Comparative Study between Intrathecal Morphine and Nalbuphine Added to Hyperbaric Bupivacaine 0.5% in Elective Cesarean Delivery

Khaled Mohammed Hassan, Hamza Aboalam Mahmood, Islam Khaled Moustafa*, Ghada Abd el-Gaber Rezk
Department of Anaesthesia, Intensive Care and Pain Management, Faculty of Medicine, Sohag University, Egypt
***Corresponding Author:** Islam Khaled Moustafa, **Mobile:** 002 01224081113, **Email:** eslamelmaghraby40@yahoo.com

ABSTRACT

Background: Many additives have been used to improve spinal anesthesia; morphine and nalbuphine are commonly used drugs.

Objective: This work aimed to compare intrathecal morphine and different doses of nalbuphine in elective cesarean section (CS).

Patients and Methods: This double-blinded, randomized controlled study was done on 150 patients, American Society of Anesthesiologist (ASA) grade I to II undergoing elective CS. Patients underwent spinal anesthesia 3 ml with 10 mg hyperbaric bupivacaine 0.5 % with the addition of a 1 ml volume (morphine or nalbuphine) according to the group; Group M: 150 µg morphine, Group N1: 1 mg nalbuphine, and Group N2: 2 mg nalbuphine.

Results: Intraoperative and postoperative hemodynamics, respiratory rate, SPO_2 and Apgar score were insignificantly different in all groups. Postoperative VAS was significantly decreased in group M and was insignificantly different between group N1 and group N2. Postoperative BROMAGE was significantly higher in group M. Time of rescue analgesia was significantly increased in group M and was insignificantly different between group N1 and group N2. Postoperative nausea and vomiting (PONV) was insignificantly different in all groups, and pruritus was significantly decreased in group N1.

Conclusions: As additives to hyperbaric bupivacaine in the spinal block, morphine was superior to nalbuphine in decreasing VAS and increased time for rescue analgesia by prolonged sensory block. Increasing the dose of nalbuphine up to 2 mg did not increase the analgesic effect. Nalbuphine is superior to morphine in decreasing pruritus, and both drugs have similar effects on neonatal APGAR score and hemodynamics

Keywords: Morphine, Nalbuphine, Cesarean Delivery.

INTRODUCTION

Spinal anesthesia (SA) for cesarean section (CS) is the most common and the most effective maneuver since it is quick to execute with fast onset and full relaxation of muscles. Lower rate of blockade failure, reduced doses of medications, minimal depression of neonates, and reduced aspiration pneumonia incidence are additional benefits of SA [1, 2].

Opioids used intrathecally synergize with local anesthetics (LA) and potentiate the sensory blockade (prolonging the postoperative analgesic role) with no increase in the sympathetic block. They are usually used as additives to LA to potentiate their role, minimize the doses of LA and decrease side effects of LA, and maintain hemodynamic stability [3].

Morphine is the basic reference drug of opioids to compare with its kind. It is a phenanthrene derivative that opiates prototypically in mu and kappa opioid receptors [4]. Efficient analgesia can be acquired from 0.1 to 2.5 mg of morphine. Low doses of intrathecal morphine are used to minimize adverse effects (pruritus, postoperative nausea and vomiting (PONV) and respiratory depression) and to provide effective and safe CS analgesia [5].

Nalbuphine, an agonist-antagonist opioid, has the ability to mitigate symptoms of mu and strengthen the effects of kappa. It was manufactured in an effort to generate analgesia without mu agonist's unwanted side effects [6]. Many researchers tried combining µ agonist opioids to reduce both incidence and severity of the common µ-agonist side effects (PONV, pruritus, urinary retention, unwanted sedation, and respiratory depression) with obtaining the advantages of analgesia of mu and kappa [7-8].

SUBJECTS AND METHODS

This double-blinded, randomized, and controlled clinical study was conducted at Sohag University Hospital from June 2019 to June 2020. Written consent was taken from all patients. 150 patients were included and their ages ranged from 18 to 35 years old with ASA grade I to II, and undergoing elective CS.

Ethical approval:

An approval of the study was obtained from Sohag University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

Aim of the study: comparative study between intrathecal morphine and nalbuphine and between different doses of nalbuphine (1 & 2 mg) in elective cesarean delivery regarding haemodynamics, block assessment, postoperative analgesia and analgesic requirement as primary outcome, side effects and neonatal assessment as secondary outcome.

Exclusion criteria: Patient refusal, patient with significant neurological, psychiatric, or neuromuscular disease, drug abuse, alcoholism, suspected coagulopathy, known allergy to some medications,

Received:2 /10 /2020
Accepted:20 /11 /2020

morbid obesity, septicemia, local infection at the block site and history of PONV or motion sickness.

Preoperative patients' evaluation included: 1) Complete history of any medical disease. 2) All patients fasted for 8 hours before the procedure 3) Clinical examination (i. Baseline heart rate (HR), mean arterial blood pressure (MAP), respiratory rate (RR) and oxygen saturation (SPO_2) ii-Chest examination, iii- Neck and upper and lower limbs examination iv- Airway evaluation 4) Investigations: Complete blood picture, renal function tests, liver function tests and prothrombin time and concentration.

Randomization and allocation:

Patients were divided into 3 equal groups by closed envelope randomization; Group M (n = 50): received 150 µg morphine in 1 ml volume, mixed with 10 mg hyperbaric bupivacaine 0.5 % (total volume 3 ml), Group N1 (n= 50): received 1 mg nalbuphine in a 1 ml volume, mixed with 10 mg hyperbaric bupivacaine 0.5 % (total volume 3 ml) and Group N2 (n = 50): received 2 mg nalbuphine in a 1 ml volume, mixed with 10 mg hyperbaric bupivacaine 0.5 % (total volume 3 ml).

Sample size calculation [(9)]:

$n = N*X / (X + N - 1)$, where, $X = Z_{\alpha/2}^2 * p*(1-p) / MOE^2$

$Z_{\alpha/2}$: is the critical value of the normal distribution at $\alpha/2$ (for a confidence level of 95%, α is 0.05 and $Z_{\alpha/2}$ is 1.96). MOE: is the margin of error (5%). P: is the sample proportion (50%). N: is the population size (10000). n: is the sample size.

X = 384

n = 370

Anesthetic plan:

IV-line cannula (20 gauge) was inserted. Intraoperative fluids were administered (Preload: 500-1000 ml ringer lactate (10-15 ml/kg) with the maintenance of 120 ml/hr).

Baseline pulse, noninvasive blood pressure, RR, SPO_2, and ECG were monitored. Patients were put in a sitting position, and sterilization was done. The level was L3-4 space, and the needle was Quincke needle (25 gauge). SA was done by LA injection (10 mg hyperbaric bupivacaine 0.5%) + morphine (150 µg) or nalbuphine (1 & 2 mg).

Assessment of the block: a- sensory block by the loss of pinprick sensation at the midaxillary line was checked to detect the level of block. b- motor block: was assessed by using Bromage score [(10)]; 4 grades (I: Free movement of legs and feet = Nil (0%), II: Just able to flex knees with free movement of feet = Partial block (33%), III: Unable to flex knees, but with free movement of feet = Almost Complete block (66%), IV: Unable to move legs or feet = Complete block (100%)).

Resuscitating drugs (atropine & ephedrine) and airway equipment were prepared preoperatively. Ranitidine 50 mg iv (H_2 receptor antagonist) was given preoperatively to prevent PONV.

Measurements:

Hemodynamics (HR & MAP) R.R and SPO_2 monitoring: a- Intraoperative: every 5 minutes until the end of the operation. b- Postoperative monitoring: at 1/2, 1, 1.5 and 2 hrs, then at 3, 4, 6, 12 and 24 hrs).

Assessment of the block:

a- Onset of the block; i- sensory block: it is the time of full deposition of LA, the level of block was detected by a pinprick at the midaxillary line. ii- motor block: it is the time of full deposition of LA. It was assessed by using the Bromage score.

b- Duration of block:

i- sensory block: a- Intraoperatively: by a pinprick at the midaxillary line to detect if there is a segmental regression or not. It was checked every 15 minutes at (15 min, 30 min, 45min, 60 min ….. etc.) till the end of the operation. b- Postoperatively: was checked every 30 minutes until regaining of pinprick sensation at 1/2 hr, 1 hr, 1.5 hr and 2hrs, then at 3 hrs, 4 hrs, 6 hrs, 12 hrs & 24 hrs). The pain was assessed using the visual analog score (VAS) (0-10); i- 0 - 3 mild pain, ii- 4 - 6 moderate pain, iii- 7 - 10 severe pain.

ii- Motor block was checked postoperatively every 30 minutes until regaining movement at 1/2 hr, 1 hr, 1.5 hr & 2hrs) then at 3 hrs, 4 hrs, 6 hrs, 12 hrs & 24 hrs).

Analgesic requirement: it is the time between loss of pinprick sensation and the first analgesic inquiry by the patient intraoperative and postoperative. Type and total dose of required analgesia: IM injection of Ketorolac 0.5 mg/kg (maximum daily dose 120 mg) was given as rescue analgesia when the patient complains of pain (VAS > 3).

Side effects:

a- Hemodynamically; 1. bradycardia (HR < 60 beats / min), IV atropine 0.01mg/kg/dose was given. 2. hypotension (MAP < 60 mmhg mean blood pressure and treated by exclusion of surgical causes, IV fluids and IV ephedrine 10 mg/dose were given) 3. Respiratory depression (SPO_2 < 95% and < 14 cycle/min RR and was corrected by good oxygenation).

b- Pruritus and itching: dexamethasone 4-8 mg was given to prevent and treat pruritus.

c- PONV. Metoclopramide 10 mg iv was given for treatment.

The neonatal assessment was done by Apgar score at 1 and 5 minutes after birth

Statistical analysis:

Statistical analysis was performed using the Statistical Package for the Social Sciences version 25 (IBM Inc., Chicago, IL, USA). Shapiro-Wilks normality test and histograms were used to test the distribution of quantitative variables to select accordingly the type of statistical testing; parametric or nonparametric.

Parametric variables were expressed as mean and standard deviation (SD) and were compared using F test among the three groups with post hoc (LSD) test to compare every two groups. Non-parametric variables

(e.g. VAS) were expressed as median and interquartile range (IQR) and were analyzed using the Kruskal-Wallis test; further analysis was performed by Mann–Whitney (U) test to compare every two groups. Categorical variables were expressed as frequency and percentage and were statistically analyzed by the Chi-square test. P value ≤ 0.05 was considered statistically significant.

RESULTS

In this study, 167 patients were assessed for eligibility, nine patients did not meet the criteria, and eight patients refused to participate in the study. The remaining 150 patients were randomly allocated into three groups (50 patients in each one). All 150 patients were followed-up and analyzed statistically (Figure 1).

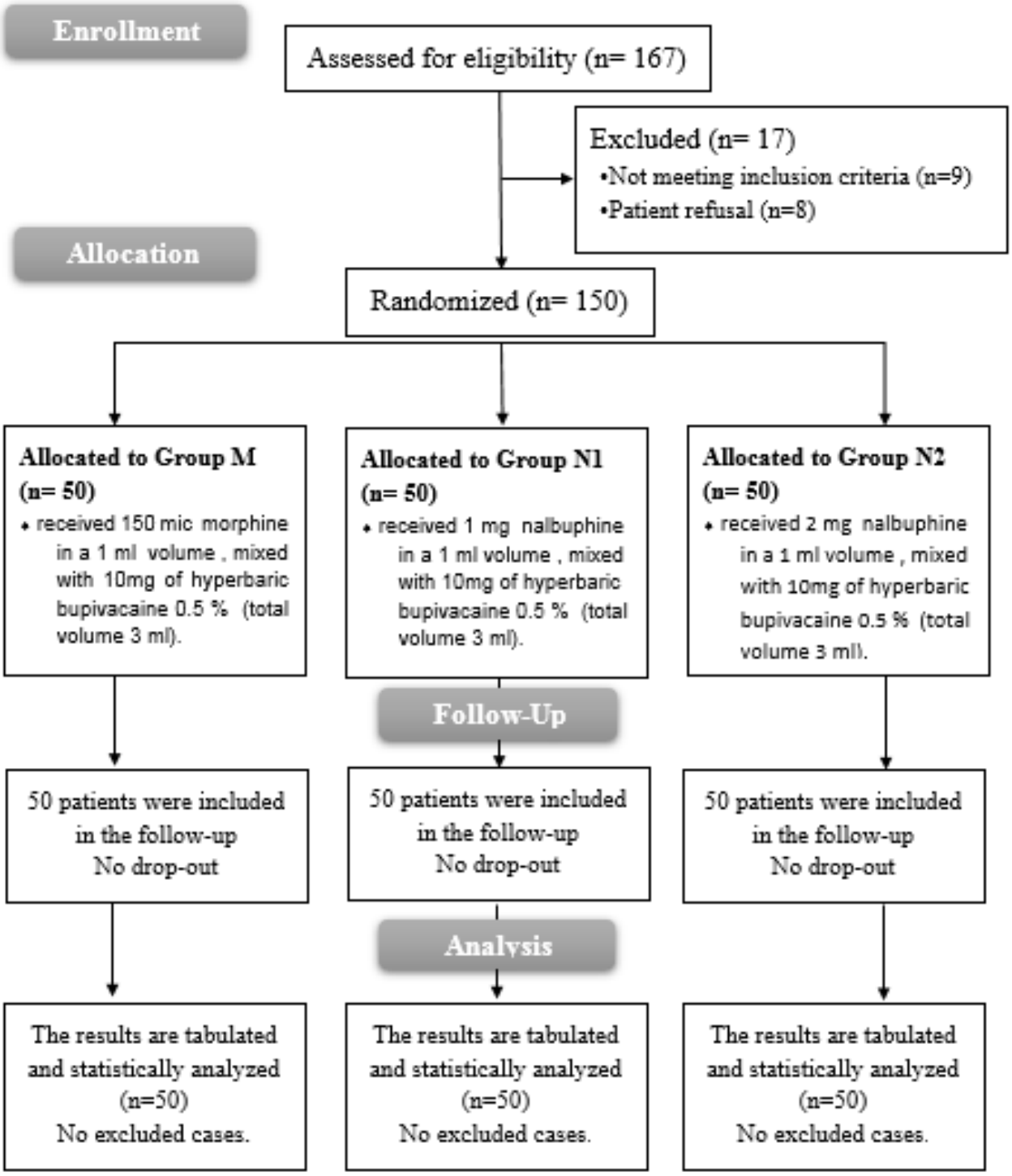


Figure (1): CONSORT flow diagram of the participants through each stage of the trial

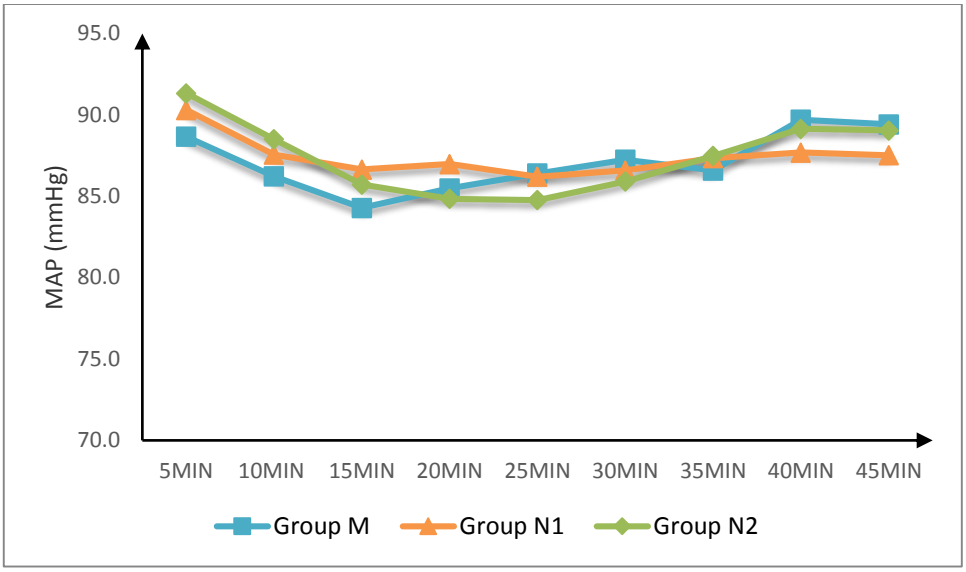
Patients' characteristics (age, BMI, and ASA) were insignificantly different among the three groups (P = 0.265, 0.55, and 0.811, respectively) (Table 1).

Table (1): Patients' characteristics among the three groups

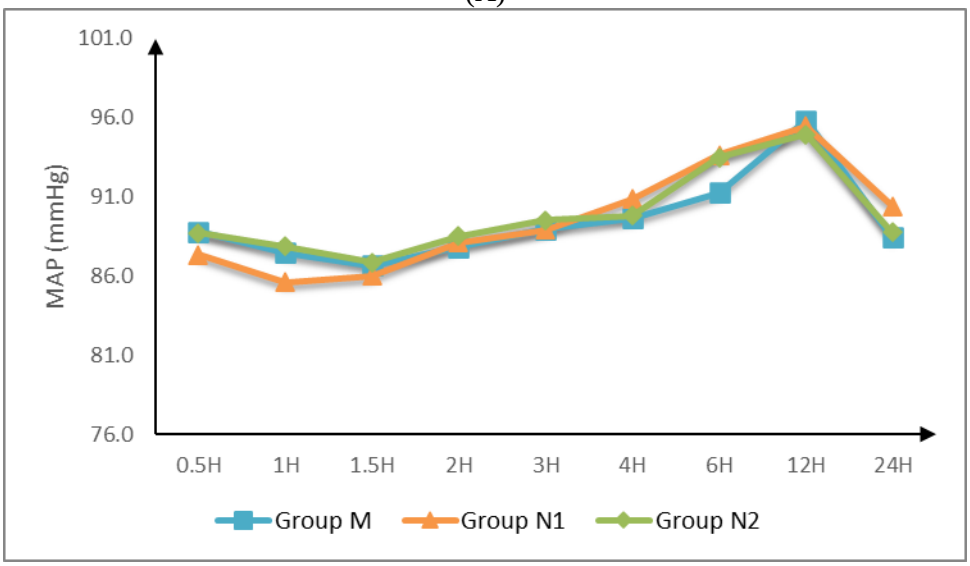
		Group M (n = 50)	Group N1 (n = 50)	Group N2 (n = 50)	P value
Age (years)	**Mean ± SD**	26.3 ± 3.47	26.78 ± 4.05	25.52 ± 4.11	0.265
	Range	18-30	18-33	18-32	
BMI (Kg/m^2)	**Mean ± SD**	25.82 ± 2.49	26.22 ± 2.38	26.31 ± 2.16	0.55
	Range	22-29.9	22-29.9	22-30	
ASA physical status	**I**	32 (64%)	35 (70%)	33 (66%)	0.811
	II	18 (36%)	15 (30%)	17 (34%)	

BMI: body mass index, ASA: American Society of Anesthesiologist

Intraoperative and postoperative hemodynamics (MAP and HR) were insignificantly different among the three groups at all time measurements. (Figures 2, 3).



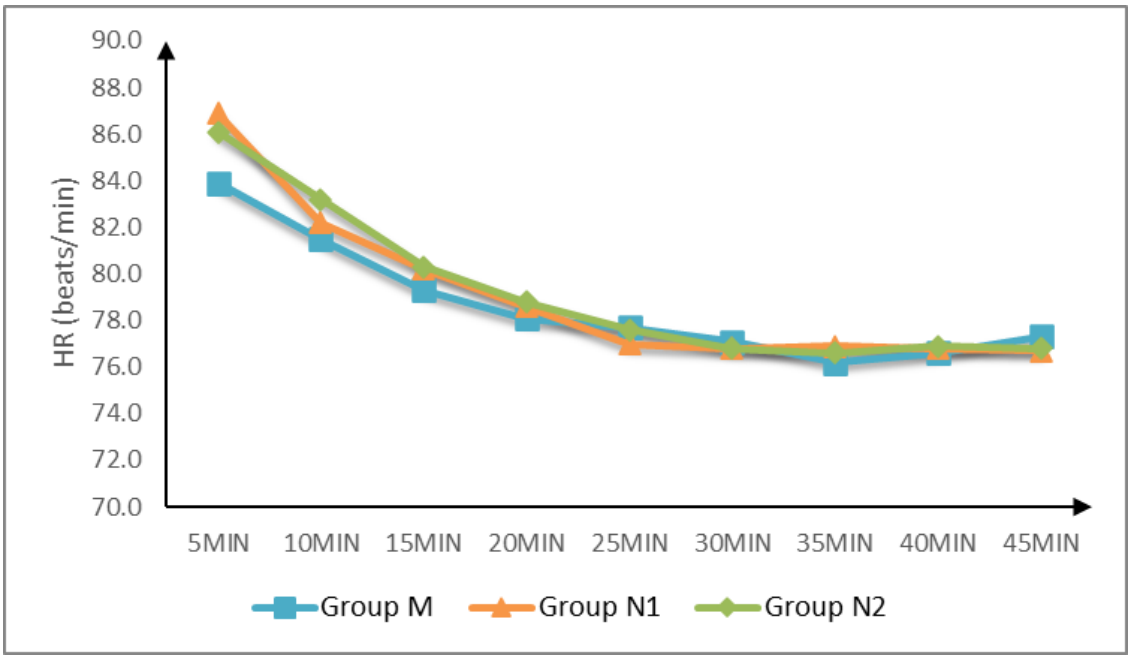
(A)

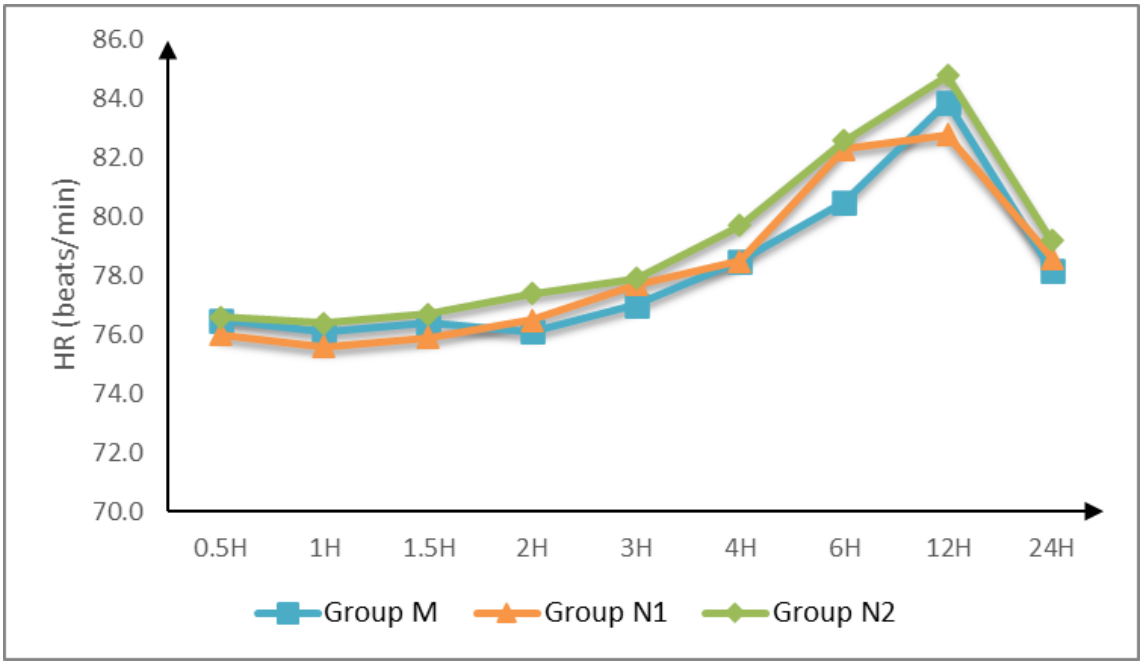


(B)

Figure (2): a) Intraoperative and **b)** postoperative mean arterial blood pressure (MAP) of the three groups

(A)





(B)

Figure (3): a) Intraoperative and **b)** postoperative heart rate (HR) of the three groups

Respiratory rate and SPO_2 were insignificantly different both intraoperatively and postoperatively among the three groups.

Postoperative VAS at 3, 4, and 6 hours was significantly decreased in group M than group N1 and group N2 (P1 <0.001 and P2 <0.001) and was insignificantly different between group N1 and group N2 (P3 = 0.627, 0.703 and 0.611 respectively). (Table 2)

Postoperative Bromage at 1.5, 2, 3, 4 and 6 hours was significantly increased in group M than group N1 and group N2 (P1 = 0.003, <0.001, <0.001, <0.001 and <0.001 respectively, P2 = 0.006, <0.001, <0.001, <0.001 and <0.001 respectively) and was insignificantly different between group N1 and group N2 (P3 = 0.854, 0.205, 0.255, 0.521 and 0.317 respectively). (Table 2).

Table (2): **Postoperative visual analogue scale (VAS) and BROMAGE among the three groups**

		0.5H	1H	1.5H	2H	3H	4H	6H	12H	24H
VAS										
Group M (n = 50)	**Median**	0.0	0.0	0.0	0.0	0.0	1.0	2.0	5.0	1.0
	IQR	0-0	0-0	0-0	0-0	0-0	0-1	2-3	4-5	0-1
Group N1 (n = 50)	**Median**	0.0	0.0	0.0	0.0	1.0	2.0	4.0	4.0	0.0
	IQR	0-0	0-0	0-0	0-0	0-0	1-3	4-5	4-5	0-1
Group N2 (n = 50)	**Median**	0.0	0.0	0.0	0.0	1.0	2.0	4.0	4.0	1.0
	IQR	0-0	0-0	0-0	0-0	0-1	2-3	4-5	4-5	0-1
P value		1	1	1	0.368	**<0.001***	**<0.001***	**<0.001***	0.699	0.446
P1						**<0.001***	**<0.001***	**<0.001***		
P2						**<0.001***	**<0.001***	**<0.001***		
P3						0.627	0.703	0.611		
BROMAGE										
Group M (n = 50)	**Median**	4.0	4.0	4.0	4.0	4.0	4.0	2.0	0.0	0.0
	IQR	4-4	4-4	4-4	4-4	4-4	4-4	1-2	0-0	0-0
Group N1 (n = 50)	**Median**	4.0	4.0	4.0	2.0	1.0	0.0	0.0	0.0	0.0
	IQR	4-4	4-4	4-4	1-2	0-1	0-0	0-0	0-0	0-0
Group N2 (n = 50)	**Median**	4.0	4.0	4.0	2.0	1.0	0.0	0.0	0.0	0.0
	IQR	4-4	4-4	4-4	2-2	0-2	0-0	0-0	0-0	0-0
P value		1	1	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	1	1
P1				**0.003***	**<0.001***	**<0.001***	**<0.001***	**<0.001***		
P2				**0.006***	**<0.001***	**<0.001***	**<0.001***	**<0.001***		
P3				0.854	0.205	0.255	0.521	0.317		

IQR: Interquartile range *significant as P value <0.05, P1: P value between group M and group N1, P2: P value between group M and group N2, P3: p value between group N1 and group N2

Apgar score was insignificantly different among the three groups at 1 and 5 minutes. The time of rescue analgesia was significantly different among the three groups (P < 0.001). Time of rescue analgesia was significantly increased in group M than in group N1 and group N2 (P1 < 0.001 and P2 < 0.001) and was insignificantly different between group N1 and group N2 (P = 0.903). VBGs (pH, PCO_2, PO_2, and HCO_3) were insignificantly different among the three groups. As regards side effects, PONV was insignificantly different among the three groups (P = 0.131), and pruritus was significantly decreased in group N1 than in group M and group N2 (P = 0.018) (Table 3).

Table (3): Apgar score, time of rescue analgesia, VBGs (umbilical vein sample) and side effects among the three groups

		Group M (n = 50)	Group N1 (n = 50)	Group N2 (n = 50)	P value	Post hoc	
APGAR score at 1 min	**Median**	8.0	8.5	9.0	0.052		
	IQR	7-9	7-9	8-10			
APGAR score at 5 min	**Median**	9.0	9.0	9.0	0.747		
	IQR	7-10	7-9	8-10			
Time of rescue analgesia (h)	**Mean ± SD**	11.4 ± 1.09	5.56 ± 0.67	5.54 ± 0.61	**<0.001***	**P1**	**<0.001***
	Range	8-12	4-6	4-6		**P2**	**<0.001***
						P3	0.903
pH	**Mean ± SD**	7.39 ± 0.04	7.39 ± 0.04	7.4 ± 0.04	0.587		
	Range	7.32 -7.45	7.33 -7.46	7.32 -7.46			
PCO_2	**Mean ± SD**	41.26 ± 3.23	41.12 ± 4.13	41.02 ± 3.40	0.946		
	Range	35-48	32-47	35-46			
PO_2	**Mean ± SD**	13.38 ± 2.28	13.34 ± 2.61	13.58 ± 2.29	0.866		
	Range	10-18	10-19	10-18			
HCO_3	**Mean ± SD**	19.12 ± 1.19	18.86 ± 1.48	18.9 ± 1.16	0.555		
	Range	17-21	16-22	17-21			
Side effects	**PONV (n, %)**	18 (36%)	11 (22%)	20 (40%)	0.131		
	Pruritis (n, %)	12 (24%)	2 (4%)	8 (16%)	**0.018***		

PONV: postoperative nausea and vomiting *significant as P value <0.05

DISCUSSION

Anesthesia of CS can be general or regional. The recommended technique is SA. SA prevents GA's neonate depressing action and the aspiration risk, with good postoperative analgesia. The most widely used LA is hyperbaric bupivacaine, though it lasts for 1.5–2 hours only. It begins slowly with short postoperative analgesia [(11)]. In agreement with our results, **Jain** [(12)] compared the effect of clonidine (30µg) and nalbuphine (2mg) intrathecally in lower abdominal surgeries. They found that nalbuphine did not prolong the analgesic time than clonidine. Moreover the patient needed earlier rescue analgesia. In addiotion, **Singhal *et al.*** [(13)] found that 0.8 mg nalbuphine had more analgesic duration than 0.4 mg but the analgesic duration time was less than 3 h which as our results. In agreement with our results, **Ahmed** [(14)] found that the addition of nalbuphine (in three different doses (0.8, 1.6, and 2.4 mg)) to intrathecal bupivacaine significantly increased the duration of analgesia postoperatively as compared to the control group with a better outcome in 1.6 mg group. Moreover, In agreement with our results, **Fournier *et al.*** [(15)] showed that intrathecal nalbuphine (400 µg) led to a significant decrease in the onset of analgesia but with also a decrease in analgesia duration compared to morphine (160 µg). Also, **Baxter *et al.*** [(16)] revealed that pain scores were decreased in epidural morphine (150µg) compared to nalbuphine (0.2 mg) in post-thoracotomy cases. It prolonged the duration of both sensory and motor block and prolonged the duration of postoperative analgesia.

In controversy with our results, **Ahmed** [(14)] compared the effect of intrathecal nalbuphine (800 µg) and fentanyl (25 µg) for elective CS. They showed that intrathecal nalbuphine and fentanyl group showed the same duration of motor block. Also, they showed that the duration of postoperative complete and effective analgesia was highly significantly longer in the nalbuphine group than the corresponding durations in the fentanyl group. The postoperative 24-h analgesic doses of ketorolac and pethidine were less in the nalbuphine group than in the fentanyl group. The cause of controversy was that nalbuphine, at a lower dose than in our study, was effective and provided analgesia more than fentanyl at 25 µg. In controversy with our results, **Sapate *et al.*** [(17)] showed that nalbuphine (0.5 mg) offered a better quality of SA compared to bupivacaine alone (15 mg) and also enhanced the postoperative analgesia. Also, **Bindra *et al.*** [(18)] found that intrathecal nalbuphine (0.8 mg) prolongs postoperative analgesia, duration of sensory and motor block more than intrathecal fentanyl (20 µg). The cause of controversy was that nalbuphine at a lower dose than in our study was effective and provided analgesia more than fentanyl at 20 µg. Moreover, **Borah *et al.*** [(19)] compared the effect of small and large doses of intrathecal nalbuphine (0.4,0.8 and 1.6 mg) with ropivacaine alone (22.5 mg) for elective lower limb surgery. They showed that duration of sensory and motor block was prolonged in nalbuphine groups than in the control group. There was a decrease in HR and MAP with intrathecal nalbuphine, but they showed no complications with nalbuphine. Also, **Naaz *et al.*** [(20)] studied patients undergoing lower limb orthopedic surgery. They compared the effect of intrathecal 25 µg fentanyl, 0.8 mg nalbuphine and 1.6 mg nalbuphine. Moreover**, Gomaa *et al.*** [(21)] found that the duration of postoperative analgesia was more prolonged in the nalbuphine group (0.8mg) than in the fentanyl group (25µg).

In controversy to our study, **Verma *et al.*** [(22)] compared the postoperative analgesic efficacy of intrathecal tramadol (50 mg) with nalbuphine (2 mg) as an adjuvant to hyperbaric bupivacaine (12.5 mg) in SA for lower limb orthopedic surgery. They concluded that the 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. Intrathecal tramadol could not make a significant difference in postoperative analgesia compared to when bupivacaine was used alone. In contrast with our results, **Mukherjee *et al.*** [(23)] studied the duration of analgesia with different lower dosages of intrathecal nalbuphine (0.2, 0.4, and 0.8 mg) to find out the optimum dose of intrathecal nalbuphine which could prolong the postoperative analgesia without increasing the side effects. Their study concluded that effective analgesia was increased with an increase in the doses of nalbuphine without any side effects. moreover, **Culebras *et al.*** [(24)] compared the efficacy for postoperative pain relief and adverse effects of three different doses (200, 800, and 1600 µg) of intrathecal nalbuphine with 200 µg of intrathecal morphine for CS. Among the nalbuphine-treated groups, 800-µg dose gave the longest durations of both complete and effective postoperative analgesia. Increasing the nalbuphine dose to 1600 µg did not have a further analgesic effect, which may be attributed to the nalbuphine ceiling effect above 800-µg dose. In addition, [(25)] showed that intrathecal nalbuphine 0.4 mg increased postoperative analgesia in the same way as intrathecal morphine 0.4 mg did.

Regarding intraoperative and postoperative MAP and HR, **Gupta *et al.*** [(26)] agreed with our study and used a large dose of intrathecal nalbuphine (2 mg) compared with (25 µg) intrathecal fentanyl. The study had done on patients undergoing lower limb orthopedic surgeries. They found that intrathecal nalbuphine (2mg) showed a prolonged duration of the sensory block than intrathecal (25µg) fentanyl but there was no difference in HR and MAP between groups. In agreement with our study, **Mostafa *et al.*** [(27)] 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 no clinically significant difference in intensity and duration of motor block and sensory analgesia. The incidence of hypotension,

bradycardia, itching, respiratory depression, PONV, and other side effects was minimal and was well tolerated by the patients. In controversy with our study, **Gomaa *et al.* [21]** compared intrathecal nalbuphine at 0.8 mg with fentanyl 25µg. The dose of nalbuphine was less than the dose of our research. The study was done on elective CS delivered with SA. They found that no significant difference was found between both groups (0.8 mg nalbuphine and 25 µg fentanyl) as regards fetal Apgar score, hemodynamics, and oxygen. In contrast to our results, **Bindra *et al.* [18]** showed that intrathecal nalbuphine (0.8 mg) prolonged postoperative analgesia, duration of sensory and motor block in comparison with intrathecal fentanyl (20 µg) and there were decrease in HR and MAP in intrathecal nalbuphine (0.8mg) compared to control group but they showed no complications with nalbuphine. Also, **Borah *et al.* [19]** showed a decrease in HR and MAP in intrathecal nalbuphine (0.4, 0.8 & 1.6mg) but they showed no complications with nalbuphine.

Regarding Apgar score and venous blood gases results, **Gomaa *et al.* [21]** agree with our study and found no significant difference between both groups (0.8 mg nalbuphine and 25µg fentanyl) regarding fetal Apgar score.

Regarding PONV and pruritus, **Moustafa and Saleh [28]** agree with our study. They reported that adding 1 mg nalbuphine to 0.2 mg morphine during SA antagonizes the morphine-induced adverse effects such as PONV and pruritus without any effect on the duration of postoperative analgesia, analgesia quality, or the degree of postoperative rescue analgesic requirement dose. In agreement with our results, **Yoon *et al.* [29]** found that pruritus incidence decreased with the nalbuphine group, but without a difference in PONV incidence and duration of analgesia was increased in both morphine with nalbuphine group and morphine group. In controversy to our results, **Culebras *et al.* [24]** compared the efficacy for postoperative pain relief and complications of (200, 800, and 1600µg) of intrathecal nalbuphine with 200µg of intrathecal morphine for CS. Neither pruritus nor PONV was noticed with 200µg or 800µg nalbuphine. They found that intrathecal 800-µg nalbuphine was considered the optimum dose that produces a similar analgesic effect as 200-µg morphine with minimal adverse effects.

CONCLUSIONS

As additives to hyperbaric bupivacaine in the spinal block, morphine was superior to nalbuphine in decreasing VAS and increased time for rescue analgesia by prolonged sensory block. Increasing the dose of nalbuphine up to 2 mg didn't increase the analgesic effect. Nalbuphine is superior to morphine in decreasing pruritus, and both drugs have similar effects on neonatal Apgar score and hemodynamic parameters.

Financial support and sponsorship: Nil
Conflict of Interest: Nil

REFERENCES

1. **Radra A, Halder R, Sen A *et al.* (2004):** Efficacy of low dose propofol for control of emetic episodes during caesarean delivery with spinal anaesthesia. Indian J Anaesth., 48: 31-4.
2. **Bogra J, Arora N, Srivastava P (2005):** Synergistic effect of intrathecal fentanyl and bupivacaine in spinal anesthesia for cesarean section. BMC Anesthesiology, 5: 1-6.
3. **Tan P, Chia Y, Lo Y *et al.* (2001):** Intrathecal bupivacaine with morphine or neostigmine for postoperative analgesia after total knee replacement surgery. Can J Anaesth., 48: 551-6.
4. **De Gregori S, De Gregori M, Ranzani G *et al.* (2012):** Morphine metabolism, transport and brain disposition. Metab Brain Dis., 27: 1-5.
5. **Eisenach J, Carpenter R, Curry R (2003):** Analgesia from a peripherally active kappa-opioid receptor agonist in patients with chronic pancreatitis. Pain, 101: 89-95.
6. **Charuluxananan S, Kyokong O, Somboonviboon W *et al.* (2001):** Nalbuphine versus propofol for treatment of intrathecal morphine-induced pruritus after cesarean delivery. Anesth Analg., 93: 162-5.
7. **Jaillon P, Gardin M, Lecocq B *et al.* (1989):** Pharmacokinetics of nalbuphine in infants, young healthy volunteers, and elderly patients. Clin Pharmacol Ther., 46: 226-33.
8. **Errick J, Heel R (1983):** Nalbuphine. A preliminary review of its pharmacological properties and therapeutic efficacy. Drugs, 26: 191-211.
9. **Daniel W, Cross, C (1999):** Biostatistics: A Foundation for Analysis in the Health Sciences. 7th edition. New York: John Wiley & Sons, Pp: 985.http://www.wiley.com /go /permissions.
10. **Bromage P (1978):** Epidural analgesia. 1st ed. Philadelphia: WB Saunders. Pp: 144.
11. **Ahmed F (2019):** Intrathecal nalbuphine versus fentanyl as an adjuvant to bupivacaine in spinal anesthesia for elective cesarean section: a randomized double-blind study. Res Opin Anesth Intensive Care, 6: 112-8.
12. **Jain T (2020):** A comparative study of clonidine versus nalbuphine as intrathecal adjuvants to 0.5% hyperbaric bupivacaine during lower abdominal surgeries–a randomized double blind interventional study. International Journal of Medical Biomedical Studies, 4: 150-5.
13. **Singhal D, Chowdhary A, Mehta N (2018):** Two Different Doses of Nalbuphine as an Adjuvant to Bupivacaine Intrathecally in Lower Abdominal and Lower Limb Surgeries-A Comparative Study. Journal of Medical and Dental Sciences, 17: 81-6.
14. **Ahmed F, Narula H, Khandelwal M *et al.* (2016):** A comparative study of three different doses of nalbuphine as an adjuvant to intrathecal bupivacaine for postoperative analgesia in abdominal hysterectomy. Indian Journal of Pain, 30: 23-9.
15. **Fournier R, Van Gessel E, Macksay M *et al.* (1998):** Intrathecal morphine versus nalbuphine for postoperative pain relief after total hip replacement. Anesthesiology, 89: 867-73.
16. **Baxter A, Samson B, Penning J *et al.* (1989):** Prevention of epidural morphine-induced respiratory depression with intravenous nalbuphine infusion in post-thoracotomy patients. Can J Anaesth., 36: 503-9.

17. **Sapate M, Sahu P, Thatte W *et al.* (2019):** A randomized, double blind, control study of the effects of adding nalbuphine to spinal bupivacaine for lower abdominal surgeries in elderly patients. Anaesthesia, Pain Intensive Care Med., 12: 145-8.
18. **Bindra T, Kumar P, Jindal G (2018):** Postoperative analgesia with intrathecal nalbuphine versus intrathecal fentanyl in cesarean section: A double-blind randomized comparative study. Anesthesia Essay and Researches, 12: 561-5.
19. **Borah T, Dey S, Yunus M *et al.* (2018):** Effect of different doses of intrathecal nalbuphine as adjuvant to ropivacaine in elective lower limb surgeries: A dose finding study. Indian Journal of Anaesthesia, 62: 865-69.
20. **Naaz S, Shukla U, Srivastava S *et al.* (2017):** A Comparative Study of Analgesic Effect of Intrathecal Nalbuphine and Fentanyl as Adjuvant in Lower Limb Orthopaedic Surgery. Journal of Clinical and Diagnostic Research, 11: 25-8.
21. **Gomaa H, Mohamed N, Zoheir H *et al.* (2014):** A comparison between postoperative analgesia after intrathecal nalbuphine with bupivacaine and intrathecal fentanyl with bupivacaine after cesarean section. Egyptian Journal of Anaesthesia, 30: 405-10.
22. **Verma D, Naithani U, Jain D *et al.* (2013):** Postoperative analgesic efficacy of intrathecal tramadol versus nalbuphine added to bupivacaine in spinal anaesthesia for lower limb orthopaedic surgery. Journal of Evolution of Medical Dental Sciences, 2: 6196-207.
23. **Mukherjee A, Pal A, Agrawal J *et al.* (2011):** Intrathecal nalbuphine as an adjuvant to subarachnoid block: What is the most effective dose? Anaesthesia Essays and Researches, 5: 171-5.
24. **Culebras X, Gaggero G, Zatloukal J *et al.* (2000):** Advantages of Intrathecal Nalbuphine, Compared with Intrathecal Morphine, After Cesarean Delivery: An Evaluation of Postoperative Analgesia and Adverse Effects. Anaesthesia & Analgesia, 91: 601-5.
25. **Lin M (1992):** The analgesic effect of subarachnoid administration of tetracaine combined with low dose morphine or nalbuphine for spinal anesthesia. Aana J., 30: 101-5.
26. **Gupta K, Rastogi B, Gupta P *et al.* (2016):** Intrathecal nalbuphine versus intrathecal fentanyl as adjuvant to 0.5% hyperbaric bupivacaine for orthopedic surgery of lower limbs under subarachnoid block: A comparative evaluation. Indian Journal of Pain, 30: 90-96.
27. **Mostafa M, Mohamad M, Farrag W (2011):** Which has greater analgesic effect: intrathecal nalbuphine or intrathecal tramadol. J Am Sci., 7: 480-4.
28. **Moustafa M, Saleh R (2012):** Nalbuphine added to intrathecal morphine in total knee arthroplasty, effect on postoperative analgesic requirements and morphine related side effects. Alexandria Journal of Medicine, 48: 120-5.
29. **Yoon H, Jee Y, Hong J (2002):** A Comparison of Analgesic Effects and Side Effects of Intrathecal Morphine, Nalbuphine and a Morphine-Nalbuphine Mixture for Pain Relief during a Cesarean Section. Korean Journal of Anesthesiology, 42: 627-33.