Comparative study of efficacy of intrathecal bupivacaine-ketamine with bupivacaine-fentanyl for caesarean section

Dr. Nitish Gupta, Dr. Sanhita J Kulkarni, Dr. Vasanti M Sasturkar, Dr. PV Bhale and Dr. Pradnya S Joshi

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Abstract
Background: Various adjuvants have been used with local anaesthetics in spinal anaesthesia for lower segment caesarean section (LSCS) to provide better haemodynamics & prolonged postoperative analgesia. The aim of this study was to compare onset & duration of sensory & motor block with haemodynamic stability of intrathecal ketamine and fentanyl added to Bupivacaine in spinal anaesthesia for two different group of patients posted for LSCS

Method: Sixty patients of age between 18-35 years and ASA grade I and II were included and randomly divided into two groups of 30 each. Group K received injection bupivacaine 10 mg with 10 mg Ketamine and Group F received injection Bupivacaine 10 mg with 12.5 mcg Fentanyl. The sensorimotor characteristics, haemodynamic parameters, neonatal outcome and side effects were noted and compared between two groups.

Results: Group K showed higher sensory level (<0.05), rapid sensory (P<0.05) and motor (P<0.05) onsets, prolonged sensory (P>0.05) and motor (P<0.05) blocks as compared to group F. Hyperbaric bupivacaine-Ketamine had better haemodynamic stability and significantly reduced incidence of hypotension (P<0.05) and bradycardia (P<0.05). Apgar scores at 1 and 5 min were comparable in both groups (P = 0.2734 and 0.6731 respectively). Tachycardia was found in 16.66% cases in group K, whereas no patient developed tachycardia in group F.

Conclusion: The combination of hyperbaric bupivacaine (0.5%) 10mg with ketamine (10mg) can be used as a safe and effective alternative to hyperbaric bupivacaine (0.5%) 10mg with fentanyl 12.5mcg for spinal anaesthesia in LSCS.

Keywords: bupivacaine, fentanyl, ketamine, spinal anaesthesia

Introduction
Spinal anaesthesia (SA) is the most widely used anaesthetic technique for caesarean section. It produces rapid onset of analgesia and complete muscle relaxation. Risk of aspiration, drug induced neonatal depression associated with general anaesthesia may largely be avoided by using neuraxial techniques [1]. Bupivacaine a long acting amide is the most popular local anaesthetic agent used for spinal anaesthesia in parturient undergoing LSCS. Commonly used dose of bupivacaine (10-15mg) is associated with hypotension and longer duration of motor block [2, 3]. Decreasing the dose of bupivacaine in spinal anaesthesia helps to minimize these adverse effects but simultaneously may result in anaesthetic failure. To avoid such instances many drugs such as opioids (morphine, fentanyl), midazolam, clonidine, ketamine have been used as adjuvant to bupivacaine [3].

In parturient most commonly used adjuvant is fentanyl. Since fentanyl is lipophilic opioid, when used intrathecally, there is minimal cephalad spread thus least likely to cause delayed respiratory depression compared to morphine [3]. Ketamine, a phencyclidine derivative and commonly used intravenous induction agent, has been also found to be effective by intrathecal route. Intrathecal ketamine possesses some definitive advantages such as stimulation of cardiovascular system thus decreasing incidence of hypotension [7, 8].

There are very few studies that had used intrathecal ketamine as an adjuvant in caesarean section. Hence this study was undertaken to assess the efficacy of intrathecal ketamine (10mg) compared to fentanyl (12.5mcg) in above mentioned doses along with bupivacaine (10mg) in parturient undergoing caesarean section.
Material and Methods

After obtaining Institutional Ethical Committee approval and written informed consent from patients, this prospective, randomized, double blind study was conducted in 60 patients of ASA grade I and II, age between 18-35 years, height 150-170 cms, weight 50-80 kgs, gestational age >37 weeks posted for elective caesarean section delivery from May 2016 to May 2018. Patients having contraindication for spinal anaesthesia such as coagulation disorder, local infection at the site of spinal anaesthesia, known allergy to local anaesthetics, foetal distress, patients with medical disorders like pregnancy induced hypertension, heart disease were excluded from the study. Using a sealed envelope method 60 patients was randomly allocated into two groups of 30 patients in each group. Group K: 0.5% Hyperbaric Bupivacaine 10 mg plus Ketamine 10 mg and Group F: 0.5% Hyperbaric Bupivacaine 10 mg plus Fentanyl 12.5 mcg.

All patients were kept nil orally for 6 hours. After shifting the patients in operation theatre (OT) baseline heart rate, non-invasive blood pressure, spo2, Electrocardiogram was recorded. With the help of 20G canula, IV line was established. One anaesthetist prepared the drugs and gave spinal anaesthesia, other anaesthetist (observer) who was blind to the study drug used, monitored the patient in the intra operative period and collected the data. Spinal anaesthesia was performed in sitting position with 23 gauge Quincke spinal needle by midline approach at L3-L4 level. After confirming free flow of CSF, study drug was injected in sub-arachnoid space and patient was made supine. After spinal anaesthesia the vital parameters pul.

Statistical analysis

For calculating sample size, following formula was applied:

\[ n = \frac{\left( Z_{0.005/2} + Z_{p} \right)^2}{d^2} \]

Where SD = Pooled Standard Deviation
\[ Z_{0.005/2} = \frac{1.96}{\sqrt{2}} = 1.36 \] at type I error
\[ Z_{p} = Z_{0.20} = 0.84 \text{ at } 80\% \text{ power} \]
\[ d = \text{effect Size } = \text{difference between two mean} \]

Minimum sample size required is 20 (approximately). Considering the drop-out; we included 30 patients in each group.

For the analysis of collected data SPSS version 20th was applied. The qualitative data was represented in form of frequency and percentage. The quantitative data was represented in form of Mean, SD etc. Both these qualitative and quantitative data was represented on visual impression like bar diagram, pie diagram. A p value < 0.05 was considered statistically significant.

Observations and results

Sixty patients posted for elective caesarean section delivery were enrolled and divided into two groups of 30 patients in each. Both the groups were comparable with respect to the mean age, weight, height and duration of surgery (p>0.05) as shown in table 1.

Table 1: Demographic data and duration of surgery

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean ± SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td>Group K</td>
<td>Group F</td>
</tr>
<tr>
<td></td>
<td>23.63±2.53</td>
<td>24.3±2.59</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>53.67±3.54</td>
<td>53.7±3.00</td>
</tr>
<tr>
<td>Height in Cm</td>
<td>154.97±3.84</td>
<td>154.47±3.61</td>
</tr>
<tr>
<td>Duration of Surgery</td>
<td>54.97±3.84</td>
<td>54.47±3.61</td>
</tr>
</tbody>
</table>

The onset of sensory and motor block was significantly faster and total duration of sensory and motor block was significantly prolonged in ketamine group as compared to fentanyl group, (p value < 0.05). The mean time of sensory and motor characteristics is shown in table 2.

Table 2: Comparison of sensory and motor characteristics between two groups

<table>
<thead>
<tr>
<th>Variables (min)</th>
<th>Mean ± SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of onset of sensory block</td>
<td>Group K</td>
<td>Group F</td>
</tr>
<tr>
<td></td>
<td>2.72±0.51</td>
<td>3.87±0.47</td>
</tr>
<tr>
<td>Time for sensory regression to L1</td>
<td>168.23±5.51</td>
<td>162.3±2.33</td>
</tr>
<tr>
<td>Onset of motor block</td>
<td>3.40±0.64</td>
<td>6.62±0.54</td>
</tr>
<tr>
<td>Time of complete motor recovery</td>
<td>160.66±4.61</td>
<td>150.3±4.21</td>
</tr>
</tbody>
</table>

In both the groups median level of maximum sensory block achieved was T6. In group K, sensory block up to T4 was
achieved in 16.67% patients (5 patients) and in group F 43.33% patients achieved T4 level (p value < 0.05), (Figure 1).

Fig 1: Comparison of highest level of sensory block between two groups

Apgar scores at 1 and 5 min were comparable in both the groups (P = 0.2734 and 0.6731 respectively) as depicted in figure 2.

Fig 2: Comparison of mean Apgar score between two groups

The preoperative vitals (HR, SBP, DBP and MAP) were comparable between the two groups with no statistically significant differences (p > 0.05). Pulse rate (PR) in group K was on higher side at 2, 120, 150 minutes than in group F which was statistically significant (p value < 0.05). Systolic blood pressure (SBP) in group K was more than group F at 2, 30, 40, 90, 120, 150 minutes, (p value < 0.05). There was no statistical difference in diastolic blood pressure (DBP) between group K and group F. The value of mean blood pressure recorded in group K and group F were statistically significant at 2, 8, 20, 25, 30, 40, 50, 60 minutes, (Figure 3). The mean values of respiratory rate and oxygen saturation were comparable and found no statistically significant difference in group K and group F.

Fig 3: Comparison of haemodynamic parameters between two groups
Incidence of Hypotension & bradycardia was higher in group F than in group K which was statistically significant (p<0.05). Tachycardia was found in 16.66% cases in group K, whereas no patient developed tachycardia in group F, the difference was statistically highly significant. (Table 3).

Table 3: Comparison and incidence of side effects between two groups

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Group K</th>
<th>Group F</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>3 (10%)</td>
<td>11 (36.67%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.0</td>
</tr>
<tr>
<td>Shivering</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.0</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0 (0%)</td>
<td>7 (23.33%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>5 (16.66%)</td>
<td>0 (0%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Discussion

Spinal anaesthesia is the most popular regional anaesthetic technique in parturient undergoing caesarean section as it is easy to perform, has rapid and predictable onset, produces more intense and complete block and has very high success rate [9]. Various additives such as clonidine, midazolam, fentanyl, ketamine etc. in different doses have been used in combination with local anaesthetic that can effectively help in reduction of the dose of local anaesthetic which leads to early motor recovery and also can increase the duration of analgesia [10]. There are various studies available with use of intrathecal fentanyl in LSCS with varying doses like 7.5 mcg [11], 12.5, 20 mcg [12, 13] and 25 mcg [13, 14]. From the results of previous studies, 25 μg of fentanyl is associated with higher incidence of adverse effects like pruritus [15-17]. Ketamine is a potent analgesic at sub anaesthetic plasma concentrations and its analgesic and anaesthetic effect may be mediated via non-competitive antagonism at N-methyl d-aspartate (NMDA) receptors [6]. In most of the studies doses of ketamine used was 25mg and they observed some of side effects like nystagmus, nausea, vomiting, and sedation [9, 18]. Therefore we used lower dose of ketamine (10mg) and fentanyl (12.5mcg) with bupivacaine (10mg) to study and compare the onset and duration of sensory and motor block, hemodynamic parameter, foetal wellbeing and side effects such as nausea, vomiting, pruritus, respiratory depression.

In our study, onset of sensory and motor block was faster in ketamine group as compared to fentanyl group and the difference in the onset time for the two drugs was statistically significant, (p<0.05). These results are in accordance with the studies by Jamadar NP et al. & Shrestha SK et al. [18-20]. In group K maximum level of sensory block achieved was T4 (16.67%) while its median value was T6 and in group F, maximum level of sensory block achieved was T4 (43.33%) while its median value was T6. Unlugenc et al. [19] showed maximum level of sensory block in ketamine (0.05mg/kg) and fentanyl (25mcg) group as T3. These results vary might be because of dosage used, dose used in fentanyl group was on higher side as compared to our study.Patel et al. [9] observed that highest level of sensory block (median) with use of intrathecal ketamine (25mg) + bupivacaine (1.8ml) was T5. Similarly Shrestha et al. [20] found that the highest level of sensory block both in ketamine (2ml bupivacaine + 25mg ketamine) and fentanyl (2ml bupivacaine + 25mcg fentanyl) group was T5. This higher level of sensory block may be because dosages used in their study were on higher side.

The total duration of sensory and motor block was significantly prolonged in ketamine group as compared to fentanyl group and which was statistically significant. This result is similar to the study done by Khezri et al. [21] but duration of sensory block in our study was longer than their study. This may be because they had considered regression level up to T10, while in our study we have considered duration of sensory block up to L1. Unlike the present study, Unlugenc et al. [19] observed duration of sensory block was shorter in ketamine group (95.7 ± 20.4 min) as compared to fentanyl group (114.5 ± 31.8 min); this may be because they have used lower doses of ketamine (0.05mg/kg) and higher doses of fentanyl (25mcg) as compared to our study.

There was no statistical difference between Apgar score of both ketamine and fentanyl group at 1 and 5 min which is comparable to Jamadar et al. [18] and Biswas et al. [22] study. SBP were higher in ketamine group as compared to fentanyl group at 2, 30, 40, 90,120,150 minutes (P value < 0.05). This result is correlated well with the previous studies [9, 20]. The difference between diastolic pressures of both the group shows no statistically significant difference, this result is similar to Shrestha et al. [20]. The mean arterial pressure of ketamine group was higher than that of fentanyl group at 2, 8,20,25,30,40,50,60 minutes, (P value< 0.05). Hypotension occurred in 3 patients of ketamine group and 11 patients of fentanyl group, which did not require any treatment. In Jamadar et al. [14] study 2 patients of ketamine (25mg) group were having hypotension so these results are comparable to our study. In our study bradycardia was seen in 7 patients in group F which was corrected with single dose of inj. atropine 0.3mg intravenously whereas none of the patient developed bradycardia in ketamine group, these results was similar to Biswas et al. (21) who observed bradycardia in 4 patients out of 20 patients in fentanyl group (12.5mcg). Tachycardia was controlled with single dose of inj Esmolol 10mg Side effects such as pruritus, respiratory depression, nausea and vomiting in both the We did not observe groups.

Conclusion

The combination of hyperbaric bupivacaine (0.5%) 10mg with ketamine (10mg) can be used as a safe and effective alternative to hyperbaric bupivacaine (0.5%) 10mg with fentanyl 12.5 mcg for spinal anaesthesia in caesarean section as, it provides comparable sensory and motor block characteristics, better haemodynamics with good foetal wellbeing.

Acknowledgement

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