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Comparison of Intrathecal Bupivacaine + Nalbuphine with Bupivacaine alone for Intraoperative Analgesia in Patients undergoing Caesarean Section

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ABSTRACT

Objectives: To compare the efficacy of intrathecal bupivacaine combined with nalbuphine and bupivacaine alone for intraoperative analgesia in cesarean section procedures. **Study design:** Randomized controlled trial. **Place and duration of study:** Department of Anesthesia, Fauji Foundation Hospital Rawalpindi from March 2025 to May 2025. **Methods:** A total of 70 pregnant women aged >18 to < 45 years with a gestational age ≥ 37 weeks, scheduled for elective cesarean section under spinal anesthesia were enrolled in this study and randomized into two equal groups of 35 patients each. Women in Group BN received intrathecal bupivacaine with nalbuphine, while women in Group B only received intrathecal bupivacaine. The primary outcomes were set as block onset time and block duration (both sensory and motor) while secondary outcomes included time to rescue analgesia and the occurrence of adverse events. **Results:** The mean age of women in this study was 28.74 ± 5.4 years ranging from 19 to 42 years. The results of primary outcomes of the study showed that addition of nalbuphine significantly accelerated the block onset (both sensory and motor, with p< 0.0001 and p<0.001 respectively) and prolonged duration of block (Both sensory and motor, p<0.001 for both). Time required for the first rescue analgesia was also significantly higher in Group BN compared to Group B (p<0.001). There was no significant difference between the two groups for different adverse events recorded during the study. **Conclusion:** Nalbuphine when combined with intrathecal bupivacaine offered significantly faster onset of both sensory and motor blockade, prolonged duration of anesthetic effect, and prolonged time to rescue analgesia in cesarean section procedures.

INTRODUCTION

Caesarean section (CS) is among the commonly performed procedures in women undergoing childbirth. With a continuing advancement in health care facilities, there is continuous icrease in these procedures, observed in all regions the world. As per the World Health Organization (WHO) report, CS accounts for approximately 21% of all births at global level, while some regions experience even high rates exceeding 50%.[1] This surgical intervention is often life-saving for both mother and infant, however presents some unique challenges related to anesthesia.[1,2] These challenges appear in the shape of providing optimal surgical conditions, maternal comfort, fetal safety, and rapid recovery. Providing effective analgesia with minimal hazards is thereby crucial in a successful CS procedure. Spinal anesthesia (SA) is the preferred technique for CS due to ease of administration, rapid onset, reliability, superior analgesia, reduced aspiration and minimal neonatal depression risks. This also allows maternal consciousness during child birth and facilitate the immediate maternal-infant bonding.[3,4]

Optimal outcomes of the SA are associated with the selection of anesthetic agents which can provide adequate intraoperative analgesia along with minimal adverse effects related to anesthesia.[5] Bupivacaine, a long-acting local anesthetic, has been used with confidence over decades for SA during cases of CS. Predictable pharmacokinetics of Bupivacaine give the confidence of its use for procedures lasting 2 to 3 hours. With the intrathecal administration, bupivacaine provides effective sensory and motor blockade (within 2–5 minutes). However, hyperbaric bupivacaine has some inherent limitations, especially when used alone as local anesthetics (LA).[6] The pain associated with CS is complex, arising from multiple sources including peritoneal stretching, visceral manipulation, and uterine exteriorization. While bupivacaine effectively blocks somatic pain pathways, it inadequately attenuates visceral pain components, leading

to intraoperative pain and postoperative discomfort for the patient. The quest for enhanced analgesic action has led researchers to explore various adjuvant medications that can be safely combined with LA to improve the quality of SA.[7]

Various spinal adjuvants have been studied, including α2 agonists, neostigmine, ketamine, and opioids, though none have shown efficacy without causing side effects. Opioids (like morphine and fentanyl) improve block quality and prolong postoperative analgesia, allowing lower doses and better analgesia, however, still cause incidences of adverse effects.[8]

Nalbuphine (a semi-synthetic opioid) primarily acts as a κ-receptor agonist and partially as μ-receptor antagonist. This mixed profile exhibits a ceiling effect for respiratory depression while maintaining potent analgesic properties and markedly reducing pruritus, nausea, and urinary retention. With these actions, nalbuphine is more adjuvant for obstetric anesthesia and a safer option than traditional pure μ-agonists.[9]

Recent studies have reported that addition of intrathecal nalbuphine to bupivacaine prolongs sensory block, improves intraoperative comfort, reduces breakthrough pain, and increases patient satisfaction. This synergistic pharmacological effect, also allows dose reduction compared to bupivacaine alone.[10]

CS is a frequently performed procedure in Pakistan and SA is the mostly commonly employed anesthetic technique. Evaluating this combination is vital for evidence-based decisions in CS and a comparative efficacy data remains an area of interest for our local health care professionals, however, limited evidence is available in our native population, performed in our local healthcare settings. This study therefore aimed to compare the intraoperative analgesic efficacy of intrathecal bupivacaine with nalbuphine versus bupivacaine alone in CS procedures. The findings of our research will provide guidance for a more effective and longer-lasting spinal analgesia to improve outcomes.

METHODOLOGY

This randomized control trial was conducted at the Department of Anesthesia, Fauji Foundation Hospital Rawalpindi from March 2025 to May 2025 over a period of 3 months. Approval from the institutional review board was obtained prior to the start of this study. A written consent was obtained from each participant.

Sample size was calculated as per following assumptions:

m1 (Motor block onset time with Bupivacaine) = 5.51 ± 0.73 min.

m1 (Motor block onset time with Bupivacaine+ Nalbuphine) = 4.83 ± 0.95 min.[11]

With alpha = 5% (two sided) and power= 90%, the estimated sample size n1=33, n2=33.

We, however, selected 70 patients, with 35 patients in each group.

A total of 70 pregnant women aged >18 to < 45 years with a gestational age ≥ 37 weeks, planned for elective CS under SA having ASA Grade I or II were included in this study. After the enrolment women were divided in to two equal groups of 35 patients each, Group B (Bupivacaine group) and Group BN (Bupivacaine+ Nalbuphine group) through computer generated sheet.

Exclusion criteria was set as women with weight < 60 kg or > 100 kg; any CNS disease; significant cardiac or respiratory pathology; temperature < 36.1 °C or > 37.2 °C; hypersensitivity to study drugs; hypotension; or anticipated neonatal prematurity/low birth weight. Women with any contraindications to spinal anesthesia like coagulopathy (INR ≥ 1.4 or platelets < 100×10^9 L^{-1}) or infection at puncture site were also excluded.

Demographic details and clinical history was noted for each study participant. All women received a preload of Ringer's lactate 15 mL kg^{-1}. With the patient in the sitting position, a 25-gauge Quincke needle was inserted at the L3–L4 interspace; the study drug was then injected intrathecally over 10 s, after which the patient was positioned supine with left uterine displacement. Standard ASA monitoring was applied in each case.

Women in Group B received 2.5 mL of 0.5% hyperbaric bupivacaine (12.5 mg) combined with 0.8 mg nalbuphine in 0.5 mL sterile water (total volume 3 mL), while women in Group BN received 2.5 mL of 0.5% hyperbaric bupivacaine with 0.5 mL preservative-free saline (total volume 3 mL).

The primary outcomes were set as block onset time and block duration (both sensory and motor) while secondary outcomes included time to rescue analgesia and the occurrence of adverse events.

Sensory block onset time was measured as the time (in minutes) from the intrathecal injection to the disappearance of pain sensation (assessed using a pin-prick test) at the T5 dermatome.

Motor block onset time was calculated as the time (in minutes) from the intrathecal injection until the patient reaches a Bromage score of 3. (The Bromage scale: 0 – full flexion of the extended leg at the hip joint; 1 – inability to flex the extended leg but ability to flex the knee; 2 – ability to move only the foot; and 3 – complete inability to move the foot).

Sensory block duration was determined as the time interval (in minutes) from the administration of the spinal block until the patient reports the first pain sensation. (Assessed by a Visual Analogue Scale 0-10 (VAS) score> 3 where 0 indicated no pain and 10 indicated a worst imaginable pain.)

Motor block duration was measured from the time of administration of intrathecal injection until complete recovery of motor function (Bromage score=0).

Analgesia duration was measured as the time (in minutes) from the administration of intrathecal injection until the patient required the 1st dose of rescue analgesia (VAS score >3).

Adverse events were monitored throughout the intraoperative and postoperative period (upto 8 hours) and included hypotension, bradycardia, nausea/vomiting, pruritus, urinary retention, and respiratory depression.

The data was analyzed by using SPSS version 25. Descriptive statistics were used to calculate mean and standard deviation for continues variables (age, BMI, duration of surgery, sensory and motor block onset, duration of sensory and motor block and analgesia

duration) while frequencies and percentages for categorical variables (ASA status and the incidences of adverse effects). Data normality of continuous variables was assessed by utilizing Shapiro-Wilk test. Independent t-test was applied on continues variables while Chi-square test was used to compare the categorical variables. A p value < 0.05 was taken as significant to establish the significance of difference between the two groups.

RESULTS

The mean age in this study was 28.74 ± 5.4 years ranging from 19 to 42 years. The group wise details of demographics and clinical characteristics are shown in Table-I.

TableI

Demographics and clinical characteristics (n= 70)

Demographics and clinical characteristics		Group B (n=35)	Group BN (n=35)
Age (Mean± SD) years		29.09± 5.22	28.4±5.64
Gestational age (Mean± SD) weeks		38.74±0.92	38.89±0.83
BMI (Mean± SD) Kg/m²		27.94±2.09	28.63±2.24
ASA grade	I n (%)	22 (62.86)	13 (37.14)
	II n (%)	24 (68.57)	11 (31.43)
Duration of surgery (Mean± SD) minutes		46.63±4.8	47.26±4.47

The results of primary outcomes of the study showed that addition of nalbuphine significantly accelerated block onset (Both sensory and motor, p<0.0001 and p<0.001 respectively) and prolonged duration of block (Both sensory and motor, p<0.0001 for both) as shown in Table-II.

Table II

Onset of block, duration of block and duration to require first analgesia (n= 70)

Primary outcomes variables	Group B (n=35)	Group BN (n=35)	p-value
Sensory block onset (Mean± SD) minutes	2.4±0.54	1.74± 0.46	< 0.0001
Motor block onset (Mean± SD) minutes	5.67±0.75	5.1±0.59	< 0.001
Duration of sensory block (Mean± SD) minutes	119.74±6.34	144.34±18.45	< 0.0001
Duration of motor block (Mean± SD) minutes	145.77±17.81	172.49±7.84	< 0.0001

Time to first analgesia required was also significantly higher in Group BN compared to Group B (p=0.001). The comparison showed no significant difference between the two groups for adverse events including hypotension, bradycardia, Nausea/Vomiting and other events, may be related to this treatment regimen, as shown in Table-III.

Table III

Duration of analgesia and adverse events (n=70)

Secondary outcomes variables		Group B (n=35)	Group BN (n=35)	p-value
Duration of analgesia (Mean± SD) minutes		161.83± 5.22	207.66± 6.9	< 0.0001*
Incidences of adverse events	Hypotension n (%)	6 (17.1)	5 (14.3)	0.74*
	Bradycardia n (%)	2 (5.7)	3 (8.6)	0.1**
	Nausea/Vomiting n (%)	4 (11.4)	6 (17.1)	0.73**
	Pruritus n (%)	1 (2.9)	1 (2.9)	0.1**
	Urinary retention n (%)	2 (5.7)	1 (2.9)	0.55**
	Respiratory depression n (%)	0 (0)	0 (0)	----

DISCUSSION

The primary outcomes of our study showed that addition of nalbuphine significantly accelerated the block onset (both sensory and motor, with p< 0.0001 and p<0.001 respectively) and prolonged duration of block (Both sensory and motor, p<0.001 for both). Time to first rescue analgesia required was also significantly higher in Group BN compared to Group B (p<0.001). There was no significant difference between the two groups for different adverse events recorded during the study.

Numerous studies have worked on various spinal adjuvants that can be safely combined with local anesthetics to improve the efficacy of SA. The clinical relevance of such adjuvants arises from the substantial burden of intraoperative pain reported during CS. A systematic review by Charles EA including 34 studies (11,351 patients) revealed a concerning 17% pooled incidence (95%CI: 13%-22%) of intraoperative pain during CS using neuraxial anesthesia, highlighting the significant burden of visceral pain during CS. While SA demonstrated superior efficacy with 14% pain incidence compared to epidural top-up at 33%, the review emphasized the requirement for further research to optimize pain management strategies for cesarean delivery.[12]

Addition of intrathecal nalbuphine is discussed in national and international studies with varying outcomes; however, most have demonstrated benefits of nalbuphine as a spinal adjuvant. Amin SR compared intrathecal bupivacaine (12.5 mg) alone and with adjuvants nalbuphine (0.8 mg). The adjuvant use of nalbuphine showed faster sensorimotor block onset than the alone bupivacaine including sensory onset (p<0.01), motor onset (p=0.02) and offered prolonged sensory block (p< 0.001) and motor block (p< 0.001) with enhanced analgesia (p<0.001), without adding adverse effects.[11] Similarly, Bachula L et al. compared the intrathecal bupivacaine 0.5% with nalbuphine 0.8 mg versus bupivacaine alone in 60 patients undergoing CS with SA. The adjuvant use of these drugs showed significantly superior outcomes, including faster onset of both sensory and motor blocks (p<0.0001 and p<0.001, respectively) and prolonged duration of both blocks (p<0.0001 for each).The combination also provided longer analgesia (203.33 vs. 120.16 min) with stable hemodynamics and minimal side effects making nalbuphine as a viable opioid alternative.[13] Adjuvant nalbuphine has also demonstrated unique advantages when compared to other established adjuvants. Deori KC et al compared nalbuphine (0.8mg) versus fentanyl (25µg) as adjuvants to intrathecal bupivacaine. Nalbuphine significantly prolonged sensory and motor block regression time (P<0.0001) compared to fentanyl, although, fentanyl achieved faster Bromage-3 motor block (p=0.04) compared to the adjuvant nalbuphine.[14] Furthermore, Mohamed SA et al. reported that intrathecal nalbuphine significantly reduced visceral pain incidence (p<0.0001) and rescue analgesic requirements compared to the control group (11.1% vs.

60% respectively) during CS with uterine exteriorization. As found in other studies this combination was safer than fentanyl, demonstrating fewer side effects making nalbuphine a safer alternative in obstetric procedures.[15]

The benefits of advent nalbuphine are also shared in lower limb procedures beyond obstetrics. Gupta KL et al studied the adjuvant use of intrathecal nalbuphine (1 mg) combined with hyperbaric bupivacaine in orthopedic surgeries under SA. While this combination did not show significant differences in sensory and motor block onset times ($p > 0.05$), it significantly prolonged postoperative analgesia ($p<0.0001$) supporting its use as an effective adjuvant without adding significant side effects across various surgical specialties.[16] Shalini A et al. also compared the intrathecal nalbuphine (1mg) versus clonidine (30µg) as adjuvants to bupivacaine and demonstrated nalbuphine's superior onset profile with faster sensory and motor block). On the other hand, clonidine provided significantly longer duration of analgesia and motor blockade indicating that the choice between adjuvants may depend on specific clinical requirements. [17]

In view of the significant burden of intraoperative pain during CS delivery and the need for optimal maternal comfort, nalbuphine-bupivacaine combination, is a valuable advancement in obstetric anesthesia procedures for anesthesiologists to confidently incorporate this to improve patient outcomes and satisfaction in these procedures.

Single center settings and small sample size, are the major limitation to the generalizability of our findings. Future studies covering these limitations will add up in this important data regarding pain management during CS procedures.

CONCLUSION

The addition of intrathecal nalbuphine to bupivacaine alone significantly enhances SA and demonstrated significantly faster onset of both sensory and motor blockade in patients undergoing CS. This administration prolongs the duration of anesthetic effect and extends time to first rescue analgesia requirement without increased incidence of adverse effects. These findings suggest nalbuphine as an effective and safe adjuvant to bupivacaine for SA in CS offering clinically advantageous anesthetic option for this commonly performed surgical process.

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