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ORIGINAL ARTICLE

# Comparison of intrathecal fentanyl and nalbuphine: A prospective randomized controlled study in patients undergoing total abdominal hysterectomy

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## ABSTRACT

Objectives: 0.5% bupivacaine used in subarachnoid block provides only about 3 hours of analgesia. Opioids especially morphine and fentanyl are used as adjuvants to produce extended postoperative analgesia. Nalbuphine is an agonist antagonist and does not require a narcotic license, which is a must for procuring other opioids, so is easily available even in peripheral hospitals. This study was carried out to evaluate the efficacy of nalbuphine versus fentanyl as intrathecal adjuvant.

Methodology: One hundred ASA 1-3 patients, aged 30-65 years posted for elective total abdominal hysterectomy (TAH) were included in this study and were randomly divided into two groups of fifty each. Group FB received 15 mg of 0.5% bupivacaine (3 ml) plus 25 µg of fentanyl (0.5 ml) and Group NB received 15 mg 0.5% bupivacaine (3 ml) plus 1 mg nalbuphine (0.5 ml). No sedative or analgesic was given preoperatively. The parameters noted were; the time for sensory block to reach T10 dermatome, time for the sensory level to fall from T6 to T8 dermatome, time for the first request of rescue analgesia, duration of motor block and any untoward side effect or complications. The statistical analysis was performed by STATA 11.2 (College Station TX USA). Students t-test were performed for to find the significance difference between the study parameters.

Results: The onset of sensory blockade, time to attain peak sensory block and complete motor block was significantly faster in Group FB ($p < 0.001$). The duration of motor block was comparable in both the groups. The time for sensory block to regress by two segments was significantly longer in Group NB, 97.72 ± 9.50 min, than in Group FB, 88.88 ± 9.48 min. The time to first analgesic requirement in Group NB was 460.78 ± 77.98 min compared to 283.44 ± 78.97 min in Group FB ($p < 0.001$). No statistical difference was seen in terms of adverse effects. Two patients in both groups complained of nausea. Hypotension and pruritus were seen in two and one patient respectively in Group FB.

Conclusion: Although the time to onset and peak sensory level is longer with nalbuphine as intrathecal adjuvant than fentanyl, time for sensory level to regress by two segments and the postoperative analgesia time is longer with nalbuphine. So, nalbuphine is a good adjuvant in spinal anesthesia and has an advantage in centers without narcotics license.

Key words: Nalbuphine; Intrathecal adjuvant; Fentany.

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## INTRODUCTION

Total abdominal hysterectomy (TAH) is preferably done under regional anesthesia as it is less cumbersome compared to general anesthesia, and offers good control on the stress response, reduced blood loss and good muscle relaxation. Hyperbaric bupivacaine used alone gives analgesia for 2-3 hours only. Additives used with bupivacaine can enhance the intensity of the block and duration of the postoperative analgesia. Intrathecal opioids have been widely used as adjuncts, resulting in a longer duration of analgesia and good patient satisfaction.[1,2,3,4]

Intrathecal opioids bind to pre and postsynaptic opioid receptors in lamina 1 and 2 of the dorsal horn. The mu and delta opioid receptor activation causes G protein mediated K channel opening while kappa opioid receptor activation causes $Ca^{++}$ channel closure. These events lead to a fall in intracellular $Ca^{++}$ levels, reducing the release of excitatory neurotransmitters and hence antinociception.[3,4]

Fentanyl, a potent synthetic mu agonist has been used extensively in intrathecal route to improve the quality and duration of anesthesia, but minimal side effects.[5] It is a potent synthetic mu receptor agonist. Fentanyl has structural similarities to local anesthetics. It has local anesthetic action on the primary afferent sensory C nerve fibers causing analgesia.

Nalbuphine hydrochloride is a mixed agonist-antagonist synthetic opioid. It act as agonist at kappa and antagonist or partial agonist at mu receptors. It has agonist action at kappa receptors and is antagonist at mu receptors.[6,7] Therefore, it produces analgesia without producing mu receptor associated adverse effects.[8,9] Nalbuphine is freely available, whereas, fentanyl is less readily available due to regulatory restrictions. Hence, we conducted this study to compare the effects of nalbuphine and fentanyl as adjuvants to intrathecal 0.5% bupivacaine in patients undergoing TAH.

## METHODOLOGY

On obtaining the departmental ethical committee approval and written informed consent, one hundred patients ASA 1-3, aged 30-65 years, posted for elective TAH in our institution were included in this study. This was a prospective randomized double blind study. A thorough pre-anesthetic checkup followed by a series of lab investigations like hematocrit, coagulation profile, electrocardiogram, chest x ray, blood sugars, electrolytes were conducted. Patients with contraindication for spinal anesthesia were excluded from this study. The patients were randomly allocated to two groups of fifty each by computer generated program -Research Randomizer.

All patients were familiarized with the visual analogue pain scale- 0 being no pain and 10 worst pain imaginable. They were also briefed about the pin prick method of sensory assessment and lower limb movement for motor block assessment. A good peripheral intravenous access was secured with 18 g cannula and preload was done No sedative or analgesic was given preoperatively with 10 ml/ kg ringer lactate solution. Intraoperative routine monitoring was done. Spinal anesthesia was administered with the patients in the sitting posture at L3-4 interspace in the midline with 26 gauge spinal needle. The drug was loaded and handed over by the assistant. Group FB received 15 mg of 0.5% bupivacaine (3 ml) plus 25 µg of fentanyl (0.5 ml) and Group NB received 15 mg 0.5% bupivacaine (3 ml) plus 1 mg nalbuphine (0.5 ml). The anesthesiologist was not aware of what the adjuvant was being given. The patients were immediately made supine with 10 degree Trendelenburg tilt. Any fall in heart rate below 50/min was treated with atropine 0.6 mg. A fall in systolic blood pressure below 20% of the baseline reading was managed by inj ephedrine 6 mg in increments. Any signs of respiratory depression were noted and were dealt with oxygen supplementation and assisted ventilation.

We compared the characteristics of the subarachnoid block between the two groups. After the intrathecal instillation of the drugs, the time for sensory block with pin prick method, to reach T10 dermatome (the umbilicus) was noted as 't10'.The time for the loss of sensation to reach T6 dermatome, the peak sensory level, was taken as 't6'. The time to complete motor block, 'tm', was taken as inability to flex the knee (Bromage 3). The time for the sensory level to fall from T6 to T8 dermatome, 't8' was also recorded. The time for effective analgesia, i.e. the time for the first request of rescue analgesia was taken as 'ta'. Duration of motor block, i.e. time to reach Bromage 1; just able to move knees was noted as 'dm'. Any untoward events were looked and noted. Diclofenac 75 mg was given intramuscularly as a rescue analgesic.

Statistical methods: The statistical analysis was performed by STATA 11.2 (College Station TX USA). Students t-test were performed to find the significance difference between the group regarding age, height, weight, onset of sensory blockade, time to peak sensory block, time to attain complete motor block, 2 segment regression of sensory level (t8), duration of motor block, time to first analgesic with the treatment

Table I: Demographic profile of the two groups

| Parameter | Fentanyl | Nalbuphine | p-value |
|---|---|---|---|
| Age | 52.26 ± 8.13 | 50.34 ± 8.55 | 0.252 |
| ASA Grade | | | 0.910 |
| I | 27 (54%) | 29 (58%) | |
| II | 18 (36%) | 16 (32%) | |
| III | 5 (10%) | 5 (10%) | |
| Height | 155.92 ± 9.04 | 157.88 ± 6.26 | 0.211 |
| Weight | 57.32 ± 6.95 | 58.06 ± 4.65 | 0.534 |

Table 2: Characteristics of spinal anesthesia

| Parameter | Fentanyl | Nalbuphine | p-value |
|---|---|---|---|
| Onset of sensory blockade (t10) min | 3.09 ± 0.47 | 4.20 ± 0.52 | < 0.001 |
| Peak Sensory Blockade (t6) [min] | 6.31 ± 0.58 | 6.76 ± 0.54 | < 0.001 |
| Time to attain complete motor block (tcm) | 6.85 ± 0.66 | 7.93 ± 0.67 | < 0.001 |

Table 3: Regression of block with nalbuphine and fentanyl [Mean ± SD]

| Variable | Fentanyl | Nalbuphine | p-value |
|---|---|---|---|
| 2 segment regression of sensory level (t8) [min] | 88.88 ± 9.48 | 97.72 ± 9.50 | < 0.001 |
| Duration of motor block (dm)[min] | 136.24 ± 12.23 | 129.78 ± 24.07 | 0.096 |
| time to first analgesic (ta) [min] | 283.44 ± 78.97 | 460.78 ± 77.98 | < 0.001 |

Table 4: Types of adverse effects with nalbuphine and fentanyl

| Adverse effect | Fentanyl Group | Nalbuphine Group | Total |
|---|---|---|---|
| Hypotension | 2 (4%) | 0 | 2 |
| Nausea | 2 (4%) | 2 (4%) | 4 |
| Pruritus | 1 (2%) | 0 | 1 |
| Total* | 5 (10%) | 2 (4%) | 7 (7%) |

*p-0.240

groups (fentanyl and nalbuphine) and expressed as mean and standard deviation. Chi square or fisher exact test was used to measure the association between the adverse event, ASA grade and the treatment groups. P < 0.05 was considered as statistically significance.

## RESULTS

There was no significant difference between two groups in regards to age, ASA grade, height or weight (Table 1).

The onset of sensory block was faster in group FB than in group NB (p < 0.001). Time to attain peak sensory blockade was faster in group FB (p value < 0.001) (Table 2). Time for complete motor block was significantly shorter in group FB, as compared to group NB (p < 0.001) (Table 2). The time to two segment sensory level regression was longer in Group NB, than Group FB (p < 0.001) (Table 3). The duration of motor block in Group FB was comparable to that in Group NB (p = 0.096). The time to first analgesic requirement was significantly prolonged in Group NB as compared to Group FB (p < 0.001) (Table 3). There was no statistical difference in the adverse events in the two groups (p = 0.240). In Group FB two patients developed hypotension and one had pruritus. Nausea was seen in two patients in either group (Table 4). No active intervention was required. None developed respiratory distress.

## DISCUSSION

Intrathecal opioids have a significant place in management of acute postoperative pain. The presence of intrinsic opioid apparatus in human body has popularized their use both intrathecally and in epidural. Intrathecal opioids do not produce analgesia solely by acting on spinal cord receptors, a phenomenon described as spinal selectivity of an opioid.

Some of intrathecal opioid absorbs back in the blood stream and produces analgesia by stimulating opioid receptors at brain level. Degree of this absorption is mainly determined by lipophilicity of the drug. Highly lipid soluble opioids like fentanyl or sufentanyl diffuse into blood stream quickly compared to less lipophilic morphine therefore producing short duration of analgesia. Morphine, in addition to producing prolong analgesia at spinal level, however, can travel rostrally into cerebrospinal fluid resulting in delayed respiratory depression due to its slower clearance form intrathecal space.[10] However morphine is associated with a higher incidence of adverse effects. Lipophilic opioids given intrathecally tend to sequestrate in the epidural fat and are rapidly cleared from plasma. This does not let them to get a good concentration at the site of action. This explains the limited intensity and duration when given intrathecally. The analgesic property of the intrathecal opioids is attributed to spinal selectivity. The lipophilic ones due to their good vascular uptake and redistribution rapidly reach higher concentration in the brain as well.[10] They do not produce

sympathetic and motor block but enhance analgesia, and this property makes opioids as good adjuncts. Early postoperative ambulation is possible as the volume of bupivacaine gets reduced.[11,12]

Nalbuphine is a lipophilic opioid with agonist action at the kappa opioid receptor and antagonist at the mu receptor. Unlike morphine, it has a short duration of action due to its liposolubility and rapid plasma clearance.[13] Nalbuphine interferes in the nociceptive pathway by post synaptic inhibition of interneurons and output neuron of spinothalamic tract. Its analgesic potency is equivalent to morphine on weight basis and causes respiratory depression in same degree as equianalgesic morphine dose, but has a ceiling effect. Doses above 30 mg do not aggravate respiratory depression.

There is limited data on comparison of spinal effects of nalbuphine and fentanyl; the latter being more lipid soluble has a rapid tissue uptake compared to nalbuphine. H M Gomaa et al.[14] compared the effects of intrathecal nalbuphine and fentanyl in cesarean patients and concluded that there was no significant difference in onset and duration of sensory and motor block but the onset of motor block was faster with fentanyl. We observed that the duration of motor block in the two groups as not significantly different. Also the time for sensory block to fall by two segments i.e., from T6 to T8 level was lesser in group FB compared to group NB. Again the pharmacokinetics of fentanyl explains it. This result was consistent with that of a study by Gomaa et al.[14]

The time of first analgesic requirement was less in group FB than Group NB. Postoperative analgesia was more prolonged with intrathecal nalbuphine than fentanyl. Gupta et al.[15] studied the two drugs intrathecally and observed that 2 mg nalbuphine extended the duration of sensory block and extended postoperative analgesia more than fentanyl. Culebras et al.[16] also studied these drugs intrathecally in cesarean patients and concluded that nalbuphine prolonged analgesia without any side effects. Mukerjee et al.[17] studied 0.2 mg, 0.4 mg, and 0.8 mg nalbuphine and came the conclusion that a higher intrathecal dose resulted in better analgesia without increasing adverse effects. No significant side effects were encountered. We also observed no major side effects. Two patients developed hypotension and one developed pruritus in group FB. Only two patients complained of nausea in our study. The incidence of pruritus is higher with high doses, but there are conflicting results in various studies for average doses.[4,18,19] Pruritus is mainly in the face and is a known opioid side effect. Its cause is the presence of a type of C fibers mediating the itch response linked to central receptor network. Quite a number of mu opioid and 5HT3 receptors are located in and around the trigeminal nucleus

We did not encounter respiratory depression in any of our patients in either groups. The risk of respiratory depression is increased with increasing age, presence of chronic respiratory disease or concomitant use of sedatives; all of these factors were not present in our study subjects.

## CONCLUSION

We conclude that nalbuphine is a good intrathecal adjuvant to intrathecal bupivacaine, providing intense and extended postoperative analgesia without any significant adverse effects. It being an agonist-antagonist, is devoid of the usual opioid side effects. Unlike fentanyl and other opioids, it is not included under the Narcotic Act, making it available in the pharmacy on prescription. So in centers where fentanyl is difficult to procure, nalbuphine may be used as intrathecal adjuvant.

Conflict of interest: None declared by the authors

Author's responsibility/contribution:

SB: Concepts, Design, Clinical studies, Data acquisition, Data analysis, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review, Guarantor

DR: Concepts, Clinical studies, Data acquisition, Manuscript preparation

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