Comparative study between intrathecal nalbuphine and dexmedetomidine for post-operative analgesia in lower abdominal surgeries.

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Abstract:

Background: Nalbuphine and Dexmedetomidine has been used intrathecally as an adjuvant in many studies. The purpose of our study was to establish the effectiveness of intrathecal nalbuphine as an adjuvant, and compare with dexmedetomidine and determine prolonged analgesic effect and minimal side-effects. **Materials and Methods:** In this prospective, randomized, controlled study, 100 ASA I and II patients undergoing lower abdominal surgery under subarachnoid block (SAB), were randomly allocated to two groups: N and D, to receive 0.8 mg nalbuphine made up to 0.5 ml with NS added to 0.5% hyperbaric bupivacaine 18 mg (total volume 3.5 ml),and 5µg dexmedetomidine made up to 0.5 ml with NS added to hyperbaric bupivacaine 18mg [total volume 3.5ml] respectively. The onset of sensory and motor blockade, two-segment regression time of sensory blockade, duration of motor blockade and analgesia, visual analogue scale (VAS) pain score and side-effects were compared between the groups. **Results:** Two-segment regression time of sensory blockade and duration of effective analgesia was prolonged in groups D (5 µg dexmedetomidine) and N(0.8 mg nalbuphine) The onset of sensory and motor blockade, two-segment regression time of sensory blockade, duration of motor blockade and analgesia, visual analogue scale (VAS) pain score and side-effects were compared group D was better than group N. **Conclusion:** Nalbuphine and dexmedetomidine used intrathecally is a useful adjuvant in SAB and, prolongs postoperative analgesia without increased side-effects.

Keywords: Dexmedetomidine, Hyperbaric bupivacaine, Napuphine.

Introduction:

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. The sole essence of anaesthesia is pain relief in peri-operative period. Regional anaesthesia has emerged as an important technique with simplicity, effectiveness and safety as its added advantages. Neuraxial block for lower abdominal surgeries have become popular as it has many advantages over general anaesthesia. Spinal anaesthesia consists of temporary interruption of nerve transmission in the subarachnoid space produced by the injection of a local anaesthetic solution. Spinal anaesthesia has many

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advantages like easy to perform, rapid onset of action, good muscle relaxation and early recovery. Main disadvantage is its limited duration of action and hence lack of post-operative analgesia. Spinal anaesthesia with hyperbaric bupivacaine is commonly used in lower abdominal surgeries.

Addition of drugs to local anaesthetics is called adjuvants. They increase the efficacy or potency of local anaesthetics. They increase the speed of the onset of neural blockade, improve the quality and prolong the duration of blockade.

Opioids (morphine, fentanyl, nalbuphine, buprenorphine) and a α_2 agonist (clonidine, dexmedetomidine) are used as an adjuvant to spinal anaesthesia for lower abdominal surgeries to prolong post-operative analgesia.[1,2]

Nalbuphine is an adjuvant drug with mixed mu-antagonist and a kappa agonist property is related chemically to oxymorphone and naloxone. It is equal in potency as analgesic to morphine, and one-fourth as potent as nalorphine as an antagonist. They have a short duration of action, consistent with their lipid solubility and rapid clearance. Studies have shown that the addition of intrathecal nalbuphine 0.4mg, 0.8mg, 1.6mg to hyperbaric bupivacaine for spinal anaesthesia improved the quality of intra-operative and post-operative analgesia with minimal pruritis and respiratory depression.[3]

Dexmedetomidine an adjuvant is α_2 agonist is used as short-term sedative, analgesic in the intensive care unit it causes sedation without causing respiratory depression. It is an S-enantiomer of medetomidine .The elimination half life is 2 hours. Intrathecal dexmedetomidine produces its analgesic effect by inhibiting the release of C-fibres transmitters and by hyperpolarization of post synaptic dorsal horn neurons. The prolongation of motor effect might because of direct impairment of excitatory amino acids release from spinal interneurons. It produces sedative effect by acting on α_2 adrenergic receptors in locus ceruleus. α_2 adreno receptors do not have an active role in the respiratory system, so minimal effect on respiratory system. 5 and 10 micrograms of dexmedetomidine added to intrathecal 0.5%bupivacaine significantly prolongs postoperative analgesia.[3]

This study examines comparison between dexmedetomidine and nalbuphine as an adjuvant to hyperbaric bupivacaine in spinal anaesthesia.

Materials and Methods:

After obtaining approval from the hospital ethical committee, a written informed consent was obtained from all the patients who were a part of this study. The study was conducted in 90 patients, aged 18-50 years, of both sex with various indications scheduled for lower abdominal surgery. All the patients with significant systemic illness were excluded from the study and only American Society of Anaesthesiogists I and II patients were included in the study. None of the patients had any contraindications to spinal anaesthesia.

Pre-anaesthetic check-up was done on the previous day and on the morning of operation. Detailed history of present complaints, significant past, family and personal history was taken. General and systemic examination was done and vitals recorded. Routine and specific investigations were noted. All the patients were explained in general terms the procedure of the study and their queries were answered. Patients were to receive

Bupivacaine and Nalbuphine and Bupivacaine and Dexmedetomidine in each group. All assessments were made by single observer.

The patients received the following dose of drugs intrathecally. Total volume with saline in both the groups was 3.5 ml.

- **Group N:** Inj. Bupivacaine hyperbaric 18mg (0.5%) (3.3ml) + Inj. Nalbuphine 0.8mg (0.05ml)
- **Group D:** Inj. Bupivacaine hyperbaric 18mg (0.5%) (3.3ml) + Inj. Dexmedetomidine 5µg (0.05ml).

Upon entering the operation theatre, all standard monitors (Electrocardiogram, Non-invasive blood pressure and Saturation probe) were applied and the baseline blood pressure, pulse rate, oxygen saturation and respiratory rate were recorded. Intravenous line was secured with an 18G cannula, Inj. Ondansetron 4 mg I.V. was given to all the patients. All the patients were preloaded with 1000 ml ringer lactate solution. Subarachnoid block was then performed under aseptic and antiseptic precautions with the patients in the lateral decubitus position, after local infiltration with 2 ml of 2% lignocaine. In the L_2-L_3 interspace, mixture of drugs according to the assigned groups was injected through 23G spinal needle after the aspiration of clear, free flow of cerebral spinal fluid with the bevel facing cephalad. Then the patient was turned supine and position of table was kept horizontal.

Recording of the heart rate, blood pressure, oxygen saturation and respiratory rate was done every 2 minute for the first 10 minutes, then every 5 minute for next 30 minutes, every 15 minute for 1 hour, then 30 minutes till 3 hours, hourly till 6 hours and then 2 hourly till 12 hours after giving the subarachnoid block. The onset of sensory blockade was assessed by pin prick method at the left mid clavicular line. A sensory level of T_6 was considered adequate to allow surgery to proceed. Time to onset of T6 sensory level was recorded. Time to regression of sensory blockade from T_6 to L_1 was recorded which was considered as the duration of sensory blockade. The time to onset of complete motor blockade was recorded as the time to achieve modified bromage scale grade-III. The duration of motor block was time to achieve modified bromage scale grade III to grade 0.

Modified Bromage Scale:

- Grade 0: Able to move hip, knees and ankle.
- Grade I: Unable to move hip, able to flex knees and ankle.
- Grade II: Unable to move hip and knees, able to move ankle.
- Grade III: Unable to move hip, knees and ankle.

Post-operative pain was assessed hourly using 10 cm visual analogue scale (0 - no pain; 10 - worst pain). Duration of effective analgesia (time from subarachnoid drug injection to the first dose of rescue analgesic) was recorded. Intra venous Diclofenac sodium 2 mg/kg was given as the rescue analgesic if the pain score was 4or more. Peri-operative degree of sedation was assessed by using Campbell Sedation Score starting 30 minutes from sub-arachnoid injection of drugs till 12 hours post operatively.

***Campbell Sedation Score**:*

0 - Awake and alert

1 - Easy to arouse opens eye on command

2 - Opens eyes when shaken

3 - Unarousable.

Episode of peri-operative hypotension -mean arterial blood pressure < 70 mmHg or [20% or more reduction from baseline] was treated with fast infusion of intravenous fluids and Inj. Mephentermine 6mg intravenous in incremental doses.

Bradycardia (pulse <60/min) was treated with Inj. Atropine 0.6 mg intravenously. Respiratory depression (RR<10/min) was recorded. Desaturation (Spo2<90%) was recorded and was managed with 100% oxygenation. Peri-operative emetic response was recorded. Inj. Metoclopramide 10 mg intravenously was given as rescue antiemetic. Pruritis was treated with Inj. Diphenhydramine 25 mg intravenously.

All the observations were recorded and the results were analyzed. Statistically data are presented as mean ± S.D. For comparing data between two groups, ANOVA test (Analysis of variance) was used and p values <0.05 were interpreted as clinically significant.

Results:

Table 1: Demographic data

	Group D	Group N	P Value
Age (years, Mean±SD)	49 ± 8.91	47.1 ± 6.17	0.3409
Sex ratio (M:F)	1:1	1:2	-
Weight (kg, Mean±SD)	57.27 ± 9.24	59.93 ± 5.35	0.1777
Height (cm, Mean±SD)	154.20 ± 4.49	155.7 ± 3.86	0.1706
ASA Grading (I/II)	19/11	20/10	-

Table 2: Duration of Surgery

Duration (minutes)	Group D	Group N
60-90	1	4
91-120	13	23
121-150	7	3
151-180	9	0
Total	30	30
Mean ± SD	136.89 ± 32.27	108.66 ± 11.95
P value <0.0001		

Table 3: Mean onset time of sensory and motor blockage

	Group D	Group N	P value
Time to reach T6	1.41 ± 0.22	4.43 ± 0.75	0.01
Time to reach bromage III	4.21 ± 0.76	5.43 ± 0.67	001

The onset of sensory and motor block was faster in group D than in group N. The Table 3 is showing that, in dexmedetomidine there is an early onset of sensory and motor effect.

Image 1: Type of Surgery

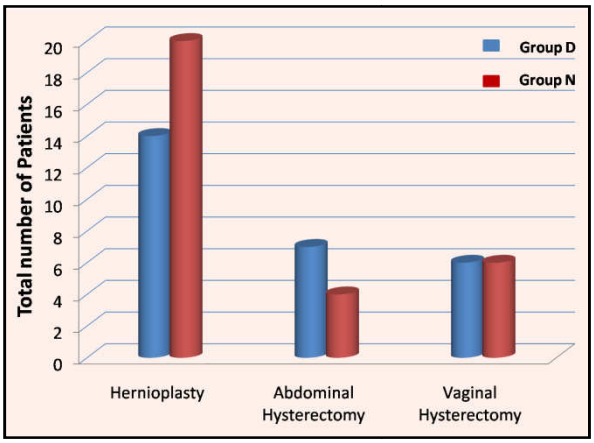
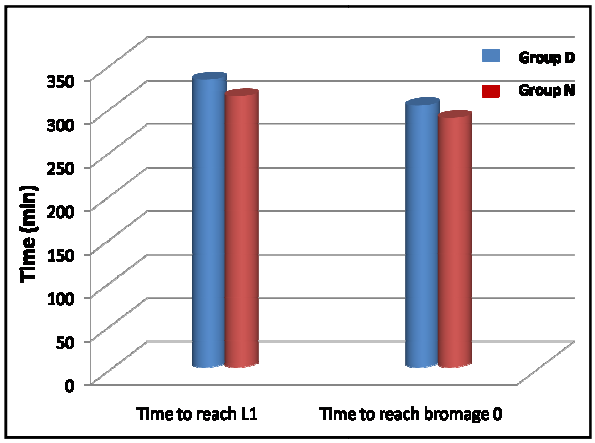


Image 2: Duration of Sensory & Motor blockage



Duration of sensory and motor block were higher in group D than in group N. Dexmedetomidine has more sensory and motor block effects than Nalbuphine.

Table 4: Changes in Pulse Rate

Time (min)	Group D		Group N		P Value
	Mean	SD	Mean	SD	
0 min	83.10	9.6	86.8	4.66	0.045
2 min	84.52	8.07	86.87	4.52	0.194
4 min	85.17	7.09	86.93	4.77	0.218
6 min	85.89	6.45	84.93	6.88	0.548
8 min	83.93	6.29	78.56	6.44	0.014
10 min	84.31	6.34	77.03	5.92	0.015
15 min	81.96	7.87	76.60	6.56	0.014
20 min	81.90	7.30	76.97	5.75	0.023
25 min	81.62	7.79	79.96	6.57	0.041
30 min	80.72	7.94	81.47	5.65	0.612
45 min	81.14	7.58	82.47	6.87	0.423
60 min	82.70	8.67	82.50	5.82	0.986
90 min	81.93	7.85	83.13	5.93	0.427
120 min	82.31	8.28	83.43	6.12	0.460
150 min	81.90	8.66	84.40	5.61	0.146
180 min	81.03	9.17	84.80	4.83	0.055
240 min	81.00	8.18	84.33	4.64	0.055
300 min	80.86	8.01	85.03	5.02	0.054
360 min	80.38	7.69	85.47	4.42	0.054
480 min	80.75	8.41	85.66	4.10	0.056
600 min	81.10	7.81	86.10	4.69	0.062
720 min	82.00	7.69	86.23	4.53	0.060

Table 5: Changes in Mean Arterial Pressure

Time (min)	Group D		Group N		P Value
	Mean	SD	Mean	SD	
0 min	88.66	8.71	91.27	6.42	0.132
2 min	87.89	8.96	91.13	5.64	0.071
4 min	89.00	8.28	91.43	6.34	0.144
6 min	88.24	10.69	87.07	5.92	0.041
8 min	89.21	9.70	83.50	8.45	0.031
10 min	88.79	8.88	80.53	5.95	0.021
15 min	85.96	9.84	80.6	6.40	0.013
20 min	85.79	10.45	82.7	7.87	0.042
25 min	85.24	7.59	84.03	7.52	0.538
30 min	85.31	7.69	85.46	7.09	0.958
45 min	84.43	6.59	87.4	6.42	0.072
60 min	85.06	7.31	87.6	6.15	0.133
90 min	84.03	5.30	89.13	5.88	0.055
120 min	84.14	5.99	88.77	6.09	0.054
150 min	82.79	6.09	89.13	6.06	0.055
180 min	84.27	6.02	89.03	5.60	0.054
240 min	85.41	6.75	89.37	5.34	0.053
300 min	85.28	6.67	89.43	5.54	0.055
360 min	85.52	6.88	89.60	5.01	0.100
480 min	85.69	8.30	89.03	5.79	0.054
600 min	84.76	7.11	89.73	5.95	0.055
720 min	85.28	7.88	88.97	5.58	0.058

Mean pulse rate was lower with use of dexmedetomidine. (Table 4)

Mean arterial pressure was lower in dexmedetomidine than nalbuphine as an adjuvant. (Table 5)

Image 3: Changes in Respiratory Rate

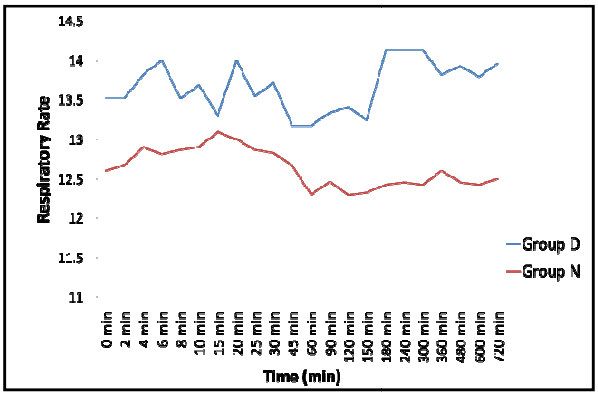


Image 4: Changes in SPO_2

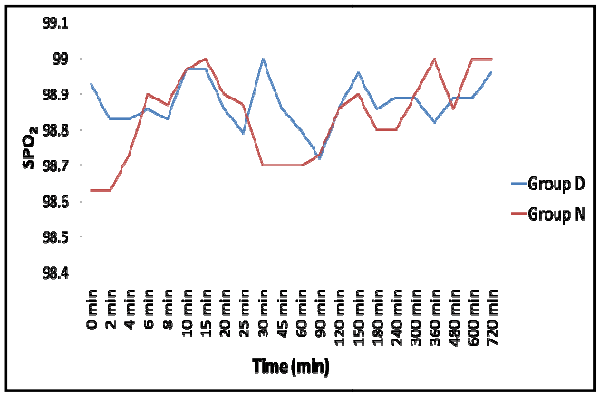


Image 5: Sedation Score

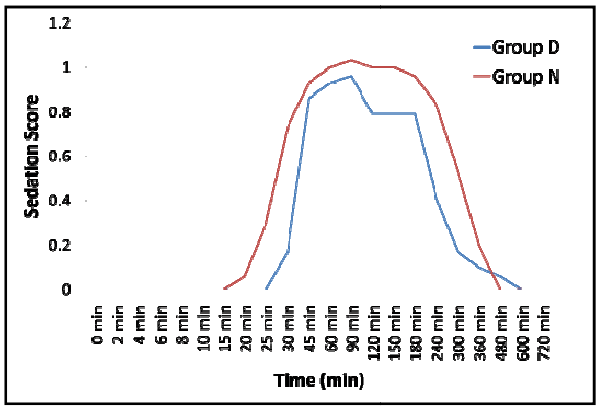
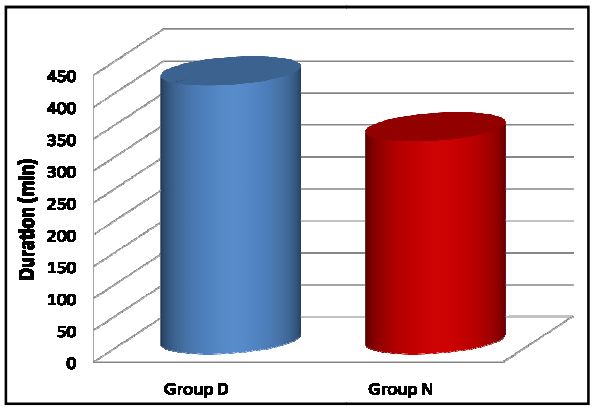


Image 6: Duration of effective analgesia



Respiratory rate was on slightly higher side with the use of dexmedetomidine. (Image-3) Intrathecal dexmedetomidine causes more sedation than intrathecal nalbuphine. (Image 5) With the use of dexmedetomidine effective duration of analgesia was higher.

Table 6: Perioperative Complication

	Group D	Group N
Hypotension (MAO<70)	2 (6.67%)	1 (3.33%)
Bradycardia (HR <60)	1 (3.33%)	1 (3.33%)
Nausea	0	0
Vomiting	0	0
Pruritus	0	0
Respiratory Depression	0	0

Discussion:

Spinal anaesthesia has been commonly used for lower abdominal and lower limb surgeries because of simplicity, speed, reliability and minimal exposure to depressant drugs. Adding an intrathecal adjuvant to local anaesthetics forms a reliable method to prolong the duration of anaesthesia. A number of adjuvants to local anaesthetics for spinal anaesthesia like opioids (fentanyl and buprenorphine), benzodiazepine (midazolam), ketamine and neostigmine have been used. In our study, we decided to compare the effects of Nalbuphine (mixed opioid) with Dexmedetomidine (α_2 adrenergic agonist), intrathecally as an adjuvant to Bupivacaine in spinal anaesthesia.[1]

Pain signals from nociceptors may results in sensitization of secondary nociceptive neurons in the dorsal horn. This is mediated by a decrease in inhibitory input or an increase in synaptic efficiency or membrane excitability triggered by wind up neurokinin and NMDA receptor mechanism. Subsequently activity in nociceptors and non-nociceptor A-beta fibres will be amplified, which leads to increase pain allodynia. Local aesthetic bupivacaine acts mainly by blockage of voltage gated sodium channels in the axonal membrane. It can also interfere with synaptic transmission by a presynaptic inhibition of calcium channels in addition to their effect on nerve conduction.

Dexmedetomidine is a α_2 agonist and is being commonly used as an additive to local aesthetic agent in subarachnoid block.[3] As a neuraxial adjuvant a2 agonists can activate a number of aminoceptive mechanisms depending on the dose, however the main site for their antinociceptive effect in physiological pain conditions seems to be spinal dorsal horn. They produce analgesia by depressing release of C-fibre transmitters and by hyperpolarization of post synaptic dorsal horn neurons. [3]

Thus both dexmedetomidine and local anaesthetics have similar action with different mechanism, enhancing and prolonging the effect of spinal anaesthesia when given in combination intrathecally.

Intrathecal opioids have ability to produce extensive analgesia when used as adjuvants and has an advantage of allowing early ambulation of patients because of their sympathetic and motor nerve sparing activities. Nalbuphine is an opioid, structurally related to oxy-morphine. It is highly lipid soluble opioid with an agonist action at the ‘k’ opioid receptor and an antagonist activity at the ‘mu’ opioid receptor. Nalbuphine and other ‘k’ agonists had provided reasonably potent analgesia in certain models of visceral nociception. [2]

Kanazi et al (2006)[8] showed that the combination of 12 mg of intrathecal bupivacaine with 3microgram of dexmedetomidine significantly shortened the onset of sensory block and motor block, in comparison with bupivacaine alone. ($p<0.001$). Similar results were found in our study.

Mukharjeeet al (2011)[9], performed a study by comparing different doses of intrathecal nalbuphine i.e. 0.2,0.4, and 0.8 mg to find out which dose prolonged post-operative analgesia without any side effects. Hence in our study we decided to compare the effect of 5microgram of dexmedetomidine with 0.8mg of nalbuphine as an adjuvant to bupivacaine in spinal anaesthesia.

Subhi M al-Ghanem et al (2009) [10] studied the supplementation of spinal bupivacaine with 5 microgram dexmedetomidine intrathecally and found that the onset time of sensory block and motor block was significantly reduced. ($p<0.001$)) Similarly we found that the onset of sensory and motor block was faster in group D than in group N.

Conclusion:

In our study we found that intrathecal dexmedetomidine in a dose of 5 microgram when given as an adjuvant to bupivacaine, decrease the mean onset of sensory and motor blockade significantly as compared to intrathecal nalbuphine 0.8mg. The duration of sensory and motor blockade was prolonged in the dexmedetomidine group in comparison with

nalbuphine group. The duration of analgesia was significantly prolonged with intrathecal dexmedetomidine. No complications were noted in any patient of either group. In our study we prove that adding an adjuvant to local anaesthetics is very helpful for longer duration of surgery and post-operative pain. We give dexmedetomidine as an adjuvant for post-operative pain relief and that is very helpful to the patient in future and for further studies.

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