Original Article

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Nalbuphine as an Intrathecal Adjuvant is a Good Alternative to Fentany l

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Abstract

Background: 0.5% Bupivacaine used in subarachnoid block provides about 3 hours of analgesia. Opioids morphine and Fentanyl are used as adjuvant to produce extended postoperative analgesia. Nalbuphine is an agonist antagonist and does not require a narcotic license, which is a must for procuring other opiods. This study was carried out to evaluate the efficacy of Nalbuphine versus Fentanyl as intrathecal adjuvant.

Material and Methods: Hundred ASA 1-3 patients posted for elective Total Abdominal Hysterectomy were included in this study and were randomly divided into two groups of fifty each. Group FB received 15mg of 0.5% Bupivacaine and 25 mcg of Fentanyl. Group NB received 15mg 0.5% Bupivacaine and 1mg Nalbuphine.

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 minutes, than in Group FB, 88.88±9.48 minutes. The time to first analgesic requirement in Group NB was 460.78±77.98 minutes compared to 283.44±78.97 minutes in Group FB($p<0.001$). No statistical difference was seen in terms of adverse effects. *Conclusion:* Time for sensory level to regress by two segments and the post operative analgesia time is longer with Nalbuphine. So, Nalbuphine is a good adjuvant in spinal anaesthesia especially in centres without narcotics license.

Keywords: Nalbuphine; Intrathecal Adjuvant; Fentanyl; Bupivacaine; Analgesia.

Introduction

Total abdominal hysterectomy (TAH) is preferably done under regional anaesthesia. Spinal anaesthesia is the technique of choice as it is less cumbersome compared to general anaesthesia. There is good stress response, less 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 and duration of the post operative analgesia. Intrathecal opioids have been widely used as adjuncts, resulting in a longer duration of analgesia and good patient satisfaction [1-4].

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.

Fentanyl has been used extensively intrathecally as it has no significant side effects [5]. It is a potent synthetic mu receptor agonist. Fentanyl has structural similarities to local anaesthetics. It has local anaesthetic action on the primary afferent sensory C nerve fibres causing analgesia.

Nalbuphine hydrochloride is a synthetic opioid structurally related to oxymorphine and is an agonist antagonist opioid. It has agonist action at kappa receptors and is antagonist at mu receptors [6,7]. So, while giving good analgesia, it is devoid of opioid related adverse effects [8,9].

We conducted this study to compare the effects of Nalbuphine and Fentanyl as adjuvants to intrathecal 0.5% Bupivacaine in patients undergoing TAH.

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Material and Methods

On obtaining the departmental ethical committee approval and written informed consent, hundred patients ASA 1-3 patients, aged 30-65 years posted for elective TAH were included in this study. This was a prospective randomised double blind study. A thorough pre-anaesthetic check up followed by a series of lab investigations like haematocrit, coagulation profile, electrocardiogram, chest X-ray, blood sugars, electrolytes were conducted. Patients with contraindication for spinal anaesthesia were excluded from this study. The patients were randomly allocated to two groups of fifty each by computer generated programme. Group FB received 15mg of 0.5% Bupivacaine (3ml) and 25 mcg of Fentanyl (0.5ml) and Group NB received 15mg 0.5% Bupivacaine (3ml) and 1mg Nalbuphine(0.5ml)

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. We kept the patients nil by mouth for 8 hours prior to surgery. No sedative or analgesic was given preoperatively. A good peripheral intravenous access was secured with 18 g cannula and preload was done with 10ml/ kg ringer lactate solution. Intraoperative monitoring included non-invasive blood pressure, electrocardiogram, pulse oximetry. Under strict sterile precautions spinal anaesthesia was administered with the patients in the sitting posture at L_{3-4} interspace in the midline with 26 gauge spinal needle. The drug was loaded and handed over by the assistant. The anaesthesiologist 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 per minute was treated with atropine 0.6mg. Fall in systolic blood pressure below 20% baseline was managed by 6mg intravenous ephedrine in increments. We looked for any signs of respiratory depression and were equipped 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 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 for 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. Rescue analgesic given was injection diclofenac 75 mg intramuscularly.

Statistical Methods

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 age, height, weight, onset of sensory blockade, peak sensory blockade, time to attain complete motor block, 2 Segment Regression of Sensory Level(t8)[Min], duration of motor block, time to first analgesic with the treatment groups (Fentanyl and Nalbuphine) and its expressed as mean and standard deviation, Chi square or fisher exact test were used to measure the association between the adverse event and ASA grade with the treatment groups. $P<0.05$ considered as statistically significance.

Results

We compared the effects of intrathecal Fentanyl and Nalbuphine as adjuvant to 0.5%Bupivacaine in patients undergoing TAH. 100 patients took part in this randomized study. In group FB, 50 patients received 25 mcg Fentanyl and 3 ml 0.5%bupivacine intrathecally. The rest, group NB received 1mg Nalbuphine and 3ml 0.5% Bupivacaine.

The demographic profile of both groups were not statistically different (Table 1). The onset of sensory block was faster in group FB (3.09±0.47 minutes), than in group NB(4.20±0.52 minutes) (p value <0.001). Time to attain peak sensory blockade was faster in group FB, 6.31±0.58 minutes than in group NB, 6.76±0.54 minutes. The difference was statistically significant (p value<0.001) (Table 2). Time for complete motor block was 6.85±0.66 minutes in group FB, while it was 7.93±0.67 minutes in group NB, with statistically significant difference (p<0.001)(Table 2). The time to two segments sensory level regression was longer in Group NB, 97.72±9.50 minutes, while it was 88.88±9.48 minutes in Group FB. The difference was statistically significant (p<0.001) (Table 3). The duration of motor block in Group FB was 136.24±12.23 minutes and was comparable to 129.78±24.07 minutes in Group NB. The difference was not statistically significant (p=0.096). The time to first

analgesic requirement was 460.78±77.98 minutes in Group NB while in Group FB, it was 283.44±78.97 minutes, with statistically significant difference (p<0.001) (Table 3). There was no statistical difference in the adverse events in the two groups (p=0.240). Two patients and one in Group FB developed hypotension and pruritus respectively. Nausea was seen in two patients in either group (Table 4, 5). No active intervention was required. None developed respiratory distress.

Table 1: Demographic profile

	Fentanyl	Nalbuphine	P-Value
	Mean ± SD	Mean ± SD	
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 anaesthesia

	Fentanyl Mean ± SD	Nalbuphine Mean ± SD	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 Nalbupine and Fentanyl

	Fentanyl Mean ± SD	Nalbuphine Mean ± SD	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: Total Adverse events with Nalbuphine and Fentanyl

	Fentanyl	Nalbuphine	Total	P-Value
Yes	5 (10%)	2 (4%)	7 (7%)	
No	45 (90%)	48 (96%)	93 (93%)	0.240
Total	50	50	100	

Table 5: Types of adverse effects with Nalbuphine and Fentanyl

	Fentanyl	Nalbuphine	Total
Hypotension	2 (4%)		2
Nausea	2 (4%)	2 (4%)	4
Pruritis	1 (2%)		1
Nil	45 (90%)	48 (96%)	93
Total	50	50	100

Discussion

Intrathecal opioids have a significant place in management of acute post operative pain. The presence of intrinsic opioid apparatus in human body has popularized their use both intrathecally and epidural. Liposolubility of opioids determine their spinal selectivity. The more liposoluble ones like Fentanyl and Sufentanyl have short duration of analgesia (1-4 hours) compared to water soluble morphine which produces analgesia for nearly 24 hours post operatively [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]. As they are devoid of sympathetic and motor block while enhancing analgesia, opioids are good adjuncts. Early post operative 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.

Our study groups had subjects with similar age group, ASA grading, height and weight. The onset of sensory block was earlier in group FB compared to group NB. The time to achieve peak sensory level as well as complete motor block was earlier in group FB than group NB. This can be attributed to the fact that Fentanyl is more lipid soluble and a rapid tissue uptake compared to Nalbuphine. H M Gomaa et al [14] compared the effects of intrathecal Nalbuphine and Fentanyl in caesarean 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 in the two groups was 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 was consistent with H M Gomaa et al [14] study.

The time of first analgesic requirement was lower 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 2mg Nalbuphine extended the duration of sensory block and extended post operative analgesia more than Fentanyl. Culebras et al [16] also studied these drugs intrathecally in caesarean patients and concluded that Nalbuphine prolonged analgesia without any side effects. Mukerjee et al [17] studied 0.2mg, 0.4 mg, and 0.8mg Nalbuphine and came the conclusion that a higher dose intrathecally resulted better analgesia without any adverse effects. No significant side effects were encountered. We also observed no major side effects. Two patients and one in group FB developed hypotension and pruritus respectively. Two patients in both the groups complained of nausea. Catherine O Hunt et al [4] used intrathecal Fentanyl in caesarean patients and concluded that a good sensory block was achieved but pruritus developed with high doses. M S Khanna et al [18] found incidence of pruritus and respiratory depression with use of intrathecal Fentanyl. In a study, it was found that intrathecal Nalbuphine was associated with lesser incidence of pruritus compared to morphine [19].

Pruritus is mainly in the face and is a known opioid side effect. Its cause is the presence of a type of C fibres 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. This was because this risk is seen more in geriatric population, concomitant chronic sedative usage or co existing respiratory disease. All these factors were excluded in our study groups.

Thus, we conclude that Nalbuphine is a good intrathecal adjuvant, providing intense and extended postoperative analgesia without any significant adverse effects.

Nalbuphine being antagonist as well 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 centres where Fentanyl is difficult to procure, Nalbuphine may be used as intrathecal adjuvant.

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