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Comparative Study of Nalbuphine, Fentanyl, and Pethidine as Additives to Hyperbaric Bupivacaine in Spinal Anesthesia for Lower Limb Surgeries

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Abstract

Background

Many opioids were added to intrathecal local anesthetics to provide longer duration of analgesia; however, we have to choose the additive with the longest analgesic time and least intra and post-operative side effects. In this study, nalbuphine was compared to fentanyl and pethidine as additives to hyperbaric bupivacaine used in spinal anesthesia for lower limb surgeries.

Patient and Method

One hundred patients of both genders ASA I, and ASA II posted for lower limb surgeries under spinal anesthesia were assigned randomly into four groups: Group B, received an intrathecal injection of 0.5% hyperbaric bupivacaine (3 ml+ 1 ml sterile water; n=25). Group N, received intrathecal injection of 0.5% hyperbaric bupivacaine (3 ml+ 1 ml nalbuphine 500µg; n=25).Group F, received intrathecal injection of 0.5% hyperbaric bupivacaine (3 ml+ 1 ml fentanyl 25µg; n=25). Group P, received intrathecal injection of 0.5% hyperbaric bupivacaine (3 ml+ 1ml pethidine 10 mg ; n=25).We record the onset of sensory and motor blocks, peak sensory and motor block times, sensory block levels and two segment regression time using pin prick method, and motor block level using modified Bromage scale (table1) and any intra or post-operative complications.

Results

The mean onset of sensory block is significantly decreased in groups N, F, and P compared with group B, while the peak sensory time was none significantly changed among the whole four groups, In contrast the mean onset of the motor block in the four groups included was non considerably different while the mean time for peak motor block was significantly short in both the N group (nalbuphine and bupivacaine) and P (pethidine and bupivacaine) group when compared to B (bupivacaine alone) and F (fentanyl and bupivacaine) groups.there was significant prolongation of both two segment regression time and the first analgesic request time in groups N, F and P (all narcotics and bupivacaine) compared with group B(bupivacaine alone).

Conclusion

nalbuphine, fentanyl, and pethidine as adjuvants to spinal anesthesia prolong the duration for first rescue analgesia with minimal hemodynamic and respiratory complications; however, nalbuphine with the dose of 0.5 mg has the best quality of spinal block when added to intrathecal 0.5% heavy bupivacaine in patients undergoing lower limb surgeries.

Keywords: Intrathecal Nalbuphine; Fentanyl; Pethidine; Spinal anesthesia; Lower limb surgeries.

Introduction

Spinal anesthesia was introduced about more than 100 years back, and it is still the most common of the regional anesthetic technique. Because of the technical difficulties in detect of the epidural space and the toxicity associated with the massive doses of local anesthetics needed for epidural anesthesia, spinal anesthesia was the most popular form of neuraxial anesthesia [1]. Excessive high regional blocks and local anesthetic toxicity are the most frequent causes of mortality associated with regional blocks, so the reduction in doses of local anesthetics, the use of new techniques to avoid higher blocks and better management of local anesthetic toxicity are the new goals for decreasing mortality associated with regional anesthesia [2]. Many adjuvants like fentanyl, morphine, buprenorphine, midazolam, and clonidine have been used in the past to reduce the dose of local anesthetic and to prolong postoperative analgesia, but everyone has its side effects [3]. The opioid additives specifically have certain specific advantages like a rapid onset of action, sympathetic and motor nerve sparing activities, technical ease of administration and simplicity of postoperative management, In addition to their combination of local intrathecal anesthetic, they limit the regression of sensory block seen with local anesthetic alone [2]. The significant disadvantages of adding opioids are their side effects, some of which like respiratory depression could prove to be dangerous. To overcome these side effects, opioids with partial agonist antagonist action have been studied extensively [3]. One of the best ways to control the intrathecal opioid-related side effects is the use of mixed agonist- antagonist opioids. Nalbuphine is one of the most recently used additives to spinal bupivacaine, considering its Mu antagonist and Kappa agonist mechanisms of action which may avoid some of the opioid adverse effects [4].

Patients and Methods

This study was carried out in the anesthesia department faculty of medicine Benha university hospitals after obtaining approval from the ethical research committee and the anesthesia department. Written informed consent was obtained from 100 patients of both genders ASA I, and ASA II between ages 20-60 years old posted for lower limb surgeries, during august 2017 to august 2018, randomization was done into four equal groups by lottery method. Weight range between 60 to 100 kg, and duration of surgery in between 45 minutes to 120 minutes.

Exclusion criteria

Patient refusal either the spinal anesthesia or the research , infection at site of injection ,any coagulopathy disorder or patients on anticoagulants, pre-existing neurological disorders, patients receiving phenothiazine, other tranquilizers, hypnotics or other central nervous system depressants (including alcohol), uncooperative patients, patients with signs suggesting cardiac or respiratory problems, hepatic or renal disease evidence, patients with known history of allergy to local anesthetic drugs, pregnant patients, and failed spinal cases.

Patients were planned to be admitted less than 12 hours in the hospital, and all patients fasted at least 6 hours before the procedure. All patients were clinically assessed, and routine preoperative investigations were done (CBC, PT, PTT INR, liver function tests, renal function tests, and ECG).

On arrival to the operating room, an intravenous line was secured, and 500 ml of lactated ringer's solution was infused as a preload. After standard monitoring procedures (ECG, noninvasive blood pressure, and oxygen saturation) and recording of vital baseline data, each patient was placed in the sitting position. After scrubbing the back with antiseptic solution Whitacre spinal needle was introduced in the lumbar 3-4 inter space (one level above or below if there was any difficulty). The patients were randomly selected to be in one of four groups: Group B included twenty five patients who received an intrathecal injection of 3 ml of 0.5% hyperbaric bupivacaine plus 1 ml sterile water. Group N included twenty five patients who received an intrathecal injection of 3 ml of 0.5% hyperbaric bupivacaine plus 1 ml of pure water contains nalbuphine (preservative free) 500µg. Group F included twenty five patients who received an intrathecal injection of 3 ml of 0.5% hyperbaric bupivacaine plus 1 ml of sterile water contains preservative free fentanyl 25µg. Group P included twenty five patients who received an intrathecal injection of 3 ml of 0.5% hyperbaric bupivacaine plus 1 ml of sterile water contains preservative free pethidine 10 mg. All study mixtures were prepared by a well-trained anesthesia resident not involved in the patients follow up or data collection. After spinal injection, all patients are made to lie down in the supine position. The block level was tested every minute aiming for the sensory block of the 10th thoracic dermatome.

Intra-operative, the patients were continuously monitored for the blood pressure, heart rate, oxygen saturation, and respiratory rate. If the systolic blood pressure decreased to less than 20% of the baseline 5 mg of intravenous ephedrine was injected incrementally. Patients were excluded if intra-operative pain requires the use of opioids or conversion to general anesthesia. The intra-operative recordings included the conscious level, ephedrine doses, operation time, sensory block level using pin prick method, and motor block level using a modified Bromage scale (Table1).

Any intra-operative complications were recorded and treated symptomatically.

Post-operatively, all patients in the four groups were assessed every 15 minutes in the first hour then every hour for the subsequent 4 hours for: conscious level, respiratory rate, heart rate, oxygen saturation, and noninvasive blood pressure.

Table 1. Modified Bromage scale [1].

0	No motor movement
1	Inability to raise extended leg; able to move knee and feet
2	Failure to lift the extended leg and move knee; ready to move feet
3	Complete block of motor limb

In addition; we recorded the time for the first request of analgesia (active analgesic time) according to visual analogue scale VAS (it ranges from 0 indicating no pain till 10 indicating severe intolerable pain with a variable degree of ascending pain in between, the first request of analgesia was considered when VAS scale was above 4).

Any complication like hypotension (systolic below 90mmHg), bradycardia; (heart rate below 60 beats/ minute), pruritus or rash, nausea, vomiting, shivering, breathlessness (respiratory rate below ten breath/ minute), urine retention.

Complications were treated symptomatically as follow

Patients with vomiting were given 10mg of metoclopramide, those with shivering were treated with pethidine 20 mg, and pruritus was managed with 10mg chloropheniramine maleate. Ephedrine 10mg and atropine 0.5mg IV were injected in boluses for hypotension and bradycardia respectively, while patients who developed Urine retention were catheterized for evacuation

All data were analyzed using SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as the mean±SD & median (range), and the categorical variables were expressed as a number (percentage). Continuous parameters were checked for normality by using Shapiro-Wilk test. One way ANOVA was used to compare normally distributed variables between four groups while Kraskall Wallis H test was used for non-normally distributed variables. Independent samples Student's t-test was used to compare two groups of normally distributed data while Mann Whitney U test was used for non-normally distributed data. Percent of categorical variables were compared using Chi-square test. All tests were two tailed. P-value < 0.05 was considered statistically significant (S), p-value<0.01 was considered highly statistically significant (HS), and p-value > 0.05 was considered statistically insignificant (NS).

Results

Hundred patients were enrolled in this study. In table (2), there were no significant differences between the four groups as regard age, weight, gender, ASA classification or duration of surgery. The results regarding the block sensory and motor times were summarized in table (3). The onset of sensory block is significantly decreased in groups N, F, and P compared with group B with bupivacaine alone, while the peak sensory time was non significantly changed among the whole four groups.

In contrast regarding the motor parameters of the block, the onsets of the motor block in the four groups included were non significantly different while the means for peak motor block were significantly short in both N group (nalbuphine and bupivacaine) and P (pethidine and bupivacaine) group when compared to B (bupivacaine alone) and F (fentanyl and bupivacaine) groups.

As regard the parameters describing the sensory duration in table (3), there were significant prolongations of both two segment regression time and the first analgesic request time in groups N, F and P (all narcotics plus bupivacaine) compared with group B(bupivacaine alone).

Table 2. Comparison between group B, group N, group F and group P as regard demographic data.

Variables	Group B (N=25)	Group N (N=25)	Group F (N=25)	Group P (N=25)	Test	p-value (Sig.)
Age						
Mean ± SD	37.80 ± 12.49	36.04 ± 11.12	35.12 ± 9.81	38.32 ± 12.13	0.427*	0.734 (NS)
Median	34	35	35	38		
Range	20 – 60	21 – 56	20 – 59	20 – 60		
Sex						
Male	16 (64%)	14 (56%)	13 (52%)	13 (52%)	0.974§	0.808 (NS)
Female	9 (36%)	11 (44%)	12 (48%)	12 (48%)		
Weight (Kg)						
Mean ± SD	85.48 ± 13.70	83.48 ± 11.88	77.84 ± 11.83	81.84 ± 11.49	1.748*	0.162 (NS)
ASA						
ASA I	13 (52%)	15 (60%)	18 (72%)	18 (72%)	3.886§	0.692 (NS)
ASA II	12 (48%)	10 (40%)	7 (28%)	7 (28%)		
Duration of surgery (min)						
Mean ± SD	99.20 ± 17.01	95.20 ± 18.24	90.08 ± 16.77	99.48 ± 17.70	5.474Ÿ	0.140 (NS)

Categorical variables was expressed as number (percent).
*One way ANOVA test. ● Kraskall Wallis H test. ♣Chi-square test. p< 0.05 is significant. Sig.: Significance.

Table 3. Comparison between group B, group N, group F and group P as regard sensory block, motor block and analgesia.

Variables	Group B (N=25)	Group N (N=25)	Group F (N=25)	Group P (N=25)	Test	p-value (Sig.)
sensory onset (sec.)						
Mean ± SD	119.52 ± 16.87	88.84 ± 12.23	86.84 ± 13.19	86.68 ± 14.21	31.826*	<0.001 (HS)
motor onset (sec)						
Mean ± SD	183.76 ± 26.51	187.32 ± 28.45	181.20 ± 24.60	173.32 ± 28.69	3.824Ÿ	0.281 (NS)
peak sensory time (sec)						
Mean ± SD	369.84 ± 31.37	355.24 ± 28.48	349.40 ± 30.90	348.04 ± 35.78	2.468*	0.067 (NS)
peak motor time (sec)						
Mean ± SD	352.72 ± 19.29	326.76 ± 22.65	342.24 ± 21.76	309.76 ± 34.93	28.329Ÿ	<0.001 (HS)
Two segment regression time (min)						
Mean ± SD	104.28 ± 23.67	120.08 ± 19.36	122.48 ± 18.26	133.24 ± 27.65	7.024*	<0.001 (HS)
First request of analgesic (min)						
Mean ± SD	173 ± 27.42	234.48 ± 38.56	206.28 ± 40.44	261 ± 27.95	49.111Ÿ	<0.001 (HS)

* One way ANOVA test. Y Kraskall Wallis H test. p< 0.05 is significant. Sig.: Significance.

Table 4. Post Hoc Test for Sensory Block, Motor Block, and Analgesia.

Variables	Group B Vs Group N	Group B Vs Group F	Group B Vs Group P	Group N Vs Group F	Group N Vs Group P	Group F Vs Group P
sensory onset (sec.)*	<0.001 (HS)	<0.001 (HS)	<0.001 (HS)	0.581 (NS)	0.567 (NS)	0.967 (NS)
peak motor timeY	<0.001 (HS)	0.095 (NS)	<0.001 (HS)	0.017 (S)	0.012 (S)	<0.001 (HS)
Two segment regression time*	0.013 (S)	0.004 (S)	<0.001 (HS)	0.654 (NS)	0.058 (NS)	0.111 (NS)
First request of analgesicŸ	<0.001 (HS)	0.003 (S)	<0.001 (HS)	0.019 (S)	0.009 (S)	<0.001 (HS)

Number (string): p-value (Sig.)
* Independent samples Student's t-test. Yq Mann Whitney U test. p< 0.05 is significant.
Sig.: significance.

In tables (5) and (6), Modified Bromage scale was analyzed by two methods; first the analysis of means of the total range, it was done by Kraskall Wallis test and results had indicated highly significant increase in the 5 minutes assessments of opioid groups N, F, P versus B group and non-significant differences in the 10 minutes scale.

The second analysis was done using the categorical variables of the scale expressed as percentage using Chi Square test, it confirmed the same results which were significantly different in 5 minutes assessments of modified Bromage scale within groups N, F and P compared to the extent in group B, while there was no significant differences in the 10 minutes assessments in all four groups. In Tables (7) and (8) comparing each group against the other, indicated a highly significant difference in motor block assessment by modified Bromage scale for the pethidine group P against all other groups.

Regarding the complications; Table (8) summarized their incidence.

Heart rate and mean arterial blood pressure were stable with minimal variations which were not statistically significant. Pruritus was substantial in group F (fentanyl plus bupivacaine) when compared to other groups. Nausea or vomiting, respiratory depression, and urine retention were not statistically significant among all study groups Table (8).

Discussion

Spinal anesthesia is the most common type of anesthesia used for lower limb surgeries, however adding intrathecal opioids to local anesthetics decrease their dose, provide more hemodynamic stability and increase the time needed for post-operative analgesia. Nalbuphine is a synthetic opioid with mu agonist and antagonist properties; mechanism of analgesia relies its agonistic action on this receptor. It also stimulates kappa receptors,

Table 5. Comparison between Group B, Group N, Group F and Group P As Regard Modified Bromage.

Bromage	Group B (N=25)	Group N (N=25)	Group F (N=25)	Group P (N=25)	Test	p-value (Sig.)
5 min						
Mean ± SD	1.08 ± 0.64	1.60 ± 0.57	1.44 ± 0.71	2.32 ± 0.94	28.798Ÿ	<0.001 (HS)
10 min						
Mean ± SD	Three ± 0	Three ± 0	Three ± 0	Three ± 0	0.000Ÿ	1.000 (NS)

Y Kraskall Wallis H test. p< 0.05 is significant. Sig.: Significance.

Table 6. Comparison between group B, group N, group F and group P as regard Bromage scale.

Bromage scale	Group B (N=25)	Group N (N=25)	Group F (N=25)	Group P (N=25)	Test	p-value (Sig.)
5 min						
0	4 (16%)	1 (4%)	3 (12%)	2 (8%)	61.226§	< 0.001 (HS)
1	15 (60%)	8 (32%)	8 (32%)	2 (8%)		
2	6 (24%)	16 (64%)	14 (56%)	7 (28%)		
3	0 (0%)	0 (0%)	0 (0%)	14 (56%)		
10 min						
0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.000§	1.000 (NS)
1	0 (0%)	0 (0%)	0 (0%)	0 (0%)		
2	0 (0%)	0 (0%)	0 (0%)	0 (0%)		
3	25 (100%)	25 (100%)	25 (100%)	25 (100%)		

Categorical variables were expressed as number (percent).
♣ Chi-square test. p< 0.05 is significant. Sig.: Significance.

Table 7. Post hoc Test for Bromage.

Bromage	Group B Vs Group N	Group B Vs Group F	Group B Vs Group P	Group N Vs Group F	Group N Vs Group P	Group F Vs Group P
Five minŸ	0.004 (S)	0.047 (S)	<0.001 (HS)	0.46 (NS)	0.001 (S)	<0.001 (HS)

Number (string): p-value (Sig.)
Y Mann Whitney U test. p< 0.05 is significant. Sig.: significance.

Table 8. Post hoc test for Bromage.

Bromage scale	Group B Vs Group N	Group B Vs Group F	Group B Vs Group P	Group N Vs Group F	Group N Vs Group P	Group F Vs Group P
5 min§	0.014 (S)	0.065 (NS)	<0.001 (HS)	0.567 (NS)	<0.001 (HS)	<0.001 (HS)

Number (string): p-value (Sig.)
♣ Chi-square test. p< 0.05 is significant. Sig.: significance.

which inhibits the release of neurotransmitter that mediates pain like for example substance p, addition it acts as post synaptic inhibitor on the interneuron and output neuron of spinothalamic tract which transports nociceptive information [5]. When nalbuphine, given intrathecally, binds to kappa receptors in the brain and spinal cord areas that are involved in nociception, leading to analgesia and sedation without μ side effect [6]. It improves quality of block and offers prolonged and extended lasting post-operative analgesia. It has less incidence of adverse effects known for other opioids (e.g., respiratory depression nausea vomiting pruritus). As well as it is a cost effective drug [7]. Relying on the fact that; nalbuphine was given systemically had reduced the incidence of respiratory depression, and it also had been used to antagonize the side effects of spinal

Table 9. Comparison between group B, group N, group F and group P as regard complications.

Complications	Group B (N=25)	Group N (N=25)	Group F (N=25)	Group P (N=25)	Test	p-value (Sig.)
Hypotension						
Absent	23 (92%)	17 (68%)	20 (80%)	20 (80%)	4.500♣	0.212
Present	2 (8%)	8 (32%)	5 (20%)	5 (20%)		(NS)
Bradycardia						
Absent	24 (96%)	22 (88%)	25 (100%)	24 (96%)	4.000♣	0.261
Present	1 (4%)	3 (12%)	0 (0%)	1 (4%)		(NS)
Nausea or vomiting						
Absent	23 (92%)	24 (96%)	22 (88%)	19 (76%)	5.303♣	0.151
Present	2 (8%)	1 (4%)	3 (12%)	6 (24%)		(NS)
Pruritus						
Absent	25 (100%)	25 (100%)	22 (88%)	25 (100%)	9.278§	0.026
Present	0 (0%)	0 (0%)	3 (12%)	0 (0%)		(S)
Respiratory depression						
Absent	25 (100%)	25 (100%)	25 (100%)	25 (100%)	0.000§	1
Present	0 (0%)	0 (0%)	0 (0%)	0 (0%)		(NS)
Urine retention						
Absent	25 (100%)	25 (100%)	24 (96%)	23 (92%)	3.780§	0.286
Present	0 (0%)	0 (0%)	1 (4%)	2 (8%)		(NS)

Categorical variables were expressed as number (percent).
♣ Chi-square test.
p< 0.05 is significant.
Sig.: Significance.

Table 10. Post hoc test for complications.

Variable	Group B Vs Group N	Group B Vs Group F	Group B Vs Group P	Group N Vs Group F	Group N Vs Group P	Group F Vs Group P
Pruritus§	1 (NS)	0.235 (NS)	1 (NS)	0.235 (NS)	1 (NS)	0.235 (NS)

Number (string): p-value (Sig.)
♣ Chi-square test.
p< 0.05 is significant.
Sig.: significance.

opiates [5]. We hypothesized that spinal nalbuphine should demonstrate improved therapeutic results consistent with that seen after systemic administration. There have been few studies of varying quality that supported the utility of neuro-axially administered nalbuphine in managing post-operative pain. The general trend of these reports is that epidural or intrathecal delivery of nalbuphine produces a significant analgesia associated with minimal pruritus and respiratory depression [8].

In this prospective randomized controlled study, we compared the use of intrathecal hyperbaric bupivacaine 0.5% without additives (control group) to the use of Nalbuphine 0.5 mg, fentanyl 25 µg, and pethidine 10 mg as different adjuvant to intrathecal heavy bupivacaine 0.5 % for lower limb surgeries in 100 patients. Our choice for the nalbuphine doses depended on previous study of Mukherjee et al., in 2011[9]. Who studied 100 patients undergoing lower limb orthopedic surgery using subarachnoid block. They used different doses of nalbuphine intrathecally (200,400,800) µg added to 0.5% hyperbaric bupivacaine. They concluded that the duration of sensory block and the duration of adequate analgesia were prolonged with the 400µg and the 800µg, but the side effects were higher with the dose 800µg. So we chose adding the 500µg of preservative free nalbuphine which is very close to the best recognized dose before and practically more comfortable in calculation. The same dose 0.5 mg of intrathecal nalbuphine was used in the study of Dubey's et al., in 2014 [4,5] where they studied 40 patients of ASA ASA I & ASA II into two equal groups one control with hyperbaric bupivacaine with normal saline and the second with hyperbaric bupivacaine with 0.5 mg of nalbuphine in normal saline . Our results showed that the onset of sensory block was significantly short in opioid additive groups F, N, and P compared with bupivacaine alone in group B, while the time for peak sensory block was not significantly different among the four groups.

The mean onset of sensory time in group N was 88.84±12.23 seconds and peak sensory was 355.24±28.48 seconds, in group F mean onset of sensory block was 86.84±13.19 seconds and the peak sensory time was 349.40±30.90 seconds, and in group P the mean beginning of sensory block was 86.68±14.21 seconds and the peak sensory time was 348.04±35.78 seconds

compared with mean sensory time of 119.52±16.87 seconds and peak sensory time of 369.84±31.37 seconds in group B.

Similar results were documented by Shakooh et al., [8] in their study on 60 ASA Grade I and II patients from 18- 65 years, scheduled for lower limb and lower abdominal surgeries who were given 3 ml of hyperbaric bupivacaine 0.5% + 800 micro gram of nalbuphine intrathecally in one group and 3 ml of hyperbaric bupivacaine 0.5% + normal saline in control group. They found that intrathecal nalbuphine provided significantly faster onset of sensory block and shorter peak sensory time compared with bupivacaine alone. In contrast to this study; Sapate, et al. [7] in their research have shown that onset of sensory block and peak time for sensory block was not affected by adding nalbuphine intrathecally in 40 patients aged between 40-70 years scheduled for below umblicus surgeries.

Regarding the motor block; the onset of motor block was non-significant in all four groups, while the time for peak motor block was significantly short in opioid groups. The peak motor time in group N was 326.76±22.65 seconds, in group F was 342.24±21.76 seconds, and in group, P was 309.76±34.93 seconds, that was highly significant when compared with group B 352.72±19.29 seconds. Consequently, the five minute modified Bromage scale [1] when analyzed as mean ± standard deviation and as percentage of each range from 0 to 3 there were highly significant differences between all opioid additive groups N, F, P, and bupivacaine group B. The same result had been shown by Shakooh et al. [8] in 2014.

On the other hand Ahmed et al. [10] who studied 100 patients for abdominal hysterectomy in four groups one for plain bupivanaine and three groups of three different doses of nalbuphine 0.8, 1.6, 2.4 mg as additives, They concluded that there was no difference in the time of peak motor among the four groups. Although this conclusion is recently published (2016), we couldn't find many papers supporting it. When comparing the peak motor time among the opioid groups only, we found that pethidine as an additive has a significantly shorter peak time for motor block than nalbuphine and fentanyl groups. This result was supported by Patel et al. [11], who was using pethidine alone as intrathecal local anesthetic for endoscopic urological procedures and concluded that low dose pethidine 0.5 mg/kg is effective as spinal anesthetic agent and has few complications. The same findings were observed by Anaraki et al. [12] while they were studying the effect of different intrathecal doses of pethidine on shivering during delivery under spinal anesthesia. Another important efficacy measure of intrathecal additives is the two segment regression time; which is the time needed for regression of the sensory level by two segments. In our study; when comparing the two segment regression times of the three opioid groups N, F, P with that of bupivacaine group it was highly significant longer in opioid groups .it was 120.08±19.36 minutes in N group, 122.48±18.26 minutes in F group and 133.24±27.65 minutes in P group when compared to 104.28±23.67 minutes in B group.

The same results they found that 200µg and 400µg of intrathecal nalbuphine will prolong the two segment regression time of sensory blockade of 12.5 mg of hyperbaric bupivacaine by about 16 and 24 minutes respectively.

Shakooh et al. 2014 [8], Mukhrejee et al. 2011 [9], agreed that addition of nalbuphine to bupivacaine intrathecally slows the two segment regression time of sensory block. Even Ahmed et al. 2016 [10]"who disagreed with most of them regarding the effect of intrathecal nalbuphine on peak motor time " reached the same conclusion regarding prolongation of 2 segment regression time when nalbuphine was added to spinal anesthesia.

In the same direction, we observed that the first request of analgesics was after 234.48±38.56 minutes in N group, 206.28±40.44 minutes in group F, and 261±27.95 minutes in P group, in comparison to 173±27.42 minutes in Bupivacaine group. That was a highly significant difference between the narcotic additive groups N, F, and P from one side and the pure bupivacaine group on the other side; that confirms the apparent prolongation of analgesic time when opioids were used as additives to heavy bupivacaine in spinal anesthesia.

These results had come in agreement with Vadhanan et al. 2017 [13], Sapate et al. 2013 [7], Dubey et al. 2014 [4], Gomaa et al. 2014 [2], Shakooh et al. 2014 [8], Jyothi et al. 2014 [6], and Ahmed et al. 2016 [10].

Regarding the side effects, in our study groups, there were neither cases of respiratory depression (respiratory rate below 10 or spo2 $\leq$ 90%) nor severe persistent hypotension. Since respiratory depression is predominantly µ receptor-mediated and nalbuphine is mainly a µ receptor antagonist, respiratory depression effect is expected to be attenuated by nalbuphine even when increasing dose from 0.8 mg to 2.4 mg. Jyothi et al. 2014 [6].

Urine retention was seen in one patient in F group (fentanyl), and in two patients in P group (pethidine), was solved by bladder evacuation, but they were statistically non-significant. Nausea and vomiting happened in two patients in B group, one patient in N group, three patients in F group and six patients in P group, but they were also non-significant statistically .although in Anaraki et al. study 2012 [12] who studied fifty six parturient women scheduled for elective cesarean delivery enrolled in four groups adding pethidine 0.2 mg/kg, 0.3 mg/kg, 0.4 mg / kg to heavy bupivacaine respectively in three groups of them compared with pure bupivacaine 0.5% in control group , they concluded that intrathecal pethidine cannot be recommended for the prevention of shivering during spinal anesthesia for cesarean delivery as its use is associated with increased incidence of nausea and vomiting . The only complication which was significant in our study is the pruritis, it didn't happen in either of the groups except the fentanyl group in 3 patients representing 12% of patients received fentanyl as an additive to bupivacaine intrathecally .this result was in accordance to Gomaa et al. study 2014 [2], where they studied sixty female patients ASA I & ASA II presented for elective cesarean deliveries allocated in 2 equal groups: group F received heavy bupivacaine plus fentanyl 25µg and the other received 0.8 mg nalbuphine added to heavy bupivacaine, they found that the incidence of pruritis was higher with addition of fentanyl than in nalbuphine group.

In 2011, Mukherjee et al. [8] formulated a study to detect whether nalbuphine prolongs analgesia by comparing with control and to find out the optimum dose of intrathecal nalbuphine by comparing the 0.2, 0.4, and 0.8 treatments which prolonged post-operative analgesia without increased side effects. It was observed that effective analgesia increased with increase in

concentration, but the ultimate observation of prolongation of analgesia without any side effects was the addition of 0.4 mg with 0.5% hyperbaric bupivacaine.

Vandhanan P et al., 2017 [13], in this study, there are 66 patients undergoing lower limb surgeries then divided into two groups and received either 0.8mg or 1.6mg intrathecal nalbuphine with 3.2ml of 0.5% hyperbaric bupivacaine. They were recording hemodynamic stability, postoperative analgesia, and incidence of side effects. Results of this study show the following, a dose of 0.8mg of nalbuphine as an intrathecal seems to be safe and prolonged postoperative analgesia with fewer side effects. But at a dose 1.6mg incidence of bradycardia was more. Thus from our study, it was observed that nalbuphine, as well as fentanyl and pethidine, can be used as additives to intrathecal heavy bupivacaine They prolong the time for the first request of analgesic and slow the two segment regression time with minimal side effects.When comparing among the narcotic additives groups N, F, and P we additionally get some observations needs to be confirmed by future researches; firstly; pethidine as intrathecal additive has a significantly shorter time for motor block and substantially more extended time for both 2 segment regression time and the first request of analgesics making it superior to fentanyl and nalbuphine in the duration of analgesia , however the documented higher rate of nausea and vomiting may limit its use as the best choice . Secondly ; nalbuphine comes in the next class regarding the time of analgesia however its devoid of side effects may raise it to the first choice as opioid additive not only when compared to pethidine and fentanyl as in our study, but also when compared to morphine as in Mohamed et al. study in 2015 [14]; where they concluded that intrathecal nalbuphine; when compared to intrathecal morphine, it provides a significantly faster onset of pain relief probably because of its lipohilic properties; however, it doesn't seem to be as effective as intrathecal morphine in prolonging post-operative analgesia due to the ceiling effect of nalbuphine analgesia .

Large number of animal studies has been undertaken to prove that intrathecal nalbuphine was not neurotoxic; Rawal et al. in 1991 [15], studied the behavioral and histopathological effects following intrathecal administration of butorphanol, fentanyl, and nalbuphine in sheep, they found that nalbuphine was the least irritating to neural tissues even at large doses 15-24 mg it was not associated with any histopathological changes of the spinal cord [8].

The practice of intrathecal nalbuphine for over ten years didn't have any reports of neurotoxicity. Many studies have been conducted on pregnant patients, but they didn't reveal any unwanted effects [8].

Conclusion

The present research depicted that nalbuphine, fentanyl and pethidine as adjuvants to spinal anesthesia shorten the onset of sensory and motor block , prolong the duration of sensory and motor blockade, provide effective postoperative analgesia and prolong the period for first rescue analgesia with minimal hemodynamic and respiratory complications, however nalbuphine with the dose of 0.5 mg has a peculiar advantage over another opioid; it doesn't result in any significant adverse effects, it has the best quality of spinal block when added to intrathecal 0.5% heavy bupivacaine in patients undergoing lower limb surgeries.

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