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THE ADDITIONAL REQUIREMENT OF NALBUPHINE AS RESCUE ANALGESIC ALONG WITH PARACETAMOL AND KETOROLAC IN PAIN MANAGEMENT OF PATIENTS UNDERGOING ELECTIVE CESAREAN SECTION IN FIRST 24 HOURS

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Abstract

Background: *Nalbuphine can be used as a supplement for obstetrical analgesia during labour and delivery. Paracetamol is the drug of choice in patients that cannot be treated with non-steroidal anti-inflammatory drugs (NSAID). Ketorolac has advantages over narcotic analgesics. The aim of our study was to evaluating the requirement of nalbuphine along with paracetamol and ketorolac in post-operative cesarean patient.*

Objective: *To determine the additional requirement of Nalbuphine as a rescue analgesic along with Paracetamol and Ketorolac in postoperative pain management of patients undergoing elective cesarean section in first 24 hours.*

Material and Methods: *This descriptive study was conducted in the Department of Anesthesia at Liaquat National Hospital and Medical College, Karachi, from January 2025 to April 2025. Total 139 female patients were included. Pain assessment was conducted using the Visual Analogue Scale (VAS). Nalbuphine was administered upon reaching VAS score above 4. Postoperative analgesia protocols consisted of intravenous Paracetamol and Ketorolac. Pain severity was assessed at specific intervals following surgery. The Chi-square test and Repeated Measure ANOVA were applied for analysis.*

Results: *The mean age was 29.78±5.16 years. The need for rescue analgesia was highest at 0 hour (30.2%) and no additional requirement at 24 hours. A significant variation in pain scores over time ($p<0.001$) was observed. A statistically significant association between diabetes and hypertension with rescue analgesia requirement at 0 hours ($p=0.044$ and $p=0.050$, respectively) was also observed.*

Conclusion: *This pain intensity fluctuated significantly between different time points, peaking at 6 hours. The highest need for rescue analgesia at 0 hours and none at 24 hours.*

INTRODUCTION

Most women worldwide experience childbirth at least once in their lives.[1] In many countries, the rate of caesarean sections in the total number of births has increased from 30 to 40%.[2] In many women,

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caesarean birth is associated with moderate-to-severe postoperative pain.[3] The Pain is a complex and important protective phenomenon.[4] Adequate intra and postoperative pain relief is of utmost importance, as it reduces patient's distress and ensures a rapid, uncomplicated recovery after general anaesthesia.[5] Pain management should be an essential part of the perioperative standard operating procedures. The evidence for individual analgesic measures albeit carried out millions of times is surprisingly low.[1]

The incidence of chronic pain after caesarean section is determined between 6.1% and 11.5%, depending on the definition of the chronic pain,[6] and 9.6% of chronic pain patients after caesarean section complain of severe pain. As for chronic postoperative pain after other surgeries, it can also be stated for chronic pain after caesarean section that the intensity as well as the duration of acute postoperative pain are the main postoperative predictors.[7] At this point, preexisting chronic pain is the main predictor of a higher pain intensity of acute postoperative pain.[8] It would be desirable to state that a specific anaesthesiological or perioperative pain regimen would have a beneficial effect on the incidence of postoperative chronic pain after caesarean section.[1]

Neuraxial procedures, mostly spinal but also epidural anesthesia, have been preferred for some time compared to general anesthesia for caesarean birth.[9,10] It can be assumed that general anesthesia is used well below 5% of elective caesarean sections in developed countries.[11,12] Nowadays, the central neuraxial blockade is the preferred technique for cesarean section.[13] But, there are various conditions which are absolute indications for general anesthesia for cesarean sections like maternal refusal to the central neuraxial blockade, inadequate effect of a regional block, the urgency of cesarean section, allergic to local anesthetics and other contraindications to regional blocks like patients having coagulopathy and some other systemic disorders like cardiac brain, spinal cord and spine related problems.[14]

Paracetamol, NSAIDs, opioids,[15] incision site infiltration with local anesthesia, and different maneuvers of regional anesthesia [as transversus abdominis plane block (TAP), oblique subcostal transversus abdominis plane block (OSTAP or STAP), and paravertebral block] are the typical analgesic options for postoperative pain.[16–18] These methods, with the exception of paravertebral block, only treat somatic pain, making them insufficient in some cases.[14,19]

Ketorolac trimethamine is a nonsteroidal anti-inflammatory drug (NSAID). Because of its strong affinity for protein, ketorolac uses prostaglandin synthesis to provide its analgesic effects. Ketorolac can manage moderate to severe post-operative pain and has a similar analgesic effect to opioid medicines while lasting longer. Ketorolac has advantages over narcotic analgesics, including a better safety profile and the absence of respiratory and central nervous system depression.[20]

Assessing pain using visual analogue scale (VAS) in the postoperative period is essential to improve pain management. Regular audits are mandatory for the continuous development of patient care and improvement in pain management service.[21]

The semi-synthetic opioid analgesic, Nalbuphine belongs to the phenanthrene family. Although Nalbuphine possesses opioid antagonist activity, there is evidence that in nondependent patients it will not antagonize an opioid analgesic administered just before, concurrently, or just after an injection.[22] When used concomitantly with Nalbuphine the administered opioid analgesic, general anesthetics, tranquilizers, phenothiazines, hypnotics, sedatives and other CNS depressants may exhibit an additive effect. In such scenario of combined therapy contemplation, dose of one or both agents should be reduced.[23]

Nalbuphine is commonly used drug for per-operative pain management and is associated with certain side effects such as emesis, sedation, central nervous system depression, and pruritus due to its effect on μ^2 receptors.[23]

The aim of our study was to observe the pain management strategy used in our hospital for elective cesarean section patients by evaluating the requirement of nalbuphine along with paracetamol and ketorolac in post-operative cesarean patient.

MATERIAL AND METHODS

This descriptive study was conducted in the Operation Theater of the Department of Anesthesia at Liaquat National Hospital and Medical College,

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Karachi, over a period of six months from January 2025 to April 2025, following approval from the institutional ethical committee and the College of Physicians and Surgeons Pakistan (CPSP). The sample size was calculated using the Sample Size Calculator by Wan Nor Arifin, based on a prevalence rate of 36% for the need for additional rescue analgesia observed in a pilot study (9 out of 25 patients). A margin of error of 8% was set, yielding a required sample size of 139 patients. A non-probability consecutive sampling technique was used for patient recruitment. Inclusion criteria included patients scheduled for elective cesarean section under spinal anesthesia, with a parity of either 1 or 2, aged between 20 and 35 years, and classified as ASA-II. Patients who refused to participate, underwent emergency cesarean sections, were on sedatives or anxiolytics, had known allergies to any of the drugs under investigation, or required general anesthesia were excluded from the study.

Obesity was defined in accordance with BMI classification, where a body mass index (BMI) exceeding 25 kg/m² was considered indicative of obesity. Diabetes mellitus was characterized as a previously diagnosed medical condition in patients who had been receiving medical treatment for at least six months prior to enrollment in the study. Similarly, hypertension was defined as a previously diagnosed condition requiring medical treatment over the same six-month period. Pain was defined according to the widely accepted definition by the International Association for the Study of Pain (IASP). Within the context of current study, pain was regarded as a symptom of postoperative recovery and was assessed using the VAS. Pain assessment was conducted using the Visual Analogue Scale (VAS), a well-established measurement tool for evaluating subjective pain intensity. This scale records pain perception on a continuum from 0 to 10, where a score of 0 represents no pain, 1 to 3 corresponds to mild pain, 4 to 6 indicates moderate pain, and 7 to 10 signifies severe pain. Additional rescue analgesia was defined as the administration of Nalbuphine in patients who exhibited inadequate pain relief despite routine postoperative analgesic management with Paracetamol and Ketorolac. Nalbuphine was administered intravenously at a dose of 0.1 mg/kg upon reaching a VAS score above 4.

Patients meeting the inclusion criteria were enrolled after obtaining written and informed consent. On the day of surgery, data were recorded in a predesigned proforma, including patient identifiers, demographic information, and details of postoperative pain management. Postoperative analgesia protocols consisted of intravenous Paracetamol at a dose of 1 g every six hours and Ketorolac at 30 mg intravenously twice daily. Pain severity was assessed at specific intervals: immediately postoperative (0 hours), and at 1, 3, 6, 12, 18, and 24 hours following surgery. Rescue analgesia was administered if the VAS score exceeded 4, and the Nalbuphine dosage and timing of administration were documented.

Data analysis was performed using IBM SPSS Statistics version 27. The normality of quantitative variables was assessed using the Shapiro-Wilk test. Mean and standard deviation or median and interquartile range were computed for continuous variables, including age, height, weight, BMI, and VAS scores at different time intervals. Categorical variables, including obesity, diabetes mellitus, hypertension, and the need for additional rescue analgesia, were reported as frequencies and percentages. Stratification was conducted based on age, obesity, diabetes mellitus, and hypertension to determine their impact on the requirement for rescue analgesia. The Chi-square test or Fisher's exact test was applied for statistical analysis, with significance defined as $p \leq 0.05$.

RESULTS

The demographic and clinical characteristics of the patients are presented in **Table-1.** The results demonstrated a mean age of 29.78±5.16 years. BMI values were recorded at 23.57±3.19 kg/m², while height and weight were measured at 162.07±7.71 cm and 61.71±8.89 kg, respectively. The prevalence of obesity was low, affecting only 6 patients (4.3%), whereas diabetes mellitus and hypertension were observed in 12(8.6%) and 18(12.9%) patients, respectively. The need for rescue analgesia varied across time points, with the highest requirement occurring at 0 hours (30.2%). As time progressed, fewer patients required additional analgesia, with only 14(10.1%) requiring it at 12 hours and none at 24 hours.

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Table-1: Demographic and clinical characteristics of patients

Age [a]	
Age (years)	29.78±5.16
BMI [a]	
Height (cm)	162.07±7.71
Weight (kg)	61.71±8.89
BMI (kg/m²)	23.57±3.19
Obesity [b]	
Yes	6(4.3)
No	133(95.7)
Diabetes Mellitus [b]	
Yes	12(8.6)
No	127(91.4)
Hypertension [b]	
Yes	18(12.9)
No	121(87.1)
Need of Rescue Analgesia [b]	
At 0 hour	42(30.2)
At 1 hour	21(15.1)
At 3 hours	7(5.0)
At 6 hours	7(5.0)
At 12 hours	14(10.1)
At 24 hours	0(0.0)

a= mean±standard deviation b=n(%)

The **Table-2** showed variations in postoperative pain scores across different time intervals by applying repeated measures ANOVA, and the results confirmed a statistically significant difference ($p < 0.001$) at different time points. The mean pain score at 0 hours was 2.76±1.90, which increased to 3.24±1.28 at 1 hour. The highest pain intensity was observed at 6 hours (3.41±1.02), followed by a slight decline at 12 hours (3.16±1.41) and 24 hours (2.86±0.80).

The **Table-3** showed association between obesity, diabetes mellitus, and hypertension with the need for rescue analgesia varied across different time points. At 0 hours, diabetic patients exhibited a significantly higher likelihood of requiring rescue analgesia, with 7 out of 12 patients (58.3%) needing additional pain relief ($p=0.044$). Similarly, hypertensive patients demonstrated a notable association, as 9 out of 18 individuals (50%) required rescue analgesia compared to 33 out of 121 non-hypertensive patients ($p=0.050$). Conversely, obesity did not exhibit a statistically significant impact at any time point, with p-values remaining above 0.05. As time progressed, the association between comorbidities and analgesia needs diminished, with no statistical significance observed beyond the initial postoperative hours.

Table-2: Overall mean comparison of postoperative pain at different time points

Time Points	Pain Score	p-value
At 0 hour	2.76±1.90	<0.001*
At 1 hour	3.24±1.28	
At 3 hour	2.87±1.16	
At 6 hour	3.41±1.02	
At 12 hour	3.16±1.41	
At 24 hour	2.86±0.80	

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Repeated Measures of ANOVA is applied.
*Significant at p<0.05

Table-3: Association of obesity, diabetes and hypertension with need of rescue analgesic at different time points

Need of Rescue Analgesia	Obesity		P-value	Diabetes Mellitus		P-value	Hypertension		P-value
	Yes n=6	No n=133		Yes n=12	No n=127		Yes n=18	No n=121	
At 0 hour									
Yes	3(50)	39(29.3)	0.366	7(58.3)	35(27.6)	0.044*	9(50)	33(27.3)	0.050*
No	3(50)	94(70.7)		5(41.7)	92(72.4)		9(50)	88(72.7)	
At 1 hour									
Yes	0(0)	21(15.8)	0.591	2(16.7)	19(15)	1.000	1(5.6)	20(16.5)	0.309
No	6(100)	112(84.2)		10(83.3)	108(85)		17(94.4)	101(83.5)	
At 3 hours									
Yes	0(0)	7(5.3)	1.000	0(0)	7(5.5)	1.000	0(0)	7(5.8)	0.595
No	6(100)	126(94.7)		12(100)	120(94.5)		18(100)	114(94.2)	
At 6 hours									
Yes	0(0)	7(5.3)	1.000	0(0)	7(5.5)	1.000	0(0)	7(5.8)	0.595
No	6(100)	126(94.7)		12(100)	120(94.5)		18(100)	114(94.2)	
At 12 hours									
Yes	0(0)	14(10.5)	1.000	0(0)	14(11)	0.610	1(5.6)	13(10.7)	0.694
No	6(100)	119(89.5)		12(100)	113(89)		17(94.4)	108(89.3)	
At 24 hours									
Yes	0(0)	0(0)	N/A	0(0)	0(0)	N/A	0(0)	0(0)	N/A
No	6(100)	133(100)		12(100)	127(100_		18(100)	121(100)	

Chi-square test is applied. *Significant at p<0.05 N/A=Not applicable

DISCUSSION

The use of an intrathecal opioid for cesarean section has been characterized by tradition rather than evidence in recent decades.[24] Seki et al. clearly stated in their most comprehensive systemic review that as the data and evidence on side-effects appear to be limited, it is still unclear which opioid is best used as an adjunct to local anesthesia for caesarean section.[25] Appropriately, the PROSPECT Working Group's recommendation to prefer long-acting opioids should be interpreted as the best possible compromise between evidence and best practice.[26,27] If a pain therapy procedure enables almost 100 percent freedom from pain for a defined period, then another analgesic procedure, which in all likelihood only unfolds its effect during this period, will not provide a significant additional analgesic benefit.[24]

The severity of pain ranging from moderate to severe in acute post-operative patients is 15–60%.[28] Although regional anesthesia is the method of choice in the cesarean section, general anesthesia is administered in some situations such as fetal distress, coagulopathy, previous surgery of the spine, or mother's request.[29-32] There are many published controlled trials for the pharmacological modifications of the sympathetic response to laryngoscopy, tracheal intubation, and surgical stimulation including opioids, tenoxicam, ketorolac, lidocaine, and paracetamol.[33]

For acute post-surgical pain management after major surgeries, narcotic analgesics are most commonly used. Among them Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) used to treat pain, it has less respiratory side effects as compared to other opioids.[34] Ketorolac decreases production of

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prostaglandin by blocking cyclooxygenase 1 and 2 (COX1 and COX2).[35]

Previously, paracetamol and nalbuphine had been studied separately for its effects on maternal hemodynamic variables, postoperative pain, and neonatal APGAR score during elective cesarean section. Nalbuphine was studied extensively in labor analgesia and was proved to be acceptable analgesics during delivery and its effect on neonates vary between studies. In a study,[13] time to achieve VAS-1 in the postoperative period in the nalbuphine group was significantly higher as compared to the paracetamol group at all measuring periods.

Nalbuphine has been used intravenous or intramuscularly for pain relief in abdominal surgeries such as hysterectomies and caesarean sections due to its faster onset of action and longer duration.[36,37]

The findings of current study demonstrated a time-dependent variation in postoperative pain intensity among cesarean section patients, reinforcing the dynamic nature of pain perception in the early recovery period. The mean pain scores fluctuated significantly across different time points, with the highest recorded pain level occurring at 6 hours post-surgery (3.41±1.02), followed by a gradual decline at 12 hours (3.16±1.41) and 24 hours (2.86±0.80). The repeated measures ANOVA confirmed a statistically significant difference in pain levels ($p<0.001$), supporting the need for individualized pain management strategies.

The requirement for rescue analgesia was most pronounced at 0 hours (30.2%), indicating substantial immediate postoperative pain relief needs. Over time, the necessity for additional analgesia decreased, with only 10.1% of patients requiring it at 12 hours and none at 24 hours. These results suggest that multimodal analgesic approaches may be effective in maintaining adequate pain control beyond the initial postoperative period. Diabetes mellitus and hypertension emerged as significant predictors of early postoperative analgesia requirements, with diabetic and hypertensive patients exhibiting higher rescue analgesia needs at 0 hours ($p=0.044$ and $p=0.050$, respectively). However, these associations diminished over time, highlighting the potential influence of altered pain sensitivity or inflammatory responses associated with these conditions. Conversely, obesity did not demonstrate a statistically significant impact on analgesia requirements at any time point.

Collectively, these results reinforce the necessity of individualized analgesic regimens that account for patient-specific factors. The observed peak in pain intensity at 6 hours underscores the importance of adjusting analgesic administration schedules to effectively mitigate postoperative discomfort. Future research should further investigate the interplay between comorbid conditions and pain sensitivity, aiming to refine postoperative analgesic strategies for improved patient outcomes.

Many previous studies have studied the possibility of opioids being more efficacious in females than in males and a study by Gear *et al.* found this property of sexual dimorphism (more efficacious in females) to be more prominent for kappa agonists, that is, nalbuphine.[38-40] Paracetamol is a non-opioid analgesic and related to NSAIDs group of analgesics. Its analgesic action is probably mediated by the serotonergic mechanism and by weak inhibition of cyclooxygenase-1 and cyclooxygenase-2 and antipyretic action is through inhibition of cyclooxygenase-3 in the hypothalamus. The injectable paracetamol for IV infusion is preferred in most surgical patients because it does not affect mental status, bleeding, respiratory drive, gastric mucosa integrity, or renal function with significant opioid-sparing effect.[41-43] A study on patients of LSCS, in which IV paracetamol was compared with oral ibuprofen, IV paracetamol group showed better pain control compared to ibuprofen group.[39,44-47]

In a study[38] mean onset of action for paracetamol is a 20±3.45 min and for nalbuphine group is 7±2.96 min which is significant. The duration of action for both groups in this study is ≥6 h. Uchiyama et al.[48] demonstrated that nalbuphine provides a faster onset of action, probably because of its lipophilic properties. In a study by Solanki et al., the onset of action of nalbuphine was 7.95±3.94 min.[46] In the same study, both paracetamol and nalbuphine are found to be having better hemodynamic stability.[38]

Soltani et al. reported better hemodynamic stability with paracetamol in CS by general anesthesia.[49] This study shows that nalbuphine IV injection may be adequate for post-operative pain and paracetamol IV infusion may be used for mild-to-moderate post-operative pain. Studies by Yeh et al.[50] have also

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described adequate post-operative analgesia for various surgical procedures using nalbuphine.[49-51] Studies by Sinatra et al.[43] and Alhashemi et al.[39] found that IV paracetamol provided rapid and effective analgesia in patients of LSCS, compared to placebo.

Nalbuphine acts through kappa-opioid receptors and may attenuate mu-opioid-receptor related side effects. Woolland et al. have also showed that nalbuphine has less adverse effects than paracetamol. Further rescue analgesics used were significantly high in paracetamol group with maximum eight doses used and in nalbuphine group maximum two doses were used. Minai and Khan[52] proved that the need for supplemental analgesia was lower with patients in nalbuphine group for intraoperative and post-operative analgesia.

In a study,[4] they concluded that patients had less pain in Nalbuphine Group, mild pain 5(6.7%) as compared to Nalbuphine+Ketorolac Group,35(46.7%) one hour postoperatively. Rescue analgesia Nalbuphine (0.12 mg/kg) was given to less number of patients in Nalbuphine Group 10(13.3%) compared to Nalbuphine+Ketorolac Group 55 (73.3%) which was statistically significant.

CONCLUSION

This study results showed that pain intensity fluctuated significantly between different time points, peaking at 6 hours. The highest need for rescue analgesia at 0 hours and none at 24 hours. Diabetes mellitus and hypertension were significantly associated with early analgesia requirements, whereas obesity, age, and BMI had no substantial impact. These findings suggest that patient-specific factors influence early postoperative pain management, emphasizing the need for tailored analgesic protocols.

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