Original Research Article

Intrathecal Nalbuphine vs Fentanyl with Hyperbaric Bupivacaine for Postoperative Analgesia

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Abstract
Regional anaesthesia for gynaecological procedures has emerged as an important technique with simplicity, rapid onset of action, good muscle relaxation, and safety as its added advantage. A study was designed to compare effects of intrathecal Nalbuphine and fentanyl to hyperbaric bupivacaine for gynaecological surgeries.

Material and Method: 60 patients, 20 to 60 years of age, BMI < 35 kg/m², ASA grade I and II were divided into two groups. Grp N received Inj. Bupivacaine 0.5% (H) 3 ml (15mg) + Inj. Nalbuphine 1mg in 0.5 ml NS [Total volume 3.5 ml] Group F received Inj. Bupivacaine 0.5% (H) 3ml (mg) + Inj. Fentanyl 25 µg [Total volume 3.5 ml] They were studied for onset and duration of sensory block, onset and duration of motor block, level of intra-operative sedation and postoperative analgesia with intraoperative haemodynamic stability.

Results: Time of onset of sensory block was significantly longer in Group N (267± 36.68 sec) as compared to Group F(212± 39.42 sec). The mean time for onset of motor block in Group N (353.67± 45.37 sec) was significantly longer than Group F (296.67±39.42) (p<0.0001).Mean time required for two segment regression was significantly higher (P value =0.003) in Group N(108.17±10.33min) than Group F( 101.40± 6.17min ). Duration of postoperative analgesia was significantly longer in Group N (288.33± 22.06) min. as compared with Group F (234.00 ± 20.32) min. No significant side effects or complications were observed during the study.

Conclusion: Addition of Nalbuphine shows early onset of sensory and motor block with prolonged duration of intraoperative and postoperative analgesia and hemodynamic stability.

Introduction
Spinal anaesthesia is a popularly used technique in reducing metabolic response to surgery, reduction in blood loss, decreased incidence of thromboembolism, decreased pulmonary
compromise (particularly in patients with advanced pulmonary disease) and ability to monitor patient’s mental status.

Bupivacaine Hydrochloride is a long acting amide local anaesthetic. It has high potency, slow onset (5-8 min) and long duration of action (1.5 – 2 hrs). Various adjuvants like opioids have been used with bupivacaine in spinal anaesthesia to intensify the sensory block and prolong postoperative analgesia.

Fentanyl is a lipophilic opioid with a rapid onset. It does not migrate to the 4th ventricle in sufficient concentration to cause respiratory depression. It improves the quality of anaesthesia without producing significant side effects and also improves post-operative analgesia and hemodynamic stability.

Nalbuphine is a drug with mixed µ antagonist and k agonist properties. It has the potential to maintain or even enhance µ-opioid based analgesia while simultaneously minimizing the µ-opioid related side effects. Nalbuphine and other k agonists have provided potent analgesia in certain models of visceral nociception. They demonstrate complicated interactions with µ opiates that suggest dose-dependent synergies and significant antagonism at larger doses.

Hence, Nalbuphine is considered as an preferred adjuvant drug in terms of its ability to prolong postoperative analgesia, produce an antagonism of the side effects attendant to spinal opiates, e.g. respiratory depression, pruritus and urinary retention.

This study is designed to compare effects of Nalbuphine vs Fentanyl to hyperbaric bupivacaine for gynaecological surgeries.

Objectives
a) To compare onset and duration of sensory block.
b) To compare onset and duration of motor block.
c) To study level of intra-operative sedation.
d) To compare vitals like H.R, B.P., R.R., SpO₂.
e) To compare postoperative analgesia.

Material and Methods
After approval from ethical committee, the study was carried out on 60 ASA grade I and II females aged between 20 to 60 years, BMI < 35 kg/m², posted for Gynaecological surgeries. Patients were randomized into 2 groups with 30 in each group. Written valid Informed consent was taken from the patients for the procedure. A detailed history and thorough general and systemic examination was performed. Patients with allergic reaction to study drug, not willing for spinal anaesthesia, Patients with heart block, dysarrythmias, uncontrolled hypertension, patient on therapy with adrenergic receptor antagonists, calcium channel blocker, ACE inhibitor, coagulation disorder, infection on back, sever hypovolaemia, neurological disorder, raised intracranial tension, deformities of spine, patients with significant cardiovascular, renal and hepatic dysfunction and morbidly obese patients were excluded from the study.

Investigations like haemogram, urine routine and microscopic examination, KFT, LFT, ECG, CXR, BSL were performed prior to surgery. All patient were premedicated with Tab. Alprazolam 0.5 mg. and Tab. Ranitidine 150 mg. orally night before surgery. Preoperatively patients were preloaded with ringer lactate 10 ml/kg. All patients were monitored for Heart rate, NIBP, pulse oximetry and ECG. Patients were given sitting position and under all aseptic precautions lumbar puncture was performed with 23G spinal needle at L3-L4 intervertebral space. Patients were randomized on the basis of sealed envelope technique.

Aims
The aim of this study is to compare the effects of 1mg of Nalbuphine with 25 µg Fentanyl as an adjuvant to 15 mg of hyperbaric Bupivacaine, on onset and duration of sensory and motor block, intraoperative hemodynamic stability and postoperative analgesia.
Group N- Inj. Bupivacaine 0.5% (H) 3 ml (15mg) + Inj. Nalbuphine 1mg in 0.5 ml NS [Total volume 3.5 ml]
Group F- Inj. Bupivacaine 0.5% (H) 3ml (mg) + Inj. Fentanyl 25 µg [Total volume 3.5 ml]

Patient were made to lie supine. All patients were given 4 lit/min supplemental oxygen with face mask.

1. Sensory block assessment

Onset of sensory level was defined as time interval from completion of subarachnoid injection i.e zero time to loss of pinprick sensation at umbilicus (T10). Maximum sensory level was tested in midclavicular line every minute until the level is stabilized for two consecutive tests and thereafter every 15 min till two segment regression. Time taken to achieve maximum sensory level and 2 segment regression was noted.

Postoperatively time taken from administration of drug to time patient first demanded analgesic was noted and considered as duration of effective analgesia.

2. Motor block assessment

It was assessed by straight leg raising while lying supine and was graded according to The Bromage scale.
Grade 0- no motor block
Grade 1- inability to raise extended leg
Grade 2- inability to flex knee but able to flex ankle
Grade 3- inability to flex ankle complete motor block

Onset of motor block was defined as time taken from injection of drug till patient was unable to flex ankles.
Recovery from motor block was recorded every 15 min. Recovery of motor block was defined as ability of patient to flex hip. Duration of motor block was calculated from 0 time up to recovery of motor block.

3. Hemodynamic stability

Pulse rate and blood pressure were monitored immediately after injection and then every 2 min till 10 min and every 5 min for 30 min and then every 15 min till the end of surgery and recovery from block.

Hypotension was defined as fall in systolic BP more than 30% of baseline value. It was treated with leg elevation, O2 supplementation, IV fluids, Inj Mephenteramine 6 mg IV.

Bradycardia was defined as fall in pulse rate below 60/min. Inj Atropine was kept ready as rescue drug for bradycardia. Continuous monitoring of O2 saturation was done. Inj Ondensetron 4 mg IV was given for nausea and vomiting. Postoperative neurological symptoms and headache were enquired.

4. Central effects

The sedation was graded as per RAMSAY sedation scale.

| Score | Criteria |
|-------|----------|
| I     | Patient is anxious, agitated and restless or both. |
| II    | Patient is co-operative, oriented and tranquil. |
| III   | Patients respond to verbal commands only. |
| IV    | Patient exhibits brisk response to glabellar tap or loud auditory stimulus |
| V     | Patient exhibits sluggish response to glabellar tap or loud auditory stimulus. |
| VI    | Patient exhibits no response |

5. Duration of postoperative analgesia

Duration of postoperative analgesia was measured from the time of injection of spinal anaesthesia to the time when pain score becomes more than or equal to 4 according to VAS. Then patient was given Inj Diclofenac 75mg IV.

VAS score
0- No pain
1, 2, 3- mild pain
4, 5, 6- moderate pain
7, 8, 9 - severe pain
10 -worst pain

6. Side effects

Intraoperative side effects like sedation, nausea, vomiting, shivering, bradycardia, hypotension requiring active treatment were also noted.

Patients were observed for postoperative complications like nausea, vomiting, shivering, dryness of mouth, any neurological sequelae like pain and dysesthesias in buttocks, thigh or lower
limb, post dural puncture headache till their discharge from hospital.

Results
Demographic, sensory and motor onset and duration, hemodynamic parameters and postoperative analgesia were presented as mean±SD, categorical values were expressed in actual numbers and percentages. Unpaired t test was performed to compare demographic, sensory and motor onset and duration, hemodynamic variable, postoperative analgesia between two groups. Categorical variables (side effects) were compared by Chi square test. P value of less than 0.05 was considered as statistically significant.

Data analysis is done with the help of appropriate SPSS Software version 24.

Both the groups were comparable for Age, Height, Weight and BMI. The mean age in Group N was 46.56± 7.91 and 46.10± 8.09 in Group F (p=0.797).

The mean weight of the patients in Group N was (51.73± 4.02 kg) and (52.33± 5.09 kg) in Group F (p=0.614). The mean Height of the patients in group N was (154.50± 3.23 cm) and in Group F was 154.93± 3.43 cm (p=0.617). The mean BMI of the patients in Group N was 21.65± 1.27 and 21.78± 1.79 in Group F (p= 0.754). Hence the difference was statistically not significant in any of parameter.

Table 1: Comparison of Mean Time of Onset of action

| Parameter         | Group N Mean ± SD(sec) | Group F Mean ± SD (sec) | t-value | P-value |
|-------------------|------------------------|-------------------------|---------|---------|
| Onset Sensory     | 267.0± 36.68           | 212.00 ± 30.89          | 6.29    | <0.0001 |
| Onset Motor       | 353.67± 45.37          | 296.67 ± 39.42          | 5.17    | <0.0001 |

The mean time of onset of sensory block was significantly longer in Group N (267± 36.68 sec) as compared to Group F (212± 39.42 sec). This difference was statistically highly significant. (p<0.0001)

The mean time for onset of motor block in Group N (353.67± 45.37 sec) was significantly longer than Group F (296.67±39.42)and the difference was very significant (p<0.0001).

Table 2: Comparison of Mean Time to Maximum cephalic spread

| Parameter         | Group N Mean ± SD     | Group F Mean ± SD     | t-value | P-value |
|-------------------|-----------------------|-----------------------|---------|---------|
| Mean Time (min)   | 7.93± 1.05            | 7.37 ± 0.83           | 2.32    | 0.023   |

The Mean time to achieve maximum cephalic spread was less in Group F (7.37± 0.83 min) as compared to Group N (7.93± 1.73 min). This difference was found to be statistically significant (P=0.023).

Table 3: Comparison of Two segment regression of sensory block

| Parameter         | Group N Mean ± SD     | Group F Mean ± SD     | t-value | P-value |
|-------------------|-----------------------|-----------------------|---------|---------|
| Two segment regression(min) | 108.17± 10.33 | 101.40 ± 6.17     | 3.08    | 0.003   |

Mean time required for two segment regression of motor block Group N(108.17±10.33min) than Group F was statistically significant (P value =0.003) in (101.40± 6.17min).

Table 4: Comparison of Mean duration (min) of block

| Parameter         | Group N Mean ± SD     | Group F Mean ± SD     | t-value | P-value |
|-------------------|-----------------------|-----------------------|---------|---------|
| Duration of Sensory block | 192.83± 13.56 | 172.17 ± 10.06     | 6.70    | <0.0001 |
| Duration of Motor block | 163.50 ± 11.23 | 160.67± 10.31     | 1.01    | 0.313   |
The mean duration of sensory block was found to be longer (192.83±13.56 min) in Nalbuphine group than Fentanyl group (172.17± 10.06 min). This difference was found to be statistically significant (P value <0.0001)

Mean duration of motor block was (163.50±11.23min) in Group N and (160.67± 10.31 min) in Group F. However the difference was statistically insignificant (p=0.313)

Table 5: Comparison of Mean Duration of Postoperative Analgesia(min)

| Parameter            | Group N Mean ± SD | Group F Mean ± SD | t-value | P-value |
|----------------------|-------------------|-------------------|---------|---------|
| Post operative Analgesia(min) | 288.33± 22.06     | 234.00 ± 20.32    | 9.99    | P<0.0001|

Duration of postoperative analgesia was significantly longer in Group N (288.33± 22.06) as compared with Group F (234.00 ± 20.32). This difference was statistically highly significant (P<0.0001).

Thus, Nalbuphine (group N) had longer duration of effective analgesia than Fentanyl (Group F).

Table 6: Comparison of Side Effects

| Side Effects | Nalbuphine Group | Fentanyl Group | Chi-square value | p-value |
|--------------|-----------------|---------------|-----------------|--------|
| No | % | No | % |              |       |
| Bradycardia | 0 | 00 | 1 | 3.33% | 1.20 | P=0.313 NS |
| Hypotension | 3 | 10.0% | 1 | 3.33% | 1.07 | P=0.302 NS |
| Nausea | 1 | 3.33% | 1 | 3.33% | 0.00 | P=1.00 NS |
| Pruritus | 0 | 0 | 2 | 6.67% | 2.07 | P=0.150 NS |
| Shivering | 0 | 0 | 1 | 3.33% | 1.20 | P=0.313 NS |

(Chi square test is applied. P value is significant if <0.005)

In our study the incidence of bradycardia was 0% in Nalbuphine group and 3.3% in Fentanyl group whereas incidence of hypotension was 10% in Nalbuphine group and 3.3% in Fentanyl group. The incidence of nausea and vomiting in both groups was 3.3%

Two patients (6.7%) in Group F experienced pruritus and one patient (3.3%) had shivering. No patient in Group N experienced pruritus or shivering. However no active management was required.

The differences seen were found to be statistically insignificant after applying Chi square test. (P value>0.05). Respiratory depression (RR <10 breaths / min) and retention of urine was not observed in any of the patients in either group. No other side effects like headache, back pain, residual neurologic deficit or transient neurological symptoms were observed in our study.

All patients were compared for haemodynamic parameters in the preoperative and intra operative period in Group N and F .It was observed that mean pulse rate, mean systolic and diastolic blood pressure, SpO2 and sedation score in either group was comparable and statistically insignificant.

VAS score was used to assess pain postoperatively initially every 1 hr for 2 hrs then every 2 hrs for next 8 hrs and then every 4 hrs till 24 hrs. When score was found more than 4, Injection Diclofenac sodium was given IV as a rescue analgesic in the dosage of 1.5 mg/kg. 24 hours VAS score in postoperative period was less in Nalbuphine group as compared to Fentanyl group. This difference was statistically significant (p<0.05)

**Discussion**

Perioperative and postoperative pain management is one of the important task to anaesthesiologist. Uncontrolled pain in the postoperative period can greatly impede the return of normal pulmonary functions like inability to cough, bronchospasm leading to atelectasis and hypoxemia especially in...
upper abdominal and thoracic surgeries. Pain promotes immobility and hence increased risk of deep vein thrombosis. Stress response induces catecholamine release, increased oxygen demand and cardiac work. Increased catabolic response to surgical trauma impairs immune mechanisms and delays wound healing. Thus, postoperative pain treatment should be started even before it occurs.Regional anaesthesia for gynaecological surgeries has advantages over general anaesthesia. It reduces incidence of deep vein thrombosis, pulmonary embolism, cardiac complications in high risk patients, bleeding & transfusion requirement. Regional anaesthesia may also preserve immunity perioperatively and allow earlier wound healing.

However, spinal anaesthesia using only local anaesthetics is associated with relatively short duration of action, and hence adjuvants are added to prolong the duration of intraoperative and postoperative analgesia. Among various adjuvants Fentanyl is a popularly used adjuvant.

Seewel et al found a significant improvement in the duration and quality of analgesia produced by intrathecal Fentanyl and Bupivacaine compared to intrathecal Bupivacaine alone. Vaghadia et al observed that 20-30µg Fentanyl with bupivacaine produces faster block onset time, improved intraoperative analgesia and decreased incidence of intraoperative nausea and vomiting with excellent quality of perioperative analgesia. The effectivity of fentanyl is due to its lipophilic mu receptor agonist activity.

Nalbuphine a mixed µ antagonist and κ agonist has the potential to maintain or even enhance µ-opioid based postoperative analgesia while simultaneously minimizing the µ-opioid related side effects like respiratory depression, pruritus and urinary retention.

Nalbuphine has been used intrathecally in varying doses ranging from 0.2 to 2.4 mg. Swati Bisht and Rashmi Dubey studied the effect of Nalbuphine 1mg to 3ml of 0.5% hyperbaric Bupivacaine and compared it with Fentanyl 25µg added to 0.5% Bupivacaine 3 ml. They concluded that Fentanyl had shortened the time to achieve maximum sensory level (6.31 ± 0.58 min) as compared to Nalbuphine (6.76±0.54 min).

In our study, mean time for the onset of sensory block was significantly shorter (p<0.001) in Group F (212.0±30.89 sec) as compared to Group N (267.0±36.68 sec). Whereas time to achieve motor block required was more with Nalbuphine group than Fentanyl group.

We observed the maximum cephalic spread up to T4 in 26.67% patients in Group N and 33.33% patients in Group F and up to T6 in 66.67% in Group N and 63.33% patients in Group F. The mean time to achieve onset of motor block in Group N (353.67±45.37sec) was significantly higher (P<0.000) than Group F (296.67±39.42sec). Postoperatively, mean time taken for 2 segment regression was significantly higher (P value=0.003) in Group N (108.17±10.33min) than Group F (101.40±6.17min).

Gupta K, Rastogi et al observed significantly longer duration for two segment regression with 2 mg Nalbuphine (127.86 ± 18.23 min) as compared to 25µg Fentanyl (116.75 ± 12.82 min). Duration of motor block was calculated from 0 time up to recovery of motor block. Mean duration of motor block was significantly higher in group D (301.67±19.45min) as compared to group F (267.50±11.2).

The duration of postoperative analgesia was noted and was found to be significantly longer in Group N(288.33±22.06min) as compared with Group F (234.00±20.32 min). Similar results were observed by Swati Bisht et al in which time of rescue analgesia was 460.78 ± 77.98 min in nalbuphine group as compared to 283.44 ± 78.97 min in Fentanyl group.

The capacity of spinal opiates to reduce the release of excitatory neurotransmitter from C fibres and to decrease the excitability of dorsal horn neuron is believed to account for the powerful and selective effect of opiates on spinal nociceptive processing.

In our study the mean sedation scores were found to be comparable during various time intervals.
and statistically insignificant (p>0.05) preoperatively and intraoperatively among the two groups. Intraoperative sedation in any form was avoided to minimize the interference during assessment of the blockade characteristics.

Preoperative baseline parameters like mean baseline pulse rate (PR), mean systolic blood pressure (SBP), mean diastolic blood pressure (DBP), mean arterial pressure (MAP), mean Respiratory rate (RR), peripheral oxygen saturation (SPO2) were comparable and statistically insignificant (p>0.05) between two groups.

Opioids are known to depress all phases of respiration by their action on the opioids receptors in the ventral medulla, irrespective of route of administration, but one of the serious side effects is respiratory depression reported after both intrathecal and epidural injections. But, it is not necessary to nurse these patients in an ICU, and simple bedside assessment of level of consciousness and respiratory rate is adequate. Guidelines have been issued by European Society of Regional Anaesthesia, that irrespective of age all patients who receive spinal opioids can be nursed in regular wards. (9)

Intrathecal narcotics, along with enhancing the sensory blockade, provide prolonged postoperative analgesia. But it is associated with increased risk of nausea, vomiting, itching and respiratory depression(10). Fentanyl is a µ receptor agonist which can be administered safely in subarachnoid space. It is highly lipophillic which prevents its rostral spread. But, systemic absorption of the drug could contribute to the lower respiratory rates by direct depressant action on µ receptors in brainstem. We did not observe respiratory depression in our study as Fentanyl is a highly lipid soluble opioid known to penetrate and egress rapidly from the CSF and this leaves only small quantities of free drug in the CSF for redistribution to higher centres and are therefore less prone to cause delayed respiratory depression. Nalbuphine has not been reported to produce any respiratory depression.

In our study the incidence of bradycardia was 3.3% in Fentanyl group and none of the patient in nalbuphine group experienced bradycardia. The patients were treated with Inj Atropine 0.6mg IV. The incidence of hypotension was 10% in nalbuphine group and 3.33% in Fentanyl group. Hypotension was treated with leg elevation, IV fluids and Inj Mephenteramine 3mg IV.

In our study the incidence of nausea and vomiting was 3.3% in both the groups (Group N and Group F). It was treated with inj. Ondansetron 4 mg IV.

After spinal injection, opioids undergo redistribution by rostral spread leading to direct stimulation of chemoreceptor trigger zone in the floor of fourth ventricle thereby causing nausea and vomiting.

The likely cause of pruritus with spinal opioids is cephalad migration of opioids in CSF, and subsequent interaction of opioids receptors in trigeminal nucleus. Opioids release histamine from mast cells can be another reason of pruritus (11).

The VAS score was significantly less in Group N as compared to Group F for during all time intervals postoperatively.

Conclusion

It can be concluded that addition of intrathecal 1mg Nalbuphine to Bupivacaine in the present study provided with a considerably higher duration of sensory block to carry out surgeries, having sufficient time for 2 segment regression with minimum intraoperative side effects and greater duration of postoperative analgesia than 25µg of Fentanyl. It also offers better haemodynamic stability throughout the procedure. The side effects like respiratory depression, pruritus or urinary retention can be better avoided by the use of Nalbuphine and hence can be preferred over fentanyl.
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