COMPARISON OF POSTOPERATIVE ANALGESIC EFFECT OF INTRATHECAL KETAMINE AND FENTANYL ADDED TO BUPIVACAINE IN PATIENTS UNDERGOING CESAREAN SECTION: A PROSPECTIVE RANDOMIZED DOUBLE-BLIND STUDY

MARZIEH BEIGOM KHEZRI*, ELHAM TAHAEI**, AND AMIR HOSSEIN ATLASBAF***

Objectives: To compare the analgesic efficacy of intrathecal Ketamine and fentanyl added to bupivacaine in patients undergoing cesarean section.

Methods: Ninety patients 18-40 years old were recruited in a prospective double-blinded, randomized way. Spinal anesthesia was performed in the three groups by using bupivacaine 10mg combined with 0.1mg/kg ketamine in group K, bupivacaine 10mg combined with 25 µg fentanyl in group F and bupivacaine 10mg combined 0.5 ml distilled water in group P. The time to first analgesic request, analgesic requirement in the first 24 hours after surgery, sensory and motor blockade onset time, duration of sensory and motor blockade, the incidence of adverse effects were recorded.

Results: The mean time to first analgesic request was longer in group K (296.80 ± 32.46) compared to group F (277.87 ± 94.25) and group P (235.43 ± 22.35). The difference between group K and F (P = 0.504) was not significant but the difference between group K and group P (P <0.001) and group F and group P (P = 0.042) was significant.

Conclusion

Addition of ketamine or fentanyl to spinal bupivacaine were equally effective in pain control after cesarean section and therefore, based on the specific conditions of patients, ketamine at concentrations mentioned earlier, could be a proper alternative to achieve postoperative analgesia

Keywords: Ketamine, fentanyl, intrathecal, cesarean, Pain

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Introduction

Spinal anesthesia has been introduced as alternative anesthetic technique to general anesthesia in obstetric setting with many advantages such as dulling of the stress response, reducing amount of blood loss, and enhancing the postoperative analgesia and satisfaction of patient leading to improvement in the final outcomes. Decreasing the dose of bupivacaine used in spinal anesthesia helps to achieve rapid anesthetic recovery with minimal adverse effect, but may result in anesthetic failure1.

Pain control after cesarean delivery is associated with improved breastfeeding and infant rooming in. However, in parturient women, we must balance the benefits of analgesia and known fetal and maternal side effects induced, including bradycardia, respiratory depression, arterial hypotension, emetogenesis, and pruritus2.

Many drugs have been adjusted to local anesthetics to provide optimal analgesia with lower side effects such as opioids, midazolam, clonidine, ketamine, magnesium, and neostigmine3,4,5,6.

Currently, opioids are widely used for pain relief, but they often provide sub-optimal analgesia with occasional serious side effects. Fentanyl is the most frequently intrathecal lipophilic opioid used as analgesic agent with minimal cephalad spread making it the least likely of all the intrathecal opioids to cause delayed respiratory depression7. However, it is reported that only a single administration of an opioid may also induce a long lasting reduction of threshold of pain sensitivity, leading to delayed hyperalgesia8. Ketamine is an anesthetic agent with potent analgesic properties used as an adjunct in spinal anesthesia. It has a local anesthetic effect and a noncompetitive antagonistic effect on N-methyl d-aspartate receptors9,10. Ketamine binds to opiate receptors and interacts with cholinergic, adrenergic and 5-hydroxitryptamine systems11. It can block the N-methyl-d-aspartate excitation of central neurons12. However, despite extensive discourses, there is still controversy in the literature as to the safety and analgesic efficacy of ketamine through the intrathecal route13-18.

Preservative-free racemic ketamine was shown to be devoid of neurotoxic effects after both single and repeated administration in animals17,19.

Yu et al20 reported that ketamine provided potent protective effects against the ischemic reperfusion induced spinal cord injuries20. Furthermore, in obstetrics, ketamine has no detrimental effect on uterine blood flow, and maternal or fetal hemodynamics. Moreover, Horacek et al reported that a subanesthetic dose of ketamine infusion induced changes similar to those by monoaminergic-based antidepressants21. We hypothesized that ketamine might provide better pain relief after cesarean section than fentanyl without pruritus, respiratory depression, hemodynamic instability, or hyperalgesia. In order to test our hypothesis, we designed a randomized, double-blind, placebo-controlled study to compare the postoperative analgesic effects of ketamine and fentanyl added to spinal bupivacaine in patients undergoing cesarean section.

Methods

Following the approval by the Ethics Committee of Medical School, Qazvin University of Medical Sciences, and obtaining informed patient consent, ninety patients 18-40 years old, with American Society of Anesthesiologists (ASA) physical status I or II, scheduled for cesarean section under spinal anesthesia, were recruited in a prospective, double-blind, randomized way. The Consolidated Standards of Reporting Trials (CONSORT) recommendations for reporting the randomized, controlled clinical trials22 were followed (Figure 1).

Exclusion criteria included significant coexistence of conditions such as cardiovascular and hepatorenal diseases, allergy to bupivacaine or ketamine, long-term opioid use, or a history of chronic pain or any contraindication to regional anesthesia such as local infection or bleeding disorders. The patients were randomly allocated to one of the three groups of 30 patients each by using the computer-generated randomization list. Three syringes were labeled as A, B, and C and were filled with equal amounts of drugs (2.5 ml) All of the syringes prepared by the personnel who were not involved in the study, and were randomly handed to the anesthetist who was unaware of the drugs. The ketamine group received bupivacaine
intrathecal ketamine and fentanyl plus bupivacaine in C-section

10mg combined with 0.1mg/kg ketamine, the fentanyl group received bupivacaine 10mg combined with 25 µg fentanyl, and the placebo group received bupivacaine 10mg combined with 0.5ml distilled water, intrathecally. All patients received 5-7 ml/kg lactated Ringer’s solution before spinal anesthesia. After using an aseptic technique, a 25-gauge Quincke needle was inserted intrathecally via a midline approach into the L4-5 interspaces while the patient was in sitting position. The primary outcomes of this study are to evaluate the time to first requirement of analgesic supplement and total analgesic consumption in the first 24 h postoperative period. The secondary outcomes included the assessment of sensory block onset time, onset of motor block, duration of blockade, hemodynamic variables, the incidence of hypotension, ephedrine requirements, bradycardia, hypoxemia (saturation of peripheral oxygen (SpO₂) <90), and adverse events such as sedation, dizziness, pruritus, and postoperative nausea and vomiting.

In this study, the postoperative analgesia was defined as the time to first requirement of analgesic supplement from the time of injection. No additional analgesic was administered unless requested by the patient. Sensory block was assessed by a pinprick test. The onset of sensory block was defined as the time between the end of injection of the intrathecal anesthetic and the absence of pain at the T10 dermatome; the duration of sensory block was defined as the time for regression of the sensory from the maximum block height to the T10 dermatome as evaluated by pinprick. The maximum level of sensory block was evaluated by pinprick after 20 min after injection. Motor block was assessed by the modified Bromage score (0, no motor loss; 1, inability to flex the hip; 2, inability to flex the knee; and 3, inability to flex the ankle); the onset of

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motor block was defined as the time from intrathecal injection to Bromage block 1, and the duration of motor block was assumed when the modified Bromage score was zero. The duration of spinal anesthesia was defined as the period from spinal injection to the first occasion when the patient complained of pain in the postoperative period.

Patients were preoperatively elucidated to use the verbal rating scale (VRS) from 0 to 10 (0: no pain, 10: maximum pain) for pain assessment. If the VRS exceeded four and the patient requested a supplement analgesic, diclofenac Na Supp 100 mg every 8 hours was given to post-operative pain as needed (q8h PRN). If the time course following the administration of diclofenac Na decreased to less than 8h and the patient made another request for supplement analgesic, pethidine 25 mg IV was given.

The mean arterial pressure (MAP), heart rate (HR), and (SpO2) were recorded by an anesthetist blinded to the patient group5 min before the intrathecal injection and also at 2, 4, 6, 8, 10, 15, and 20 min after injection. If systolic blood pressure (SBP) was 20% below the baseline or less than 90 mmHg, ephedrine 5mg was administered intravenously. Also, if HR was less than 50 beats/min, 0.5mg of atropine sulfate was administered intravenously.

A follow up telephone call was done 24 hours after the surgery and again 1 month and 6 months later, which the patients were asked about the dysesthesia of the lower limbs or buttocks and the other side effects.

To calculate the sample size, data from previous similar studies were taken into consideration. A sample size of 25 patients per group was required to detect a 20-min difference in the mean duration of analgesia between the groups using the Mann-Whitney U-test, with a power of 0.9 and an α equal to 0.05. We included 30 patients in each group to allow for dropouts and protocol violations. Data were analyzed using SPSS (SPSS 15.0, SPSS Inc, Chicago, II, USA). Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. Parametric data were expressed as mean and standard deviation (SD) and analyzed by independent T test. The X2 test was used to analyze the incidence of side effects. A P-value <0.05 was considered as significant, statistically.

### Results

A total of 95 patients were initially enrolled in the study and 5 patients had to be excluded because of logistical reasons or other violations of the study protocol. Ninety patients were included and randomly assigned to their treatment groups [Fig. 1].

There were no significant differences in age, height, and weight among the three groups. The duration of surgery was also similar [Table 1].

Table 2 shows the mean onset of sensory block was longer in group F (95.33 ± 39.17 sec) than group P (78.5 ± 26.00 sec) and group K (89.33 ± 22.03 sec). The difference between group K versus group F (P = 0.44) and group P (P = 0.165) was insignificant, while this difference between group F and P was significant (P = 0.032) through LSD post hoc test. However the overall difference among three groups were not significant through Anova test (P = 0.094).

The mean duration of sensory block in group K

### Table 1

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group K (n = 30)</th>
<th>Group F (n = 30)</th>
<th>Group P (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.43 ± 3.70</td>
<td>30.20 ± 5.41</td>
<td>29.16 ± 5.11</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>88.5 ± 15.4</td>
<td>88.5 ± 13.6</td>
<td>89.7 ± 11.9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166 ± 4.6</td>
<td>160 ± 8.4</td>
<td>162 ± 6.1</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>85.63 ± 15.70</td>
<td>79.16 ± 20.11</td>
<td>81.70 ± 18.76</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, K = ketamin, F = fentanyl, P = placebo. There are no significant differences among the three groups.
intrathecal ketamine and fentanyl plus bupivacaine in C-section

The difference between group K versus F (P = 0.597) and P (P = 0.447) was insignificant. Similarly, the difference in group F and P was insignificant (P = 0.816). The median value for the maximum height of block was T6 for all three groups.

The mean duration of motor blockade time was significantly longer in group K (170.43 ± 22.70 min) than P (136.76 ± 28.85 min) and F groups (143.16 ± 33.94). The difference in mean duration of motor blockade time between group K versus F (P <0.000) (143.73 ± 17.77 min) was longer than group P (122.23 ± 32.78 min) and group F (133.53 ± 32.68 min) (Table 2). The difference between group K and P (P = 0.013) was statistically significant but the difference between group K and F (P = 0.356) and between group F and P (P = 0.283) was not significant through LSD post hoc test.

As shown Table 2, the mean onset of motor block was (86.00 ± 33.15) in group K, (80.00 ± 30.62) in group P, and (81.83 ± 27.21) sec in group F. The difference between group K versus F (P = 0.597) and P (P = 0.447) was insignificant. Similarly, the difference in group F and P was insignificant (P = 0.816).

The median value for the maximum height of block was T6 for all three groups.

The mean duration of motor blockade time was significantly longer in group K (170.43 ± 22.70 min) than P (136.76 ± 28.85 min) and F groups (143.16 ± 33.94). The difference in mean duration of motor blockade time between group K versus P (P <0.000)

Table 2
Characteristics of spinal anesthesia

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group K (n = 30)</th>
<th>Group F (n = 30)</th>
<th>Group P (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset time of Sensory block (second)</td>
<td>89.33 ± 22.03</td>
<td>95.33 ± 39.17*</td>
<td>78.5 ± 26.00</td>
<td>0.094</td>
</tr>
<tr>
<td>Duration of sensory block (min)</td>
<td>143.73 ± 17.77*</td>
<td>133.53 ± 32.68</td>
<td>122.23 ± 32.78</td>
<td>&lt;0.018</td>
</tr>
<tr>
<td>Onset time of Motor block (second)</td>
<td>86.00 ± 33.15</td>
<td>81.83 ± 27.21</td>
<td>80.00 ± 30.62</td>
<td>0.737</td>
</tr>
<tr>
<td>Duration of motor block (min)</td>
<td>170.43 ± 22.70**</td>
<td>143.16 ± 33.94</td>
<td>136.76 ± 28.85</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Time to first request of analgesic (min)</td>
<td>296.80 ± 32.64*</td>
<td>277.88 ± 94.25*</td>
<td>235.43 ± 22.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of spinal Anesthesia</td>
<td>211.73 ± 74.80</td>
<td>208.50 ± 35.45</td>
<td>192.33 ± 30.36</td>
<td>0.291</td>
</tr>
<tr>
<td>Total ephedrine requirement</td>
<td>1.83 ± 3.82</td>
<td>5.52 ± 2.16</td>
<td>5.58 ± 4.16</td>
<td>0.159</td>
</tr>
<tr>
<td>Total analgesic consumption in 24 h (number of analgesic request)</td>
<td>2(2-2)*</td>
<td>2(1-3)</td>
<td>3(2-3)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or median IQR, K = ketamin, F = fentanyl, P = placebo. * p <0.05 compared to the placebo group. ** p <0.05 compared to the other two groups.

Table 3
Side effects observed in three study groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group K</th>
<th>Group F</th>
<th>Group P</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>1 (%33)</td>
<td>1 (%3.3)</td>
<td>0</td>
<td>0.60</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypotension</td>
<td>7 (%23.3)</td>
<td>4 (%13.3)</td>
<td>8 (%26.7)</td>
<td>0.420</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Dryness</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (%3.3)</td>
<td>6 (%20)</td>
<td>3 (%10)</td>
<td>0.118</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>1 (%3.3)</td>
<td>1 (%3.3)</td>
<td>0.600</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1 (%3.3)</td>
<td>0</td>
<td>0.364</td>
</tr>
<tr>
<td>Shivering</td>
<td>2 (%6.7)</td>
<td>1 (%3.3)</td>
<td>4 (%13.3)</td>
<td>0.328</td>
</tr>
</tbody>
</table>

Data are presented as number of patients(%). K = ketamin, F = fentanyl, P = placebo.
Fig. 2 Blood pressure changes in the three groups

Data are presented as mean ± SD, K = ketamin, F = fentanyl, P = placebo. MAP = mean arterial blood pressure (mm Hg), SA = spinal anesthesia. * p < 0.05 compared to the other groups.

Fig. 3 Heart rate changes in three groups

Data are presented as mean ± SD, K = ketamin, F = fentanyl, P = placebo, HR = heart rate (bpm), SA = spinal anesthesia
and F groups (P <0.001) were significant whereas no significant difference in duration of motor block between F and P groups was found (P = 0.668).

The duration of anesthesia in ketamine group (211.73 ± 74.80) was longer compared to the fentanyl group (208.50 ± 35.45) and placebo (192.33 ± 30.36) groups. However the difference among three groups was not significant through Anova test (P = 0.291). (Table 2).

The mean time to first analgesic request was longer in group K (296.80 ± 32.46) compared to groups F (277.88 ± 94.25) and P (235.43 ± 22.35 min). There were no difference between group K and F (P = 0.504) but the difference between group K and P (P <0.001) and group F and P (P = 0.042) was significant (Table 2).

The total number of analgesic request by patients during 24 hours after surgery in ketamine group was significantly smaller than placebo group (P = 0.002) but this difference in group K versus F (P = 0.538) and group F versus P (P = 0.071) was not significant.

Transient hypotension occurred at various time points in three groups, despite pre-block volume loading (Fig. 2).

The mean variation of mean arterial pressure, heart rate was defined as the difference between the highest and the lowest mean arterial pressure and heart rate in each patient. The mean variation of MAP was 25.78 ± 11.64 in group K, 33.73 ± 10.73 in group P, and 50.00 ± 76.14 in group F. The difference between group K and F was significant (P = 0.040) whereas no significant difference between P versus group K (P = 0.495) and group F (P = 0.164).

The overall difference in ephedrine requirement between the three groups was not statistically significant.

The mean variation of HR was 33.9 ± 11.62 in group K, 33.43 ± 12.79 in group F, and 32.86 ± 10.17 in group P. As shown Fig. 3, the difference between group K and group F (P = 0.876) and group P (P = 0.730) groups was not significant as it was for the difference between groups F and P (P = 0.850).

The three groups were found to have no significant difference in terms of other intraoperative and postoperative side effects including pruritus, nausea, vomiting, headache, shivering, and respiratory depression. No patient in either group showed any sensory or motor complications within the next six months follow up after surgery (Table 3). All newborns in our study were free of any adverse effect.

### Discussion

Addition of ketamine or fentanyl to spinal bupivacaine results in prolonged analgesia after cesarean delivery compared with the placebo group. The total analgesic consumption within the first 24h postoperative was similar in fentanyl and ketamine groups following cesarean section. These results are in accordance with previous research12,18,26,27 but contradict other studies28,29.

However, it is reported that NMDA receptor antagonists such as ketamine have a preventive and also therapeutic effect on postoperative pain12. Furthermore, ketamine blocks the voltage-sensitive calcium channels, depresses sodium channels, and alters cholinergic neurotransmission, which is responsible for pain mechanisms; it acts as a noradrenergic and serotonergic uptake inhibitor, which is implicated in descending antinociceptive pathways30.

Our current findings suggest that ketamine significantly enhances the pethidine effects on postoperative pain management, thereby preventing the subsequent NMDA activation. The NMDA receptor antagonist potentiates the opioid antinociception by blocking the spinal C-fiber stimulation31. Analgesic consumptions known to be related to primary hyperalgesia caused by the augmentation of the sensitivity of primary afferent receptors rather than by central sensitization31.

The discrepancy of the results may be due to different methodologies and populations. For example, Kathirvel et al32 used a higher dose (10 mg) of bupivacaine in the control group than that in the ketamine group (7.5 mg). In the current study, we used 10 mg bupivacaine in both groups.

Another finding which should be noted is that the onset of sensory and motor block was similar in three groups. This finding is consistent with the results of study by Murali Krishna et al33. However the results
by Unlugenc et al [28] and Yanli and Eren [34] suggested that the addition of intrathecal ketamine to spinal bupivacaine shortened the onset of both sensory and motor blockades. Results of the clinical study by Galindo [35] suggested that the pH-adjusted solutions of local anesthetics produced a more rapid onset of blockade with better quality and longer duration than the unmodified commercial preparations, a finding in agreement with our finding. The addition of ketamine decreases the pH of bupivacaine and therefore, the onset of the sensory block is prolonged compared to control group. We used distilled water in the placebo group and ketamine 0.1 mg/kg in the ketamine group combined with spinal bupivacaine. We speculate that the pH of the solution is a possible reason why ketamine prolongs the onset of sensory block. The pH of ketamine hydrochloride is slightly acidic (3.5-5.5), whereas the pH of distilled water used in the placebo group is neutral (pH 7-7.4), and also the PH of fentanyl is 4-7.5.

The addition of intrathecal ketamine 0.1 mg/kg or fentanyl 25 µg to spinal bupivacaine prolonged the duration of motor and sensory block similarly. These findings are contrary to the findings of Unlugenc et al [28] and Shrestha et al [29]. They reported that motor and sensory duration was significantly longer in Group F than in Groups K. However, the discrepancy of the results may be due to different methodologies.

Transient hypotension episodes and vasopressor requirement in ketamine group were less than fentanyl and placebo groups, a finding in agreement with previous studies [32,33,36]. The overall results of our study are consistent with studies by Bion [36] Murali Krishna et al [33], and Kathirvel et al [32], who reported that the use of intrathecal ketamine was associated with minimal hemodynamic changes. Bion [36] suggested that the transmission of ketamine into the venous system (azygos vein) of the spinal cord leads to hemodynamic stability during spinal anesthesia. The selection of intrathecal ketamine dose of 0.1 mg/kg and fentanyl was based on the fact that several previous studies showed that the use of such dose could prolong the duration of analgesia without additional side effects [29,33,37].

In the present study, we did not find any incidence of behavioral, psycho-mimetic, or neurological complications and delayed respiratory depression in the patients receiving ketamine or fentanyl intrathecally. This result is in accordance with the findings by Bion et al [36], who reported that intrathecal ketamine acts locally on the spinal cord nociceptors and does not act systemically after being absorbed into the circulation [38]. However, it seems that the incidence of complications with intrathecal ketamine or fentanyl is a dose-dependent phenomenon and thus the routine use of such drugs at high doses in clinical practice should be postponed until its safety is proved by further studies.

In conclusion, both fentanyl and ketamine when added to spinal bupivacaine were equally effective in pain control after cesarean section and therefore, based on the specific conditions of patients, if the administration of fentanyl cannot be justified due to some possible complications, ketamine at concentrations of 0.1 mg/Kg could be a proper alternative to achieve postoperative analgesia.
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References


33. Murali Krishna T, Panda NB, Batra YK, Raje S: Combination of


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**REFERENCES:**

1. BRIDION Summary of Product Characteristics. [SPC]

Please see summary of product characteristics for full prescribing information.

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