	2.504	0.014
	Bupivacaine+Buprenorphine	50	16.24	1.533	0.217		
90 min	Bupivacaine+NS	50	15.48	1.717	0.243	1.515	0.133
	Bupivacaine+Buprenorphine	50	16	1.714	0.242		
120 min	Bupivacaine+NS	50	15.64	1.509	0.213	1.868	0.065
	Bupivacaine+Buprenorphine	50	16.22	1.595	0.225		
150 min	Bupivacaine+NS	49	15.39	1.511	0.216	1.776	0.079
	Bupivacaine+Buprenorphine	49	15.94	1.56	0.223		
180 min	Bupivacaine+NS	44	15.68	1.775	0.268	0.64	0.524
	Bupivacaine+Buprenorphine	41	15.93	1.752	0.274		
210 min	Bupivacaine+NS	30	15.77	1.569	0.286	0.215	0.83
	Bupivacaine+Buprenorphine	29	15.86	1.827	0.339		
240 min	Bupivacaine+NS	13	15.62	1.502	0.417	0.818	0.419
	Bupivacaine+Buprenorphine	22	22.68	30.935	6.595		
270 min	Bupivacaine+NS	5	16.4	2.302	1.03	0.043	0.966
	Bupivacaine+Buprenorphine	14	16.36	1.781	0.476		
300 min	Bupivacaine+NS	2	14	1.414	1.00	1.065	0.322
	Bupivacaine+Buprenorphine	7	15.57	1.902	0.719		

Respiratory rate between two groups was comparable ($p>0.05$).

Table 12: Duration of post operative analgeasia based on magills' classification

Magills	Study Group	N	Mean (Hour)	SD	SE	t test	p value
0	Bupivacaine+NS	50	1.56	0.7045	0.09963	11.435	<0.0001
	Bupivacaine+Buprenorphine	50	6.01	2.66016	0.3762		
1	Bupivacaine+NS	50	2.76	0.716	0.10126	14.988	<0.0001
	Bupivacaine+Buprenorphine	50	9.88	3.28192	0.46413		
2	Bupivacaine+NS	50	3.8	0.756	0.107	17.776	<0.0001
	Bupivacaine+Buprenorphine	50	12.88	3.532	0.5		
3	Bupivacaine+NS	50	4.92	0.82906	0.11725	17.627	<0.0001
	Bupivacaine+Buprenorphine	50	14.69	3.83045	0.54171		
4	Bupivacaine+NS	0	.	.	.		
	Bupivacaine+Buprenorphine	0	.	.	.		

Mean duration for excellent analgesia (Magills' score 0) was found to be 1.56± 0.7045 hours in control group(A) and 6.01±2.66016 hours in study group(B) which was statistically highly significant (p<0.0001). The rescue analgesia in study group (B) was demanded as late as 14.69± 3.83045 hours as compared to 4.92± 0.82906 hours in control group (A) which was statistically significant.

Table 13: Post operative period pain analysis based on magills' classification (median and range)

Magills' Score	Group					
	Bupivacaine+NS (Hours)			Bupivacaine+Buprenorphine (Hours)		
	Median	Minimum	Maximum	Median	Minimum	Maximum
0	1.00	1.00	3.00	6.00	1.50	14.00
1	3.00	2.00	4.00	10.00	2.00	16.00
2	4.00	3.00	5.00	13.00	6.00	19.00
3	5.00	4.00	7.00	15.00	7.00	22.00
4	.	.	.	.	.	.

- Analys is showed the maximum duration for excellent analgesia (Magills' score 0) was found to be 14 hours in the study group as compared to 3 hours in control group. Maximum duration to first rescue analgesia was found to be 22 hours (range 7 hours to 22 hours in study group as compared to 7 hours (range 4 hours to 7 hours) in control group.

Table 14: Comparison of duration of postoperative analgesia

Variables	Study Group	N	Mean	SD	SE	t test	p value
Duration of Postoperative Analgesia (Hours)	Bupivacaine+ NS	50	4.92	82906	0.11725	17.627	<0.0001
	Bupivacaine+Buprenorphine	50	14.69	3.83045	0.54171		

- Analysis of data showing the duration of postoperative analgesia which was significantly longer in study group (p<0.0001).

Table 15: Incidence of side effects between two groups

Variables	Study Group	N	Mean	SD	SE	t test	p value
Hypotension episode (intraoperative)	Bupivacaine+NS	50	0.12	0.328	0.046	1.043	0.299
	Bupivacaine+Buprenorphine	50	0.06	0.24	0.034		
Hypotension episode (postoperative)	Bupivacaine+NS	50	0	0	0		
	Bupivacaine+Buprenorphine	50	0	0	0		
Bradycardia episode (intraoperative)	Bupivzcaine+NS	50	0	0	0		
	Bupivacaine+Buprenorphine	50	0	0	0		
Bradycardia episode (postoperative)	Bupivacaine+NS	50	0	0	0		
	Bupivacaine+Buprenorphine	50	0	0	0		
Respiratory depression episode (intraoperative)	Bupivacaine+NS	50	0	0	0		
	Bupivacaine+Buprenorphine	50	0	0	0		
Respiratory depression episode (postoperative)	Bupivacaine+NS	50	0	0	0		
	Bupivacaine+Buprenorphine	50	0	0	0		
Nausea vomiting episode (intraoperative)	Bupivacaine+NS	50	0.08	0.274	0.039	2.064	0.042
	Bupivacaine+Buprenorphine	50	0	0	0		
Nausea vomiting episode (postoperative)	Bupivacaine+NS	50	0	0	0		
	Bupivacaine+Buprenorphine	50	0	0	0		
Shivering episode	Bupivacaine+NS	50	0.06	0.24	0.034	0.732	0.466

(intraoperative)							

- Analysis of data showed that the incidence of side effects were in significant in either groups (p>0.05).

We had conducted our research on 100 patients who were randomly distributed into 2 groups i.e control group (A) and study group (B) of 50 patients each .The mean value of age, weight, and height in two groups were statistically insignificant (p>0.05) (Table 1/2). Duration of surgery (Table 3/4) in both the groups were comparable, with mean duration of 205.2±38.505 min in control group (A) and 217.2±52.335 min in study group (B) (p>0.05) Onset of sensory block (Table 5) was significantly earlier in study group (B) with mean value of 3.82± 1.535 min as compared to control group (A) 6.86±1.906 min (p<0.0001). Onset of motor block was (Table 5) earlier in study group(B) 6.3±2.426min in comparison to control group(A) 10.26± 2.891 min(p <.0001). (Table 2).Duration of sensory block (Table 6) was found to be significantly longer in study group (B) 227.82±23.317 min than control group(A)191.72± 22.997 min(p< 0.0001). (Table 3)

In this study we found difference in duration of motor block (Table 6) to be insignificant with mean value of 169.44±20.667 min in control group (A) and 173.94 ± 21.937 min in study group(B) (p=0.294). (Table 3)

Mean duration for excellent analgesia (Magills' score 0) was found to be 1.56±0.7045 hours in control group(A) and 6.01±2.66016 hours in study group (B) which was statistically significant(p<0.0001). In the study group (B), maximum duration of excellent analgesia (Magills' score 0) was up to 14 hours in 02 patient. (Table 12/13)

Duration of postoperative analgesia was significantly longer in study group (B) with mean value 14.69±3.83045 hours as compared to 4.92±0.82906 hours in control group (A)(p<0.0001). The demand for rescue analgesia in study group (B) was as late as 14.69± 3.83045 hours as compared to 4.92± 0.82906 hours in control group (A), which was statistically significant. (Table 14)

Hemodynamic stability was generally comparable in both the groups but was significant in study group (B) in terms of variables (heart rate/systolic blood pressure/diastolic blood pressure/mean arterial pressure/pulse rate for up to 30min/180min/150min/180 min respectively) in comparison to its baseline values while control group (A) showed statistically insignificant difference. (Table7/8/9/10/11)

Insignificant difference was found in respiratory rate between both the groups in perioperative and post operative period. (Table 15)

None of the patient presented with drowsiness/nausea/bradycardia (in intraoperative and postoperative period) in our study group. Hypotension was found in 6 patients in control group (A) in comparison to 4 patients in study group and was not statistically significant.

DISCUSSION

Discovery of opioid receptor has initiated a new era of pain management. First demonstration of direct opioid analgesia at spinal cord level was given by Yaksh and Rudy et al[8] in 1976. In 1979, opioids were introduced in the clinical practice intrathecally which marked a major breakthrough in pain management. Use of neuraxial opioids facilitated in the management of perioperative pain, labor analgesia and chronic malignant pain using implantable, programmed intrathecal pumps and devices. Wang et al[9] (1979) have confirmed the efficacy of intrathecally administered opioids for postoperative pain relief. Intrathecal opioids act synergistically with local anesthetics and intensify sensory block achieving more hemodynamic stability. Buprenorphine, a mu receptor agonist with low intrinsic activity when administered intrathecally is effective in minimal doses in providing postoperative analgesia.

Spinal anesthesia is one of the simple and efficient anesthetic technique which offer advantage over general anesthesia providing postoperative analgesia and reduced stress response.[10] We had decided to reevaluate synergistic effect of intrathecal buprenorphine as an adjuvant to hyperbaric bupivacaine (0.5%) as an effective method of providing postoperative analgesia.

We carried out the study to compare the efficacy of buprenorphine (60 microgram) as adjuvant to intrathecal hyperbaric bupivacaine 0.5% (14mg) for providing post operative pain relief. This study was prospective randomized control study. Both the group were comparable demographically and of ASA physical status I and II. Most of the patients enrolled in the study belong to age group between 35-40 years with mean age of 37.64± 13.169 years in control group and 38.1±14.492 years in study group.

One of the significant observation found in the our study was increased duration of postoperative analgesia with addition of an intrathecal opioid which served as an important factor in reducing morbidity and hastening recovery in the postoperative period and reducing the duration of hospital stay. As literature support the fact that early mobilization in postoperative period in orthopedic lower limb surgeries is an essential factor for early and better outcome of surgical intervention.[11-12] Buprenorphine as an adjuvant to intrathecal hyperbaric bupivacaine (0.5%) helps in achieving these goals by providing prolonged pain free interval in postoperative period. The observation from our study having the duration of postoperative analgesia of 14.69±3.83045 hours in study group (B) when compared to control group (A) 4.92± 0.82906 hours(p< 0.0001) was highly significant and comparable to result obtained by Sunil Dixit et al[13] where they found the duration of postoperative analgesia of 491.26± 153.97 minutes

(range from 5 hours to 15 hours) when compared to their control group which had analgesia of 145.16± 25.86 minutes(range from 1.99 hours to 2.846 hours) using 1.7 ml hyperbaric bupivacaine (0.5%) alone and 1.7 ml hyperbaric bupivacaine (0.5%) + buprenorphine 0.2 ml (60 microgram) intrathecally in control and study group respectively undergoing lower segment cesarean section. Comparable result were obtained with the study conducted by Borse Y M et al[14] who compared the duration of postoperative analgesia using intrathecal hyperbaric bupivacaine (0.5%) 2.5 ml (12.5 mg) + 0.5 ml normal saline and hyperbaric bupivacaine (0.5%) 2.5 ml (12.5 mg) + buprenorphine 0.5 ml (150 mcg) as an adjuvant in control and study group respectively for lower limb orthopedic surgeries and demonstrated prolonged duration of postoperative analgesia in study group which ranged from 10 hours to 16 hours with mean duration of 909 minutes (15 hours) as compared to 0-299 minutes (0 to 5 hours) with mean value of 158 minutes in control group. Prolonged duration of postoperative analgesia of our study was supported by study conducted by Arvinder Pal Singh et al[15] in which they compared intrathecal 0.75% ropivacaine (2.8 ml) +0.2 ml normal saline with 0.75% ropivacaine (2.8 ml) +0.2 ml buprenorphine (60 mcg) and 0.75% ropivacaine (2.8 ml) +0.2 ml fentanyl (10 mcg) respectively. They concluded that duration of postoperative analgesia was longest in group which received buprenorphine with mean value of duration of7.44 ± 1.69 hours when compared to control group having a duration of 3.50±1.102 hours (p<0.001).

Khan F A et al[16] studied the effect of intrathecal fentanyl (10 mcg) and buprenorphine 30 mcg as an adjuvant to intrathecal hyperbaric bupivacaine 2 ml (0.75%) in urological surgeries and had evidenced increased duration of postoperative analgesia of 834±59 min. in the study group which received buprenorphine along with intrathecal hyperbaric bupivacaine (0.75%) as compared to 463± 28 min. in control group. Results of our study were in concordance with their study. The observations obtained in our study also coincide with study conducted on patients posted for cesarean section by Seyed Mozaffer Rabiee et al[6] who administered 0.2 ml buprenorphine (60 mcg) as an adjuvant to 65-70 mg lidocaine and concluded significant pain free interval of 18.73 hours in study group when compared to 1.25 hours in their control group. Rashmi Dubey et al[5] conducted study on 80 patients posted for lower abdominal surgeries. Intrathecal hyperbaric bupivacaine (0.5%) 15 mg+buprenorphine (60 mcg) was administered in the study group and it prolonged the duration of postoperative analgesia having a mean value of 16.2± 6.66 hours as compared to 3.73 ± 0.87 hours in their control group. The results of which were comparable to our study. G .Capogna et al [17] concluded that buprenorphine (30mcg v/s 45mcg) as an adjuvant to hyperbaric bupivacaine (0.5%) intrathecally improve the quality and duration of postoperative analgesia more so in the 45 mcg sub group. This signifies that the analgesic property is dose dependent. Results of the study conducted by Rashmi Pal et al[18] was consistent with our study with postoperative analgesic period of 294±17.93 min in buprenorphine group and 195.83±7.30 min in fentanyl group. Naresh Bhukya et al[19] also found the prolonged duration of postoperative analgesia of 292 ±35.871 min in buprenorphine group when compared to fentanyl 169± 10.698 min (p<0.001). Kamal Sonya et al[20] showedpostoperative analgesia of duration 317±54 min with intrathecal buprenorphine as compared to 214±35 min with fentanyl (p<0.001). V.Murugnantham et al[21]evidenced that buprenorphine when added as an adjuvant to intrathecal hyperbaric bupivacaine (0.5%) in varying doses significantly increases the duration of postoperative analgesia in comparison to fentanyl with visual analogue scale at all hours (6 hours,12 hours,18 hours) lower in buprenorphine group.

Evidence of present study in correlation with augmented postoperative analgesic duration with buprenorphine as an adjuvant to intrathecal hyperbaric bupivacaine (0.5%) is due to reduction of input to C fibers via presynaptic opioids receptor in dorsal horn of spinal cord. Buprenorphine a mixed agonist antagonist type opioid due to its high lipid solubility and high affinity to opioid receptor attribute to its prolong duration of action and making it good choice for post operative analgesia.[22]

Seyed Mozaffar Rabiee et al[6] suggested that property of buprenorphine to prolong the duration of postoperative analgesia is contributed by its slow dissociation from mu receptor. In our study, we have used Magills' classification[23] to quantify the duration of postoperative analgesia. End point of analgesia and demand for rescue analgesia by the patient is determined by Magills' score of 3 when patient complains of unbearable pain .In the present study, the mean duration for Magills' score to reach 3 was 14.69 ± 3.8304 hours in study group (B)as compared to 4.92 ± 0.82906 hours in control group (A) which was significantly longer and congruent to results of study conducted by Sunil dixit et al [13]where they evidenced the duration for demand of rescue analgesia to be as late as8 hours in study group in comparison to 4 hours in control group.

We have observed in the present study that time to onset for sensory block was significantly earlier in the study group (B) with the mean value of 3.82±1.535 min. as compared to 6.86±1.906 min. in control group (A). This finding is supported by result of study conducted by Sunil dixit et al.[13]They concluded that time of onset of sensory block was 1.85 +/_1.39 min. in the study group as compared to 5.35± 1.79 min. in control group (p<0.0001). Although the time taken was a little bit longer despite using higher dose of hyperbaric bupivacaine (0.5%) 14mg when compared to that used by Sunil Dixit et al[13], where they used 8.5

mg of hyperbaric bupivacaine(0.5%). This difference is due to different modality which was used to check the onset of sensory block. They used the loss of pin prick sensation in cephalad direction but we have use loss of cold sensation by alcohol swab at T12 level. Rashmi Dubey et al[5] concluded rapid onset of sensory block with onset time of 2.28±1.31 min in their study group as compared to 4.02±1.23 min.in their control group which was congruent to result of our study. However Seyed Mozaffar Rabiee et al[6] evidenced statistically insignificant difference in time to onset for sensory block in their study group and control group.

The duration of sensory block was significantly prolonged in our study with the mean value of 227.82±23.317 min in the study group as compared to 191. 72±22.997 min in control group($p<0.0001$), which was comparable to result of study conducted by Arvinder Pal Singh et al[15] ,which was 215.8 ± 24.36 min in buprenorphine group and 196.00±29.48 min in fentanyl group respectively. Seyed Mozaffar Rabiee et al[6] also evidenced prolongation of duration of sensory block. In comparison to other opioids like fentanyl as adjuvant to intrathecal hyperbaric bupivacaine (0.5%), buprenorphine provide longer duration of sensory block. This evidence was found to be congruent to study conducted by Khan FA et al[16] who evidenced that only 35 % of patient in buprenorphine group regressed to L 1 level one hour postoperatively ascompared to 70% patients in fentanyl group ($p<0.001$). Rashmi Pal et al [18] concludedprolonged duration of sensory block with 267±30.18 min in buprenorphine group as compared to 174.33±23.44 min in fentanyl group ($p<0.001$). Naresh Bhukya et al [19] showed prolonged sensory block of 226±41.838 min in buprenorphine group as compared to 187±8.142 min in fentanyl group ($p<0.001$). However our result was discrepant with previous studies by Rashmi Dubey et al[5] who concluded no significant difference in duration of sensory block in their control and study group which were 208.8± 58.0 min and 211.3± 28.8 min respectively ($p > 0.05$).

Our study observed early onset of motor block in study group (B) with mean duration of onset of 6.3 ± 2.426 min in comparison to 10.26± 2.8 91 min in control group. This observation was comparable to study conducted by Rashmi dubey et al[5] where they found onset of motor block within 1-2 min, 2- 3min, and 3-4 min in 30% ,20%,35% patients respectively in comparison to 4-5 min in 50% of patients of control group ($p<0.05$). How ever result of Arvinder Pal Singh et al[15] showed insignificant difference in onset time of motor block with 2.75± 1.020 min in buprenorphine group as compared to 3.10±0.852 min in fentanyl group ($p>0.005$).

In our study we found difference in the duration of motor block to be insignificant with mean value of 169.44±20.667 min in control group (A) and 173.94 ± 21.937 min in study group (B) ($p=0.294$). This observation of our study was consistent with result of Rashmi Dubey et al [5] who found the duration of motorblock to be 190.5±57.2 min in control group and 186.5±30.1 min in study group ($p>0.05$). Borse Y M et al [14] also evidenced statistically insignificant difference in duration of motor block of 121 min & 125 min in control and study group respectively ($p>0.05$).

Administering subarachnoid buprenorphine along with hyperbaric bupivacaine (0.5%) provide hemodynamic stability in term of variables like systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate. Difference in the study group in terms of systolic blood pressure, diastolic blood pressure and mean arterial pressure was found to be significant for up to 180 minutes, 150 min and 180 min respectively and in terms of heart rate variation was significant for up to 30 minutes in comparison to control group. Intraoperatively, after that, there was no significant difference in hemodynamic variables among the groups. This observation in the present study coincide with results of previous study by Seyed Mozaffer Rabiee et al[6] who used intrathecal (5%) lidocaine 65-70 mg +0.2 ml normal saline and (5%) lidocaine 65- 70 mg +0.2 ml buprenorphine in control and study group respectively and showed that variation in heart rate and blood pressure were significantly different after 60th minutes between case and control, and found to be more significant in control group. High lipid solubility and high affinity for narcotic receptors attributed to hemodynamic stability in the study group using buprenorphine. G. Capogna et al[17] concluded that heart rate and arterial blood pressure were maintained within physiological range in study group. Khan F et al[16]showed insignificant difference in heart rate, systolic and diastolic blood pressure between their groups. Borse Y M et al[14] demonstrated insignificant difference in hemodynamic variables like systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate between the two groups($p>0.05$) . This evidence of present study was found to be in congruent to result of Chansoriya K P et al[24], Rudra et al[25], Sinm Thomas W et al[23], Lata R K et al[26]. Reluctance to use of opioids is mostly due to catastrophic side effect of respiratory depression as described in literature which limits their clinical use. But as we know buprenorphine is a partial opioid agonist at mu (**μ)** receptor and competitive antagonist at kappa receptor centrally acting on both spinal and supra spinal component and is compatible withcerebrospinal fluid having no adverse effect when used intrathecally as adjuvant to local anesthetics. High lipid solubility contribute to rapid diffusion into neural tissues and decreased extent to rostral spread leads to decreased risk of respiratory depression and other side effects in post operative periods.[27] In present study we had not come across with this serious side effect of respiratory depression perioperatively and post operatively with no significant difference in respiratory rate and oxygen

saturation which was maintained above 98%. In our best knowledge we had not found any literature describing respiratory depression using buprenorphine as an adjuvant to intrathecal hyperbaric bupivacaine (0.5%).

In the present study we had not found nausea as side effect of buprenorphine when administered intrathecally as suggested by G. Capogna et al[17]. Our findings were in accordance with previous study conducted by Rudra et al[25], Thomas W et al,[23] Lata R KK et al[26] , Sen M[28,] who observed incidence of nausea to be statistically insignificant. Sunil dixit et al[13] showed evidence of drowsiness in their study group using buprenorphine which was discrepant with the present study. Other side effects like hypotension, bradycardia, shivering were not significant in either of the groups. It is a universal fact that there are endless possibilities for discovering and reevaluating new and existing findings in field of research. There is need for further research in deciding optimum low dose of buprenorphine to achieve best postoperative analgesia and also for maximum dose that can be safely administered intrathecally keeping hemodynamic stability and minimal side effects.

CONCLUSION

Subarachanoid block with local anesthetic is preferred technique in lower limb and infraumbilical abdominal surgeries. However hypotension is the most common side effect with this technique.[27]

Different types of drugs had been used as adjuvant to local anesthetics in subarachnoid block to achieve early onset of sensory block/motor block, increased duration of sensory block, prolonged duration of post operative analgesia, better hemodynamic stability and reduced side effects.

Present study concluded that buprenorphine in a lower dose is a better choice to achieve the above mentioned beneficial effect in subarachnoid block when used as an adjuvant to local anesthetics.

With the experience obtained in present study the following conclusion can be drawn that when buprenorphine 0.2 ml (60microgram) was added to hyperbaric bupivacaine (0.5%) 2.8 ml (14mg) in subarachnoid block:-

1. Buprenorphine reduces dose of local anesthetic to achieve good quality of sensory block and perioperative and postoperative analgesia.
2. Early onset of sensory block.
3. Prolonged duration of sensory block.
4. Early onset of motor block.
5. Do not affect duration of motor block.
6. Improved hemodynamic stability.
7. Improved hemodynamic stability.
8. Reduced incidence of side effects.
9. Respiratory depression was not observed as side effect in study group.

Thus, it can be concluded that despite side effects of opioids mentioned in the literature, they are safe to use intrathecally as an adjuvant to local anesthetics to improve quality of neuraxial block perioperatively and postoperatively and reducing morbidity in patients.

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