

“A Clinical Comparative Study of Intrathecal Nalbuphine Versus Intrathecal Fentanyl Added to 0.5% Hyperbaric Bupivacaine For Perioperative Anaesthesia And Analgesia in Lower Abdominal Surgeries.”

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Background and Aims: Nalbuphine hydrochloride is a synthetic opioid agonist-antagonist analgesic of the phenanthrene series. Nalbuphine has been used intrathecally by various investigators to enhance the postoperative analgesia and they did not document any reports of neurotoxicity. Fentanyl is a potent mu opioid receptor agonist that was discovered to identify an improved human health analgesic over morphine, an opioid frequently associated with histamine-release, bradycardia, hyper- or hypotension, and prolonged postoperative respiratory depression.

This study was aimed to perform and demonstrate that with addition of intrathecal NALBUPHINE and intrathecal Fentanyl with 0.5% bupivacaine heavy for lower abdominal surgeries to compare duration of sensory and motor blockade, post operative analgesia and time of first rescue analgesia along with Quality of perioperative anaesthesia and Incidence of side-effects, complications and sequelae.

Methods: The proposed study was carried out in S.R.N. Hospital associated with M.L.N. Medical College, Allahabad after approval from ethical committee and obtaining written and informed consent from the patient. After complete pre-anesthetic check-up and investigation, patients with a history of clinically significant cardiovascular, pulmonary, hepatic, renal, neurologic, psychiatric, or metabolic disease were excluded from the study. 60 Adult male and female patients belonging to American Society of Anaesthesiologists (ASA) physical status I – II, age group 18-60 yrs posted for Elective Lower abdominal surgeries were included in the study after thorough clinical and laboratory examination.

Results: On the basis of observations and statistical comparison following conclusions were made

- ❖ Time for sensory regression to S2 from HSL in minutes is calculated in all three groups. It reveals that all the three groups are significantly different from each other ($p < 0.05$) and more prolongation of sensory block duration in nalbuphine group than fentanyl group and control group.
- ❖ Duration of analgesia was longer in both- group I (NALBUPHINE $(404.5 \pm 22.82$ mins) and group II (FENTANYL $(295.5 \pm 21.82$ mins) in comparison to control group III (265 ± 23.5) . But group I had longer duration of analgesia than group II $(404.5 \pm 22.82$ mins Vs 295.5 ± 21.82 mins).
- ❖ Total number of rescue analgesics required in 24 hours was lesser in both group I (NALBUPHINE $(1.85 \pm 0.74$ mins) and group II (FENTANYL (2.05 ± 0.75)) in comparison to control group (3.5 ± 0.60) . But group I had lesser number of rescue analgesics required in 24 hours than group II and group III.

Conclusion: We concluded that addition of Nalbuphine to intrathecal bupivacaine causes prolongation of duration of sensory block and duration of analgesia and less requirement of analgesics in post-operative period without increasing the side effects or complication. Addition of Fentanyl also shows all these advantages but less than that with Nalbuphine.

Keywords: Nalbuphine, Fentanyl, Perioperative analgesia and anaesthesia,

I. Introduction

Neuraxial administration of opioids in conjunction with local anaesthetics improves the quality of intraoperative analgesia and prolongs the duration of postoperative analgesia without increasing the sympathetic block. They are commonly added to local anaesthetic for potentiating their effects, reducing their doses and thereby reducing their complications and side effects and offer hemodynamic stability. They also prolong the duration of postoperative analgesia.

NALBUPHINE hydrochloride is a synthetic opioid agonist-antagonist analgesic of the phenanthrene series. It is chemically related to both the widely used opioid antagonist naloxone and the potent opioid analgesic oxymorphone. Nalbuphine when used as adjuvant to hyperbaric bupivacaine, has improved the quality of perioperative analgesia with fewer side effects. Nalbuphine¹⁶ has been used intrathecally by various investigators to enhance the postoperative analgesia and they did not document any reports of neurotoxicity. Morphine, fentanyl, and other μ -opioids come under Narcotics Act, thus their availability is a major concern in many hospitals in India as one has to go through many administrative formalities, while nalbuphine is easily available and with fewer side effects such as nausea, vomiting, pruritus, and respiratory depression but sedation and hypotension is reported in some cases.

The study aims to observe and compare primarily post operative analgesia with intrathecal Nalbuphine and intrathecal Fentanyl using hyperbaric bupivacaine for spinal anaesthesia and secondarily the onset and duration of sensory and motor block, hemodynamic effects and level of sedation.

II. Material Andmethods

The proposed study was carried out in S.R.N. Hospital associated with M.L.N. Medical College, Allahabad after approval from ethical committee and obtaining written and informed consent from the patient. After complete pre- anesthetic check-up and investigation, patients with age group between 18 to 60 years, ASA I and ASA II were included. History of clinically significant cardiovascular, pulmonary, hepatic, renal, neurologic, psychiatric, or metabolic disease and obesity (BMI>30) were excluded from the study.

The patients were allocated randomly into three groups according to the drug used:

Group I: Patients received 2.8 ml of 0.5% hyperbaric BUPIVACAINE with 600 mcg (0.6 ml) of NALBUPHINE.(total vol 3.4 ml)

Group II: Patients received 2.8ml of 0.5% hyperbaric BUPIVACAINE along with 30 mcg 0.6 ml) of FENTANYL (total vol 3.4 ml)

Group III: Patients received 2.8ml of 0.5% hyperbaric BUPIVACAINE along with 0.6 ml of NORMAL SALINE (total vol 3.4 ml).

Group I & II: were study groups and **Group III** was control.

The intrathecal adjuvant solutions were prepared under strict aseptic condition prior to performing the spinal injection by a separate resident anaesthetist who had no further involvement with the patient.. Thus the anaesthetist who managed the case was unaware of which solution had been administered.

Patients baseline non-invasive arterial pressure, pulse rate, saturation, and a continuous ECG monitoring were instituted. In left lateral position or sitting position subarachnoid block was given after skin was cleaned and draped.The patients were placed in the supine position with 10° Trendelenburg position immediately after SAB to achieve the desirable level of block.

On completion of spinal injection, all patients were monitored for the following.

1. Heart rate and saturation at baseline (pre-operative), first 5 mins then every 15 mins. Bradycardia was treated with 0.6 mg atropine intravenously. Respiratory depression was defined as respiratory rate <8 breaths/min or SpO₂ <94% on room air and treated with oxygen supplementation or ventilatory support, if required.
2. A continuous ECG monitoring done till the end of surgery.
3. Non-invasive arterial blood pressure was taken at the baseline, then after every 5 min until completion of surgery. If systolic blood pressure decreased by 20% from baseline or if the patient complained of symptoms indicative of incipient hypotention, I.V mephenteramine was administered in increments of 6 mg as required.
4. The level of anaesthesia was deemed adequate for surgery by pinprick method from dermatomes L₂ to T₆ and the highest level of sensory block achieved was noted down.
5. Motor block was assessed for both legs with a four points Modified Bromage scale.

Sensory and motor block characteristics were assessed in the normal lower limb at every 2 min interval until no pinprick sensation was achieved. All time intervals were calculated from the time of end of intrathecal injection.

Onset of sensory block, defined as time to reach sensory block at T₆, maximum cephalic level, time taken to achieve maximum sensory block, and time taken to two dermatome regressions of sensory analgesia were recorded.

Onset of motor block was defined as the time taken to achieve Bromage scale 3. Time taken to achieve complete motor blockade was also noted. The surgical anesthesia was considered to be achieved when the levels of sensory block were reached to T₆ thoracic dermatome level or above with attainment of complete motor block (Bromage-3).

For recovery of block, time to two dermatome regressions and time to complete motor recoveries were recorded. The duration of effective analgesia was taken as the time from the completion of spinal injection to the time of administration of the first rescue analgesic. Patients with VAS score ≥ 3 received diclofenac 75 mg intramuscularly for rescue analgesia. The VAS score of >3 constituted the end point of the study.

The different complications occurs in all three groups were noted for adverse effects which includes from 0-9 where 0-No untoward adverse effect,1-Hypotension,2-Hypoxia,3-Bradycardia,4-Nausea/ vomiting ,5-Restlessness,6-Shivering,7-Urinary retention,8-Pruritus,9-Surgical complications

III. Statistical Analysis

Statistical analysis was performed using Microsoft Excel 2010 and statistical software plug-ins. Continuous data was analyzed by ANOVA. Data are being represented as mean \pm SD. P < 0.05 was considered statistically significant and P < 0.001 was considered statistically highly significant. All times were recorded from injection of the spinal anaesthetic. Request for postoperative pain relief was also recorded.Details are given afterwards.

IV. Results

The present study compared the clinical efficiency of intrathecalnalbuphine and fentanyl as adjuvant to intrathecal 0.5% hyperbaric bupivacaine in 60 adult consented patients, scheduled for elective lower abdominal surgery under SAB. There was no protocol deviation and all patients successfully completed the study protocol and were cooperative with subsequent assessment. Hence, all patients were included for data analysis. Surgical procedures were performed uneventfully and there were no surgical or anesthetic complications.

Patients of all the three groups were statistically comparable regarding mean age, weight, height, gender, ASA physical status, and surgical characteristics.

The study results regarding the characteristics of sensory block are summarized in (Table 1)

Table 1: Characteristics of sensory block

Groups	I	II	III	P-value
Time from injection to HSL in min.	5.2±1.75	4.8±1.01	5.55±0.99	1.97
Time of two segment regression from HSL in min.	96.5±4.00	96.75±3.35	90.75±7.48	0.001
Time for sensory regression to S2from HSL in min.	156.5±12.57	142.0±9.09	130.0±6.48	0.0001

HSL- Highest sensory level,

Comparison between the groups:

		Time from inj to HSL (Min)	Time of 2 segment regression from HSL (min)	Time for sensory regression to S2 from HSL (min)
Group I Vs GroupII	't' value	0.885	0.214	4.18
	'p' value	0.381 (NS)	0.831 (NS)	0.0002 (HS)
Group II Vs Group III	't' value	2.37	3.273	4.807
	'p' value	0.06 (NS)	0.0023 (SS)	0.0001 (HS)
Group I Vs Group III	't' value	0.778	3.031	8.380
	'p' value	0.441 (NS)	0.004 (SS)	0.0001 (HS)

❖ NS – NON SIGNIFICANT

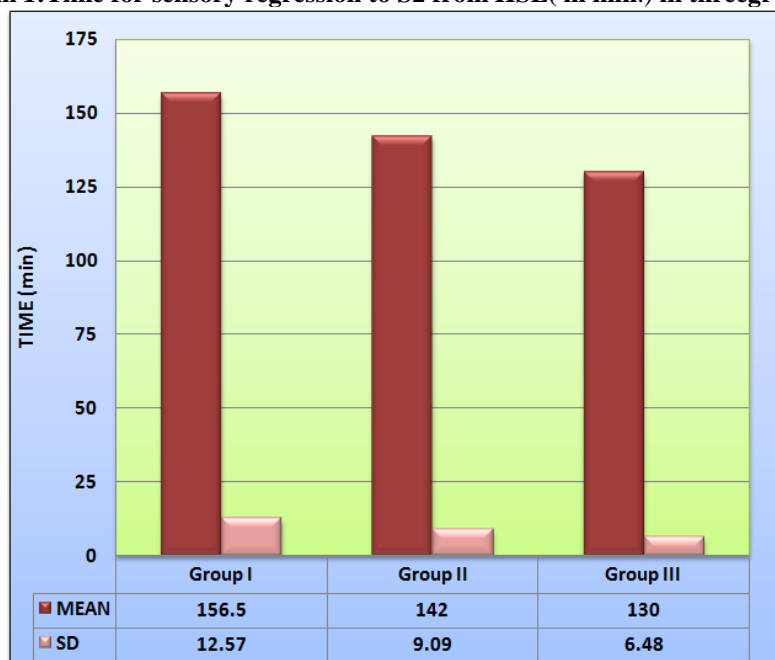
❖ SS – STATISTICALLY SIGNIFICANT

❖ HS – HIGHLY SIGNIFICANT

❖ There was no significant difference seen in time to reach highest level of sensory blockade in all the groups.

❖ For time of two segment regression from highest sensory level (HSL) in minutes there is statistically significant difference in groupIII as compared to group I and II .

Bar Diagram 1:Time for sensory regression to S2 from HSL(in min.) in threegroups(Table 1)



* Inference: Statistically ($p < 0.001$) there was highly significant difference inTime for sensory regression to S2 from HSL(in min.) amongst the three groups.

* Comparing between group I and II difference in Time for sensory regression to S2 from HSL (in min.) was highly significant.

- ❖ This means there is more prolongation of sensory block duration in nalbuphine group than fentanyl group and control group.
- ❖ There is no statistically significant difference regarding onset and duration of motor blockade in all the three groups.

Table 2: Comparison of duration of Analgesia in three groups

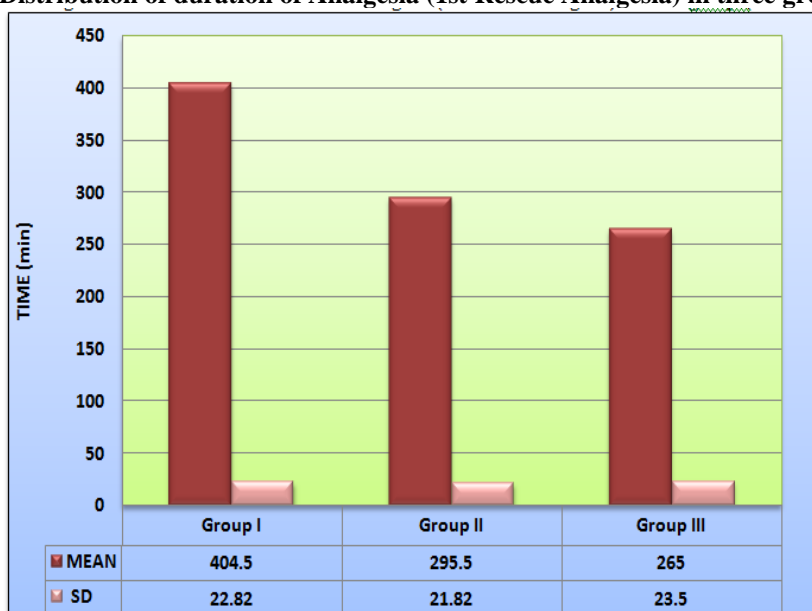
N = 20	Group I	Group II	Group Iii	P Value (Anova)
Mean ± Sd (Min)	404.5 ± 22.82	295.5 ± 21.82	265.0 ± 23.50	<0.0001
Range (Min)	370–450	250 - 340	220 – 300	

Group Comparison:

Group	‘T’ Value	‘P’ Value
Group I Vs Group Ii	15.439	0.0001(Hs)
Group Ii Vs Group Iii	4.253	0.0001(Hs)
Group I Vs group Iii	19.045	0.0001 (Hs)

- ❖ Hs – Highly Significant

Bar Diagram 2: Distribution of duration of Analgesia (1st Rescue Analgesia) in three groups (Table-2)



* Inference: Statistically (p<0.001) there was HIGHLY SIGNIFICANT difference in Duration of analgesia (min) amongst the three groups.

- ❖ Duration of analgesia was longer in group I in comparison to group II and group III, and this difference was statistically HIGHLY significant (p<0.001).
- ❖ Duration of analgesia was longer in group II in comparison to group III and this difference was statistically HIGHLY significant (p<0.001).

Table 3: Comparison of Total no. of Rescue Analgesics in 24 hrs in three groups

N = 20	Group I	Group II	Group Iii	P Value (Anova)
Mean ± Sd	1.85 ± 0.74	2.05 ± 0.75	3.5 ± 0.60	<0.0001

Table 4: Request for postoperative pain relief

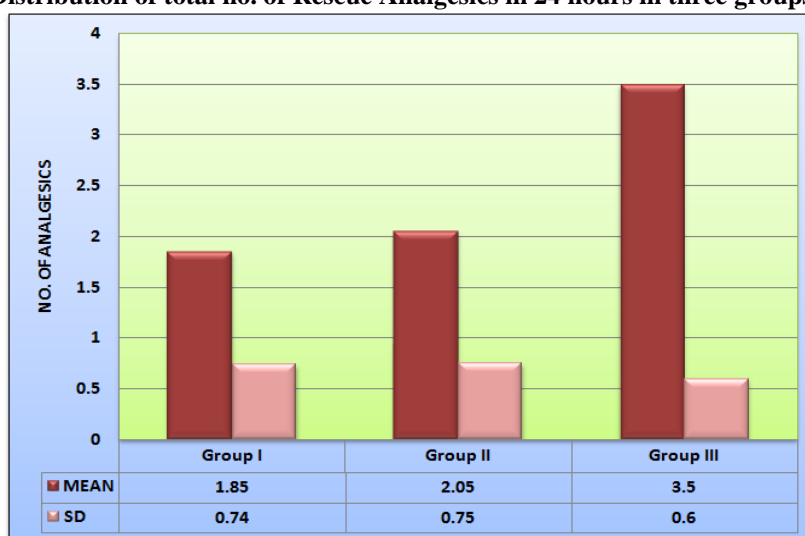
Groups	No Request for pain relief	Request for pain relief
I	18	2
II	16	4
III	10	10

Group Comparison:

Group	‘t’ value	‘p’ value
Group I vs Group II	0.848	0.0401 (S)
Group II vs Group III	6.751	0.0001 (HS)
Group I vs Group III	7.745	0.0001 (HS)

- ❖ Hs – highly significant
- ❖ S - significant
- ❖ Total no of rescue analgesics in 24 hours is lesser in group I in comparison to group II and this difference was statistically significant ($p<0.05$).
- ❖ Total no of rescue analgesics in 24 hours is lesser in group I and II in comparison to group III and this difference was statistically HIGHLY significant ($p<0.001$).
- ❖ Total no of rescue analgesics in 24 hours is least in group I and it was statistically highly significant ($p<0.001$).

Bar Diagram 4: Distribution of total no. of Rescue Analgesics in 24 hours in three groups (Table4)



* Inference: Statistically ($p<0.001$) there was highly significant difference in total no. of Rescue Analgesics in 24 hours amongst the three groups.

Adverse Effects & Complications:-

- ❖ No patient in any group had significant hypoxemia ($SpO_2<92\%$).
- ❖ There was occurrence of intraoperative and postoperative hypotension in all the groups but the difference was statistically insignificant.
- ❖ There was no occurrence of intraoperative nausea, vomiting, respiratory depression, shivering, bradycardia among all groups.
- ❖ The intraoperative sedation was present in only nalbuphine group and the difference was statistically significant (Table no. 16). But all the patients were arousable and it was not associated with respiratory depression.
- ❖ Postoperative sedation was found in both nalbuphine and fentanyl groups but the difference is statistically insignificant (Table no. 17).

V. Discussion

The combination of adjuvants to local anesthetic is synergistic for producing the analgesia of prolonged duration without measurably increasing sympathetic or motor blockade, thus allows early ambulation of patients and reduction in dosages of local anesthetics, hence the decline of their systemic side effects. Opioids selectively decrease nociceptive input from A delta and C fibers without affecting dorsal root axons or somatosensory-evoked potentials. Various μ -agonists opioids such as morphine, tramadol, nalbuphine and fentanyl are used as adjuvant to hyperbaric bupivacaine to prolong its clinical efficacy and minimize the requirement of postoperative analgesics, but they are associated with side effects of pruritus, nausea, vomiting, respiratory depression, constipation, and urinary retention.

Nalbuphine hydrochloride is a potent analgesic. Its analgesic potency is essentially equivalent to that of morphine on a milligram basis. Receptor studies show that nalbuphine hydrochloride binds to mu, kappa and delta receptors, but not to sigma receptors. Nalbuphine hydrochloride is primarily a kappa agonist/partial mu antagonist analgesic. Kappa-opioid receptors are distributed throughout brain and spinal cord areas involved in nociception. The greatest concentrations of kappa-receptors in nociceptive regions are in lamina I and II of Rexed in the spinal cord dorsal horn as well as in the spinal nucleus of the trigeminal nerve (substantia gelatinosa). Taken together, these data suggest that nalbuphine acts primarily at the level of the first synapse in the nociceptive system in producing analgesia.

The μ agonist, fentanyl exerts its action by opening K^+ channels and reducing Ca^{++} influx, resulting in inhibition of transmitter release. The μ agonist also have a direct postsynaptic effect, causing hyperpolarization and a reduction in neuronal activity .

In our study, a total of 60 patients were selected, 20 patients in each group randomly assigned in one of three groups:-

Group I: Patients received 2.8 ml of 0.5% hyperbaric BUPIVACAINE with 600 mcg (0.6 ml) of NALBUPHINE.(total vol 3.4 ml)

Group II: Patients received 2.8ml of 0.5% hyperbaric BUPIVACAINE along with 30 mcg 0.6 ml) of FENTANYL (total vol 3.4 ml)

Group III: Patients received 2.8ml of 0.5% hyperbaric BUPIVACAINE along with 0.6 ml of NORMAL SALINE (total vol 3.4 ml).

The groups were similar in respect to mean age, mean weight, sex ,mean height and were statistically not significant with $p>0.05$. By including only ASA–I and ASA–II patients, it was tried to eliminate any systemic problems confounding our results. The mean changes in heart rate, mean arterial pressure, saturation and duration of surgery during intra-operative period between groups I,II& III were statistically insignificant ($p > 0.05$).

Sensory Block :-

There is prolongation of time for two segment regression from HSL in nalbuphine and fentanyl group than control group, but there is no difference among drug groups.

Time for sensory regression to S2 from HSL is significantly prolonged in group I (nalbuphine) and group II (fentanyl) than group III (control) . There is more prolongation of sensory block duration in nalbuphine group than fentanyl group. Nalbuphine and Fentanyl increases intensity of sensory blockade and also prolongs its duration.

Tiwari et al 2013¹⁴ compared nalbuphine added to hyperbaric bupivacaine with bupivacaine alone. They concluded that the duration of sensory block and duration of analgesia was prolonged with nalbuphine without complications.

Ben David et al;¹⁵ (1997) showed that addition of fentanyl (10mcg) to a small dose of hyperbaric bupivacaine (5mg) enhanced the quality and duration of sensory block without prolonging the intensity or duration of motor block in patients undergoing knee arthroplasty.

The results of our study are consistent with that of these studies as we also found that intrathecal Nalbuphine (600mcg) and Fentanyl (30 mcg) caused prolongation of sensory block and it was statistically significant (p value <0.05).

Post-Operative Analgesia:-

Post-operative analgesia was significantly prolonged with nalbuphine group as compared to fentanyl and plain bupivacaine group.

Mukherjee et al 2011¹⁶ studied the duration of analgesia with different dosages of intrathecalnalbuphine (0.2, 0.4, and 0.8 mg) to find out the optimum dose of intrathecalnalbuphine which could prolong the **postoperative analgesia** without increasing the side effects. Their study concluded that effective analgesia was increased with increase in the doses of nalbuphine as adjuvant to 0.5% hyperbaric bupivacaine without any side effects.

Sapate et al.2013¹⁷ observed the effects of intrathecalnalbuphine (0.5 mg) with 0.5% spinal bupivacaine (3 mL) for lower abdominal surgeries in elderly patients in a randomized control study. They concluded that nalbuphine provided better quality of SAB as compared to bupivacaine alone and also enhanced the **postoperative analgesia**. No patients in their study developed any side effects.

Tiwari et al 2013¹⁴ compared nalbuphine added to hyperbaric bupivacaine with bupivacaine alone. They concluded that the duration of sensory block and **duration of analgesia** was prolonged with nalbuphine without complications.

Verma et al.2013¹⁸ compared the postoperative analgesic efficacy of intrathecal tramadol (50 mg) with nalbuphine (2 mg) as adjuvant to hyperbaric bupivacaine (12.5 mg) in spinal anesthesia for lower limb orthopedic surgery. They concluded that addition of nalbuphine to hyperbaric bupivacaine was effective in prolonging the duration of sensorimotor block and enhancing the **postoperative analgesia** following lower limb orthopedic surgery.

Ahmed et al.2016¹⁹ evaluated the potentiating effect of intrathecalnalbuphine with bupivacaine for postoperative analgesia in three different doses (0.8, 1.6, and 2.4 mg) in a randomized control study. They concluded that the combination of intrathecal bupivacaine with nalbuphine significantly **prolonged postoperative analgesia** as compared to control group and a 1.6 mg dose showed the best results.

Catherin O. Hunt et al and Varrasi et al 1989²⁰ found that intrathecal Fentanyl **increases mean duration of postoperative analgesia.**

Kang et al 1998²¹ combined intrathecal FENTANYL with heavy BUPIVACAINE during caesarean section to provide adequate depth of anaesthesia. The **duration of complete analgesia was longer** with the combination as compared to bupivacaine alone.

The results of our study are similar with that of all these studies as we also found that intrathecal Nalbuphine (600mcg) and Fentanyl (30 µg) **prolonged the duration of post - operative analgesia** which was statistically significant ($p < 0.05$).

Rescue Analgesic Requirement:-

Request for postoperative pain relief was only present in control group and the difference is found to be statistically highly significant. This means there was adequate analgesia in nalbuphine and fentanyl groups. Improved perioperative analgesia following co-administration of fentanyl or nalbuphine and bupivacaine can be explained by a synergistic inhibitory action of these agents on A delta and C fiber conduction. There is significant linear difference in VAS Score at rest and VAS score on movement trends with more scores in control group indicating inadequate analgesia.

Mostafa et al.2011²³ compared the analgesic efficacy and duration of analgesia with side effects of intrathecal tramadol 50 mg with nalbuphine 2 mg for postoperative analgesia after transurethral resection of the bladder tumor. They found the **number of rescue analgesia was less in the nalbuphine group.**

H. Singh et al²² in their study concluded that intrathecal Fentanyl **reduced requirement of analgesic** in early post operative period.

The results of our study are consistent with that of all these studies as we also found that intrathecal Nalbuphine (600mcg) and Fentanyl (30 µg) prolonged the duration of post operative analgesia which was statistically significant ($p < 0.05$) and **lesser requirement of rescue analgesic** in 24 hours as compared to control group.

VI. Conclusion

From our study we conclude that the addition of Nalbuphine to intrathecal bupivacaine causes **prolongation of duration of sensory block and post-operative analgesia and less requirement of analgesics in post-operative period** without increasing the side effects or complication. Addition of **Fentanyl also shows all these advantages but less than that with Nalbuphine.** So to establish the superiority of nalbuphine over fentanyl further studies are required .

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