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Research Article

Comparison of the Effects of Low-Dose Dexmedetomidine and Low-Dose Neostigmine as Adjuvants to Bupivacaine on Postoperative Pain after Cesarean Section under Spinal Anesthesia

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ABSTRACT

Background: Effective postoperative pain management after cesarean section enhances maternal recovery, facilitates early newborn care, and reduces postoperative complications. Due to the limitations and adverse effects of neuraxial opioids, non-opioid adjuvants have become an attractive alternative. This study compared the analgesic efficacy of dexmedetomidine and low-dose neostigmine as adjuvants to bupivacaine in spinal anesthesia for cesarean delivery.

Methods: In this double-blind randomized clinical trial, 110 women undergoing elective cesarean were randomly allocated to receive either dexmedetomidine plus bupivacaine (Group D) or neostigmine plus bupivacaine (Group N). Demographic and intraoperative data were recorded. Sensory and motor block characteristics, postoperative pain intensity (VAS scores at 2, 4, 8, and 12 hours), time to first analgesic request, total 24-hour analgesic consumption, sedation levels, muscle relaxation quality, Apgar scores, and side effects (nausea, vomiting, shivering, pruritus) were assessed.

Results: Baseline characteristics, sedation scores, muscle relaxation quality, and neonatal outcomes were comparable between groups. The onset of sensory and motor block was significantly faster in the neostigmine group, whereas their regression was markedly prolonged in the dexmedetomidine group ($P<0.001$). Pain scores were consistently lower, the first analgesic request was delayed, and total analgesic use was reduced in Group D ($P<0.001$). Nausea and vomiting occurred more frequently in Group N ($P=0.007$).

Conclusion: Dexmedetomidine as an intrathecal adjuvant to bupivacaine provides superior and longer-lasting analgesia with fewer gastrointestinal side effects than neostigmine in cesarean sections under spinal anesthesia.

Introduction

Cesarean section, as one of the most common surgical procedures in obstetrics, constitutes a significant proportion of deliveries worldwide, and its incidence continues to rise [1]. Optimal control of pain following cesarean delivery is critically important, as insufficient analgesia is associated with a wide range of negative consequences. These include delayed onset of breastfeeding, weakened maternal–neonatal bonding, limited postoperative ambulation, a higher risk of

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thromboembolic events, respiratory complications, and an increased likelihood of psychological conditions such as anxiety and postpartum depression [2-3]. Therefore, identifying effective and safe methods for postoperative pain control is a clinical necessity.

Spinal anesthesia, owing to its rapid onset, high efficacy, and technical simplicity, is the main anesthetic technique for most cesarean deliveries [4-5]. However, one major limitation of local anesthetics used in spinal anesthesia is their relatively short duration of analgesia [6]. Therefore, multiple pharmacological adjuvants have been explored for their ability to enhance the efficacy and duration of sensory and motor blockade, with particular emphasis on cesarean section surgeries [7].

Neuraxial opioids such as morphine and fentanyl have long been recognized as potent adjuvant agents, markedly extending the duration of analgesia and improving the overall quality of neural blockade [8]. Nevertheless, the occurrence of side effects such as pruritus, nausea, vomiting, urinary retention, and—most importantly—respiratory depression has limited their widespread use [9]. This limitation has prompted researchers to explore alternative or complementary drugs with comparable efficacy but superior safety profiles.

Among the agents that have gained increasing attention in recent years is dexmedetomidine, a highly selective α2-adrenergic receptor agonist with analgesic, sedative, anxiolytic, and hemodynamic-stabilizing effects [10]. Multiple studies have shown that the addition of dexmedetomidine to local anesthetics significantly prolongs sensory and motor blockade, decreases postoperative analgesic consumption, and enhances overall analgesic quality [11-12].

Furthermore, in contrast to opioids, dexmedetomidine is not associated with clinically significant respiratory depression, and its side effects are typically mild and readily manageable [13–14]. Neostigmine represents another agent that has been explored as a neuraxial adjuvant [4]. Through inhibition of acetylcholinesterase and subsequent elevation of acetylcholine levels at synaptic junctions, neostigmine enhances neurotransmission within central antinociceptive pathways. Previous reports have suggested that neuraxial neostigmine administration can extend the duration of postoperative analgesia and decrease the requirement for additional analgesic agents. Nevertheless, dose-dependent adverse effects—particularly nausea and vomiting—remain its principal limitations, underscoring the need for further assessment of its efficacy and safety profile [15]. Considering the critical role of effective post-cesarean pain management, the well-recognized drawbacks of neuraxial opioids, and the encouraging findings related to dexmedetomidine and neostigmine, a comparative evaluation of these two agents as adjuvants to bupivacaine in spinal anesthesia may offer meaningful insights into optimizing postoperative analgesic strategies. Accordingly, the present study seeks to generate novel evidence that may enhance postoperative outcomes, safety, and maternal satisfaction following cesarean delivery.

Methods

This study was conducted as a double-blind randomized clinical trial on women scheduled for elective cesarean. After obtaining written informed consent and approval from the university's ethics committee, eligible patients were enrolled. The inclusion criteria consisted of physical status I or II according to the American Society of Anesthesiologists (ASA) classification, age between 18 and 50 years, and first or second pregnancy.

Participants were randomly allocated into two equal groups using a computer-generated variable block randomization method. To ensure allocation concealment, sequentially numbered, opaque, sealed envelopes were used. Both the patients and the anesthesiologist were blinded to the type of administered drug. In the neostigmine group, patients received 50 μg of neostigmine combined with 2.5 mL of 0.5% bupivacaine. In the dexmedetomidine group, patients received an intrathecal injection of 1 μg dexmedetomidine combined with 2.5 mL of 0.5% bupivacaine. Spinal anesthesia was administered with the patient in the sitting position at either the L4–L5 or L5–S1 intervertebral space using a 25-gauge Quincke spinal needle. Standard monitoring in accordance with ASA guidelines was applied, including electrocardiography, noninvasive blood pressure measurement, heart rate, respiratory rate, and peripheral oxygen saturation (SpO_2). Demographic characteristics (age, height, and weight), along with intraoperative and postoperative variables, were systematically recorded. The evaluated variables included the duration of analgesia, duration of sensory block, mean arterial pressure (MAP), heart rate (HR), oxygen saturation (SpO_2), neonatal Apgar scores, motor block score according to the Bromage scale, pain score based on the Visual Analogue Scale (VAS), and sedation level according to the Ramsay scale at 2, 4, 8, and 12 hours postoperatively. Additionally, the time to first analgesic requirement, block quality, and potential side effects (nausea, vomiting, shivering, hypotension, and bradycardia) were assessed. In the event of nausea or vomiting, intravenous ondansetron was administered. Shivering was initially managed by warming; if persistent, second-line medications such as ketamine or opioids were used. Patients requiring second-line treatment were excluded from the study. Adequate analgesia was defined as a VAS score ≤ 3.

The sample size was determined using data from a prior study, based on an assumed mean difference of 0.7 in VAS scores with a standard deviation of 1.25. With a type

I error rate set at 0.05 and a statistical power of 80%, the calculated sample size was 51 participants per group. To account for an anticipated dropout rate of approximately 4%, 55 patients were ultimately recruited into each group. Data were analyzed using SPSS software version 26. The normality of quantitative variables was assessed using the Shapiro–Wilk test. Normally distributed variables were expressed as mean ± standard deviation and compared using the independent t-test. Non-normally distributed data were reported as median (minimum–maximum) and analyzed using the Mann–Whitney U test. Qualitative variables were compared using the chi-square test or Fisher's exact test as appropriate. Changes in pain scores over time were analyzed using repeated-measures ANOVA or, when non-normally distributed, the generalized estimating equations (GEE) model. A P value < 0.05 was considered statistically significant.

Results

A total of 110 eligible patients were randomly assigned to two groups: dexmedetomidine (Group D) and neostigmine (Group N). The age of participants ranged from 18 to 43 years in Group D and from 19 to 41 years in Group N. The median ages were 32 and 33 years, respectively, with no statistically significant difference between the groups (P = 0.189). Body mass index values varied from 18 to 34 kg/m², with median BMIs of 28.3 in Group D and 27.8 in Group N; this difference was also not statistically significant (P = 0.421). The median duration of surgery was 30 minutes in both groups (P=0.256). Baseline hemodynamic parameters—including MAP, HR, and SpO_2—were comparable between the groups. Additionally, the proportions of patients with diabetes (9.1% in Group D vs. 12.7% in Group N) and smokers (14.5% in Group D vs. 20% in Group N) did not differ significantly. Regarding neuraxial block characteristics, the onset time of sensory block was significantly shorter in the neostigmine group (median 5.75 min vs. 6.75 min; P<0.001), while the duration of sensory block regression to the S1 level was significantly longer in the dexmedetomidine group (225 min vs. 180 min; P<0.001). Similarly, the time to achieve complete motor block (Bromage grade III) was faster in the neostigmine group (5 min vs. 6 min; P=0.006), but the duration of motor block regression was longer in the dexmedetomidine group (185 min vs. 165 min; P<0.001).

The quality of muscle relaxation, as reported by the surgeon, was good or relatively good in most patients. In the dexmedetomidine group, 89.1% of patients had good and 10.9% had relatively good muscle relaxation, while in the neostigmine group, these proportions were lower (Table 1). However, the difference was not statistically significant (P=0.122).

Assessment of postoperative pain intensity using the Visual Analogue Scale (VAS) demonstrated that the median pain scores at 2, 4, 8, and 12 hours after surgery were 2, 2, 3, and 3, respectively, in the dexmedetomidine group, and 3, 3, 4, and 5, respectively, in the neostigmine group (Figure 1).

All these differences were statistically significant (P<0.001). Repeated-measures ANOVA also indicated that the rate of pain increase was significantly slower and milder in the dexmedetomidine group compared with the neostigmine group (P<0.001), even after adjusting for patients' age (P=0.027). The time to first postoperative analgesic request was significantly longer in the dexmedetomidine group, and the total analgesic consumption within 24 hours after surgery was markedly lower compared with the neostigmine group (Table 2).

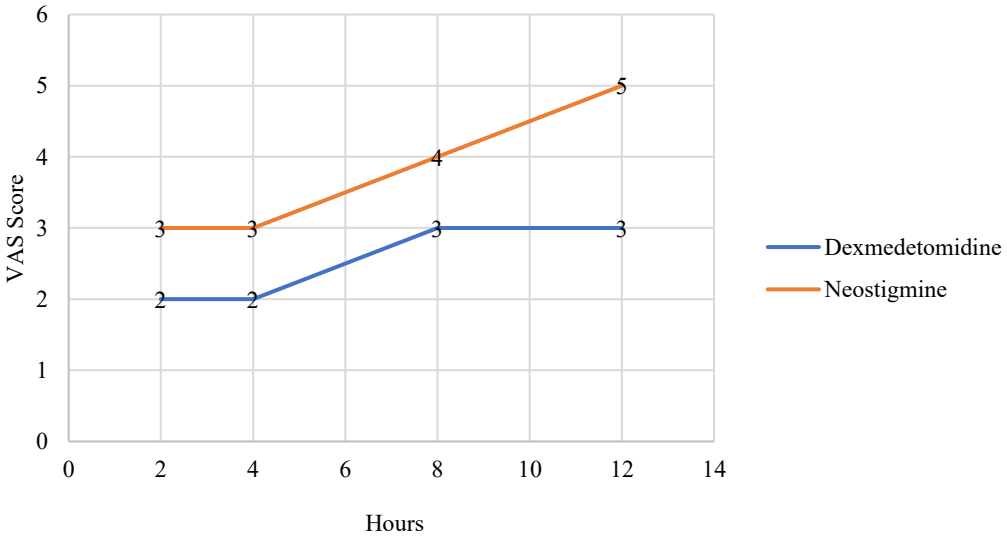

Figure 1- Comparison of pain intensity between dexmedetomidine (D) and neostigmine (N)

Table 1 - Comparison of Muscle Relaxation between Study Groups

Variable		Group D		Group N		P value
		n	%	*n*	%	Chi-Square
Muscle relaxation	Good	49	89.1	43	78.2	0.122
	Fair	6	10.9	12	21.8	
	Poor	–	–	–	–	

Table 2- Comparison of Time to First Time Analgesic Request between Study Groups

Variable	Group D			Group N			P value
	Min	Max	Median	Min	Max	Median	Mann–Whitney U
Time to first analgesic request (h)	11	24	15	2	19	4	<0.001

Regarding neonatal indices, the 1-minute Apgar score was similar between the two groups, with a median of 9 in both (P=0.974). The 5-minute Apgar score was 9 in the dexmedetomidine group and 10 in the neostigmine group, showing no significant difference (P=0.516). These findings indicate that neither of the study drugs had an adverse effect on neonatal outcomes. In terms of side effects, the incidence of nausea and vomiting was significantly higher in the neostigmine group compared with the dexmedetomidine group (34.5% vs. 12.7%; P=0.007). Conversely, the incidence of shivering (3.6% vs. 1.8%) and pruritus (5.5% vs. 3.6%) did not differ significantly between groups (P>0.05). Sedation scores based on the Ramsay scale were predominantly 2 during and after surgery in both groups, with no intergroup differences observed.

Overall, the findings of the present study demonstrated that adding dexmedetomidine to bupivacaine in spinal anesthesia results in a slower onset of sensory and motor block but a longer duration of both. Furthermore, dexmedetomidine was associated with lower pain intensity during the first 12 hours post-cesarean section, prolonged time to first analgesic request, reduced need for additional analgesics, and lower incidence of nausea and vomiting, without any adverse effects on neonatal condition or maternal vital parameters.

Discussion

The α2-adrenergic agonist effect of dexmedetomidine synergistically enhances local anesthetics by prolonging sensory block through inhibition of neurotransmitter release from spinal C-fibers, leading to hyperpolarization of postsynaptic dorsal horn neurons [16]. The prolongation of motor block is also associated with the binding of α-agonists to motor neurons in the anterior horn of the spinal cord. Intrathecal dexmedetomidine has been used at various doses ranging from 3 to 15 μg [17–21]. Sullivan et al. [22] reported that the effective dose of dexmedetomidine for suppressing C-fiber responses in dorsal horn neurons was 2.5 μg, while β responses were inhibited to a lesser extent at higher doses up to 10 μg. In the present study, a low dose of 1 μg was used to provide sufficient postoperative analgesia, limit motor block, and facilitate early recovery and ambulation.

On the other hand, neostigmine, by inhibiting cholinesterase activity, appears to increase spinal acetylcholine levels. Spinal acetylcholine may enhance motor blockade by augmenting the axonal conduction block induced by local anesthetics. Intrathecal neostigmine is considered safer than other spinal adjuvants currently in use, as it does not cause hypotension, sedation, respiratory depression, or neurological deficits [23-24]. In most previous studies, neostigmine has been used as an adjuvant to bupivacaine, typically in doses ranging from 6.25 to 150 μg [25]. Several studies have indicated that 50 μg of intrathecal neostigmine is an adequate dose [26–28], since higher doses are associated with an increased incidence of adverse effects such as nausea and vomiting. Accordingly, in the present study, 50 μg of neostigmine was used as an adjuvant to bupivacaine.

In our study, neostigmine produced a significantly faster onset of sensory block compared with dexmedetomidine (median 5.75 vs. 6.75 minutes). The onset of motor block was also significantly faster in the neostigmine group (median 5 vs. 6 minutes). In contrast, the duration of sensory block (median 225 vs. 180 minutes) and motor block (median 185 vs. 165 minutes) was significantly longer in the dexmedetomidine group than in the neostigmine group.

These findings are consistent with those of previous studies. For instance, Suryawanshi et al. [29] found that postoperative analgesia lasted longer in patients receiving dexmedetomidine than in those receiving neostigmine. Similarly, in the present study, pain scores based on the VAS were lower in the dexmedetomidine group during the first 12 postoperative hours, and the total analgesic consumption during the first 24 hours was significantly reduced. Bhaskar et al. [30] also reported comparable findings, showing lower pain scores, longer postoperative analgesia, and prolonged sensory and motor block in the dexmedetomidine group, while the onset of both blocks was shorter with neostigmine. Singh et al. [31] similarly observed better sensory and motor block quality in the dexmedetomidine group than in the neostigmine group

when used as adjuvants to bupivacaine, along with a significantly higher incidence of nausea and vomiting in the neostigmine group. Consistent with those studies, our results also demonstrated a significantly higher incidence of nausea and vomiting in the neostigmine group compared with the dexmedetomidine group (34.5% vs. 12.7%). However, Sharma et al. [32] reported no statistically significant difference between groups regarding gastrointestinal side effects.

Conclusion

It appears that adding dexmedetomidine as an adjuvant to bupivacaine in spinal anesthesia for cesarean section results in prolonged postoperative analgesia and reduced analgesic requirements compared with neostigmine as an adjuvant to bupivacaine. There were no statistically significant differences between the groups in terms of cardiorespiratory parameters, pruritus, or shivering. However, nausea and vomiting occurred significantly more frequently in the neostigmine group. Future studies are recommended to determine the optimal doses of these adjuvant agents. Such research could help identify the most effective dosing regimen that provides adequate analgesia with minimal side effects, particularly gastrointestinal complications and intraoperative or postoperative hemodynamic instability.

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Ethical Statement

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Research Ethics Committee of Mazandaran University of Medical Sciences (Ethical Code: IR.MAZUMS.IMAMHOSPITAL.REC.1402.053). The clinical trial was prospectively registered in the Iranian Registry of Clinical Trials (IRCT) under the registration number IRCT20210904052371N4. Written informed consent was obtained from all participants before their inclusion in the study, and their confidentiality and right to withdraw at any stage were fully respected.

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