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Original Research Article

COMPARATIVE ANALYSIS OF INTRATHECAL MORPHINE AND CLONIDINE FOR ENHANCED POST-CAESAREAN ANALGESIA

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Abstract

Background: Effective postoperative analgesia is crucial for improving maternal satisfaction and recovery following caesarean sections. This study aimed to compare the efficacy and safety of intrathecal morphine versus clonidine as adjuvants for post-caesarean analgesia, assessing their impact on pain relief, side effects, and neonatal outcomes. **Materials and Methods:** A randomized controlled trial was conducted with 56 parturients scheduled for elective caesarean sections under spinal anaesthesia. Participants were divided into two groups: Group M (intrathecal morphine, n=27) and Group C (intrathecal clonidine, n=29). The primary outcomes included the duration of analgesia, rescue analgesia requirements, and Visual Analog Scale (VAS) pain scores at various time intervals. Secondary outcomes included the incidence of side effects and neonatal outcomes, such as Apgar scores and birth weights. **Result:** The duration of analgesia was significantly longer in Group M (13.8 ± 2.2 hours) compared to Group C (10.6 ± 2.5 hours, p=0.003). Group M also had a lower requirement for rescue analgesia (758.6 ± 142.4 mg) than Group C (908.9 ± 162.4 mg). Pain scores were significantly lower in Group M at 6 hours (3.6 ± 0.6 vs. 4.0 ± 0.7, p=0.023) and 12 hours (4.2 ± 0.5 vs. 4.8 ± 0.6, p=0.012). However, pruritus was more frequent in Group M (33.3% vs. 10.3%, p=0.024). No significant differences in neonatal outcomes were observed between the groups. **Conclusion:** Intrathecal morphine provides superior analgesia and reduces the need for rescue analgesia compared to clonidine in post-caesarean patients, with manageable side effects and no adverse effects on neonatal outcomes. These findings support the use of morphine as a preferred adjuvant for postoperative analgesia in this population.

INTRODUCTION

Effective pain management after caesarean section is crucial for improving maternal outcomes and facilitating early recovery. Globally, caesarean delivery rates have increased significantly, with a prevalence of around 21% of all births as of 2021, and higher rates of nearly 30% in many middle- and high-income countries.[1] In India, the caesarean section rate is approximately 17.2%, reflecting a substantial portion of deliveries, making post-operative analgesia an essential component of obstetric care.[2] Adequate pain relief post-caesarean is critical for early ambulation, reducing complications like thromboembolism, and facilitating effective breastfeeding and maternal-infant bonding.[3]

Intrathecal opioids, particularly morphine, have long been the cornerstone for providing post-operative analgesia due to their potent, prolonged effects when administered into the spinal space.[4] Intrathecal morphine acts on opioid receptors in the spinal cord, providing pain relief for 18-24 hours post-administration, which makes it an attractive option for caesarean analgesia.[5] However, its use is associated with a range of side effects, such as pruritus (incidence rates as high as 80%), nausea, vomiting, and, albeit rarely, respiratory depression with an incidence of 0.1-1%.[6,7] These adverse effects can limit patient comfort and satisfaction, necessitating the exploration of alternative or supplementary analgesic agents.[8]

Clonidine, an α2-adrenergic agonist, is emerging as a potential adjuvant for intrathecal analgesia. It has shown promise in enhancing the quality and duration of analgesia when combined with local anaesthetics or opioids.[9] Intrathecal clonidine exerts its analgesic effect through presynaptic and postsynaptic activation of α2 receptors in the spinal cord, leading to a reduction in nociceptive transmission and sympathetic outflow.[10] Studies have reported that clonidine, when used as an intrathecal adjuvant, can extend the duration of sensory block by up to 30-50%

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and provides analgesia for around 6-12 hours.[11] Compared to morphine, it offers a reduced risk of opioid-related side effects, but its use is limited by the potential for hypotension and sedation, with reported incidences of sedation up to 25% in some studies.[12] Comparative studies on intrathecal morphine and clonidine as adjuvants in post-caesarean analgesia are limited, and there remains a need for a more comprehensive evaluation of their efficacy and side-effect profiles.[13] This study aimed to compare intrathecal morphine and clonidine in terms of analgesic efficacy, duration of pain relief, and side effects such as pruritus, nausea, and sedation. The outcomes of this study could inform the choice of adjuvants in post-caesarean pain management, thereby improving patient satisfaction and clinical outcomes in the context of rising caesarean rates.

MATERIALS AND METHODS

Study Design: This study was a prospective, randomized, double-blind clinical trial conducted under the Department of anesthesia and critical care, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala, Haryana. for a duration of 2 years between July 2021 and June 2023. Written informed consent was obtained from all participants.

Study Population: A total of 56 parturients scheduled for elective caesarean section under spinal anaesthesia were enrolled in the study. Inclusion criteria included pregnant women aged 18-40 years, classified as ASA physical status I or II, and gestational age of 37 weeks or more. Exclusion criteria included patients with known allergy to morphine or clonidine, chronic opioid use, coagulopathy, spinal deformities, or significant comorbidities such as uncontrolled hypertension or diabetes.

Sample Size: Based on the study by Agrawal et al., which reported a clinically significant difference of 2 hours in the duration of analgesia between intrathecal morphine and clonidine with a standard deviation of 3 hours, the required sample size for our study was calculated to be 28 patients per group, using a power of 80% and a significance level of 0.05.[14] Accounting for a 10% dropout rate, the final adjusted sample size was 30 patients per group, for a total of 60 participants

Randomization and Blinding: Participants were randomly allocated into two groups using a computer-generated randomization sequence. Group M received intrathecal morphine as an adjuvant to local anaesthetic, while Group C received intrathecal clonidine. Allocation concealment was maintained using sealed opaque envelopes, and the study drugs were prepared by an anaesthetist not involved in the study. Both the patients and the anaesthesiologist administering the spinal anaesthesia were blinded to the group assignment.

Intervention: All patients received standard pre-operative care, including intravenous hydration and monitoring of vital signs. Spinal anaesthesia was administered in the L3-L4 or L4-L5 interspace using a 25-gauge Quincke spinal needle. Each patient received 2 ml of 0.5% hyperbaric bupivacaine (10 mg) with an adjuvant as per group allocation: Group M (Morphine group): Received 0.1 mg (0.2 ml) of intrathecal morphine; and Group C (Clonidine group): Received 50 mcg (0.2 ml) of intrathecal clonidine. The total volume of the intrathecal mixture was adjusted to [e.g., 2.2 ml] by adding saline to ensure blinding. Following administration of the spinal block, patients were positioned supine with left uterine displacement to optimize venous return.

Outcome Measures: The primary outcome of the study was the duration of effective analgesia, defined as the time from the intrathecal injection to the first request for rescue analgesia (VAS score $\geq$ 4). Secondary outcomes included: Pain scores using the Visual Analogue Scale (VAS) at 1, 2, 4, 6, 12, and 24 hours post-operatively; Total dose of rescue analgesia required within the first 24 hours (measured in mg of intravenous paracetamol); and Incidence of side effects such as pruritus, nausea, vomiting, hypotension (defined as a drop in systolic blood pressure by more than 20% from baseline), and sedation (assessed using a sedation score).

Data Collection and Monitoring: All data were collected in predesigned questionnaire by a blinded observer who was not involved in the administration of spinal anaesthesia. Patients were monitored in the post-anaesthesia care unit (PACU) and followed up for 24 hours post-operatively. Adverse events and any requirement for additional medical interventions were documented.

Statistical Analysis: Data were analyzed using SPSS version 20.0. Continuous variables were compared using the Student's t-test, while categorical variables were analyzed using the Chi-square test. Statistical significance was set at a p-value of less than 0.05.

RESULTS

In our study, the initial sample size was determined to be 60 participants for both the Group M and Group C. However, due to various factors such as participant dropout and non-compliance, the final sample size comprised 27 participants in the Group M and 29 in Group C. The baseline characteristics were similar between Group M (Morphine, n=27) and Group C (Clonidine, n=29). The mean age was 28.3 ± 3.9 years in Group M and 28.8 ± 4.2 years in Group C (p=0.651), and the mean BMI was 26.7 ± 3.1 kg/m² and 26.5 ± 3.4 kg/m², respectively (p=0.782). Gestational age averaged 38.6 ± 1.3 weeks in Group M and 38.4 ± 1.6 weeks in Group C (p=0.524). Most participants had ASA I status (74.1% in Group M, 75.9% in Group C, p=0.855). The mean duration of surgery was similar, with 48.2

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± 8.4 minutes for Group M and 47.8 ± 8.1 minutes for Group C (p=0.881) [Table 1].

The onset of sensory block was slightly faster in Group M (4.8 ± 0.9 minutes) compared to Group C (5.2 ± 1.1 minutes), but the difference was not statistically significant (p=0.155). The onset and duration of motor block were also comparable between Group M (6.2 ± 1.0 minutes, 128.6 ± 12.4 minutes) and Group C (6.5 ± 1.1 minutes, 130.8 ± 13.1 minutes), with p-values of 0.208 and 0.321, respectively. Heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) remained similar between the groups at baseline and during the first 2 hours post-intervention, with all p-values above 0.05, indicating no significant differences [Table 2].

Table 1: Baseline Demographic and Clinical Characteristics of Participants.

Characteristic	Group M (n=27)	Group C (n=29)	p-value
	Frequency (%)/mean ± SD		
Age (years)	28.3 ± 3.9	28.8 ± 4.2	0.651
Body Mass Index (kg/m²)	26.7 ± 3.1	26.5 ± 3.4	0.782
Gestational age (weeks)	38.6 ± 1.3	38.4 ± 1.6	0.524
ASA physical status			
I	20 (74.1)	22 (75.9)	0.855
II	7 (25.9)	7 (24.1)	
Duration of surgery (minutes)	48.2 ± 8.4	47.8 ± 8.1	0.881

Table 2: Comparison of Sensory and Motor Block Characteristics and Hemodynamic Parameters Between Group M (Morphine) and Group C (Clonidine).

Parameter	Group M (n=27)	Group C (n=29)	p-value
	Mean ± SD		
Onset of sensory block (minutes)	4.8 ± 0.9	5.2 ± 1.1	0.155
Onset of motor block (minutes)	6.2 ± 1.0	6.5 ± 1.1	0.208
Duration of motor block (minutes)	128.6 ± 12.4	130.8 ± 13.1	0.321
Heart rate (beats/min)			
Baseline	82.3 ± 6.7	82.1 ± 6.5	0.991
15 minutes	80.0 ± 6.1	77.8 ± 6.2	0.566
30 minutes	78.2 ± 5.8	74.2 ± 5.8	0.232
1 hour	77.0 ± 5.6	72.5 ± 5.5	0.111
2 hours	76.2 ± 5.5	71.7 ± 5.4	0.086
SBP (mm/Hg)			
Baseline	121.5 ± 8.2	122.0 ± 8.0	0.767
15 minutes	118.9 ± 7.4	117.0 ± 7.5	0.505
30 minutes	116.5 ± 6.9	114.2 ± 6.8	0.188
1 hour	115.0 ± 6.7	112.8 ± 6.5	0.105
2 hours	113.5 ± 6.6	111.5 ± 6.4	0.121
DBP (mm/Hg)			
Baseline	78.0 ± 5.8	78.5 ± 5.6	0.652
15 minutes	76.0 ± 5.2	74.8 ± 5.1	0.435
30 minutes	74.0 ± 5.0	72.5 ± 5.0	0.253
1 hour	73.2 ± 4.9	71.7 ± 4.8	0.162
2 hours	72.5 ± 4.8	71.0 ± 4.7	0.175

Table 3: Comparison of Postoperative Outcomes, Pain Scores, and Side Effects Between Group M (Morphine) and Group C (Clonidine).

Outcome	Group M (n=27)	Group C (n=29)	p-value
	Frequency (%)/mean ± SD		
Duration of analgesia (hours)	13.8 ± 2.2	10.6 ± 2.5	0.003
Time to first ambulation (hours)	18.0 ± 2.3	17.5 ± 2.4	0.482
Time to first flatus (hours)	14.5 ± 2.0	14.3 ± 2.1	0.647
Time to first bowel movement (hours)	23.8 ± 3.2	23.5 ± 3.0	0.672
VAS score at various Time Point			
1 hour	1.8 ± 0.5	2.1 ± 0.6	0.121
2 hours	2.2 ± 0.6	2.5 ± 0.7	0.125
4 hours	3.0 ± 0.7	3.5 ± 0.8	0.055
6 hours	3.6 ± 0.6	4.0 ± 0.7	0.023
12 hours	4.2 ± 0.5	4.8 ± 0.6	0.012
24 hours	5.0 ± 0.7	5.4 ± 0.8	0.068
Satisfaction Score	8.1 ± 1.1	7.9 ± 1.2	0.535
Side Effects			
Pruritus	9 (33.3)	3 (10.3)	0.024
Nausea/Vomiting	6 (22.2)	4 (13.8)	0.472
Sedation	5 (18.5)	3 (10.3)	0.465
Hypotension	1 (3.7)	4 (13.8)	0.188
Respiratory Depression	1 (3.7)	0 (0.0)	0.279

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Table 4: Comparison of Neonatal Outcomes Between Group M (Morphine) and Group C (Clonidine).

Fetal Outcome	Group M (n=27)	Group C (n=29)	p-value
	Frequency (%)/mean ± SD		
Apgar score at 1 minute	8.6 ± 0.6	8.5 ± 0.5	0.633
Apgar score at 5 minutes	9.2 ± 0.4	9.1 ± 0.4	0.532
NICU admission	1 (3.7)	1 (3.4)	0.953
Birth weight (grams)	2985.3 ± 312.8	2953.4 ± 302.4	0.524

Group M (Morphine) demonstrated a significantly longer duration of analgesia (13.8 ± 2.2 hours) compared to Group C (Clonidine, 10.6 ± 2.5 hours), with a p-value of 0.003. The requirement for rescue analgesia was lower in Group M (758.6 ± 142.4 mg of Paracetamol) than in Group C (908.9 ± 162.4 mg), though the p-value was not provided. Time to first ambulation, first flatus, and first bowel movement were similar between the groups, with p-values of 0.482, 0.647, and 0.672, respectively. Visual Analog Scale (VAS) scores indicated lower pain levels in Group M at 6 hours (3.6 ± 0.6 vs. 4.0 ± 0.7, p=0.023) and at 12 hours (4.2 ± 0.5 vs. 4.8 ± 0.6, p=0.012), but not at other time points. Mean satisfaction scores were comparable between the groups (8.1 ± 1.1 for Group M and 7.9 ± 1.2 for Group C, p=0.535). Notably, pruritus occurred more frequently in Group M (33.3%) compared to Group C (10.3%, p=0.024), while other side effects such as nausea/vomiting, sedation, hypotension, and respiratory depression were similar across both groups [Table 3].

There were no significant differences in neonatal outcomes between Group M (Morphine) and Group C (Clonidine). The mean Apgar score at 1 minute was 8.6 ± 0.6 in Group M and 8.5 ± 0.5 in Group C (p=0.633), while the scores at 5 minutes were 9.2 ± 0.4 and 9.1 ± 0.4, respectively (p=0.532). NICU admission rates were also comparable, with 1 (3.7%) in Group M and 1 (3.4%) in Group C (p=0.953). Additionally, the mean birth weight was similar between the groups, with Group M at 2985.3 ± 312.8 grams and Group C at 2953.4 ± 302.4 grams (p=0.524). Overall, these findings suggest that the choice of adjuvant for analgesia did not adversely affect neonatal outcomes [Table 4].

DISCUSSION

In this study, we compared the efficacy and safety of intrathecal morphine versus clonidine as adjuvants for post-caesarean analgesia. Our findings indicate that morphine significantly prolonged the duration of analgesia (13.8 ± 2.2 hours) compared to clonidine (10.6 ± 2.5 hours), with a statistically significant p-value of 0.003. This result aligns with previous studies, such as that by Botea et al., and Uppal et al., which reported an average analgesic duration of 12.5 hours with morphine compared to 9.8 hours with clonidine in a similar cohort of post-caesarean patients.[15,16] The longer analgesic effect of morphine can be attributed to its binding affinity for mu-opioid receptors in the central nervous system, leading to prolonged pain relief compared to the alpha-2 adrenergic agonistic effects of clonidine, which primarily provides sedation and has a shorter analgesic duration.[17]

Moreover, our study demonstrated a lower requirement for rescue analgesia in the morphine group (758.6 ± 142.4 mg) compared to clonidine (908.9 ± 162.4 mg). This finding corroborates the study conducted by Weigl et al., which found that morphine significantly reduced the need for postoperative analgesics compared to clonidine.[18] Additionally, the findings by Ratnasekara et al., also support our results, reporting that patients receiving intrathecal morphine required less supplemental analgesia than those receiving clonidine.[19] The observed difference in the need for rescue analgesia underscores morphine's superior analgesic properties and supports its use as a first-line adjuvant in post-caesarean analgesia.[20,21]

We evaluated pain scores at various time points, revealing significantly lower Visual Analog Scale (VAS) scores at 6 hours (3.6 ± 0.6 vs. 4.0 ± 0.7, p=0.023) and 12 hours (4.2 ± 0.5 vs. 4.8 ± 0.6, p=0.012) for the morphine group compared to the clonidine group. These findings are consistent with the work of Khosravi et al., who reported lower pain scores with intrathecal morphine at similar intervals.[22] Additionally, the study by Vedivelu et al., reported similar trends, highlighting morphine's effectiveness in providing early postoperative pain relief.[23] The sustained release of morphine from the spinal cord can provide longer analgesia, while clonidine's action diminishes more quickly over time.[24]

Regarding side effects, pruritus was significantly more frequent in the morphine group (33.3% vs. 10.3%, p=0.024). This finding is in line with a meta-analysis by Becker et al., which noted that opioid-related pruritus occurs in approximately 30% of patients receiving intrathecal morphine.[25] While the increased incidence of pruritus is a notable concern, it is essential to weigh this against the overall effectiveness of morphine in providing superior analgesia. Additionally, the study by Nakao et al., similarly reported that pruritus was more prevalent with morphine, suggesting that careful monitoring and management strategies should be implemented in clinical practice.[26]

In terms of neonatal outcomes, there were no significant differences in Apgar scores, NICU admissions, or birth weights between the two groups, indicating that the use of morphine or clonidine as adjuvants did not adversely affect neonatal health. This finding is consistent with the study by Simon et al., which similarly reported no adverse neonatal effects when using intrathecal morphine for post-

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operative analgesia.[27] Furthermore, a study by Boatin et al., supported the safety of intrathecal morphine on neonatal outcomes, reinforcing the idea that effective pain management in mothers does not compromise infant well-being.[28]

Limitations: This study has several limitations. First, the sample size was relatively small, which may affect the generalizability of the findings. Second, the trial was conducted at a single institution, limiting the diversity of the study population. Additionally, the follow-up period for assessing long-term side effects and analgesic efficacy was short, which may overlook delayed adverse reactions. Finally, while we assessed maternal and neonatal outcomes, other factors such as patient satisfaction and quality of life post-surgery were not evaluated, which could provide a more comprehensive understanding of the interventions' impacts.

CONCLUSION

In conclusion, our study demonstrates that intrathecal morphine offers superior analgesia and lower rescue analgesia requirements compared to clonidine in post-caesarean patients, with acceptable side effect profiles and no adverse impact on neonatal outcomes. These findings support the use of morphine as a preferred adjuvant for postoperative analgesia in this population, providing a valuable contribution to existing literature on analgesic strategies in obstetric anesthesia.

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