Comparison of clonidine and fentanyl as an adjuvant to intrathecal bupivacaine for spinal anaesthesia and postoperative analgesia in patients undergoing caesarian section

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Background
Fentanyl and clonidine both prolong sensory and motor block of spinal anaesthesia and duration of postoperative analgesia when used as an adjuvant to intrathecal bupivacaine. Lack of studies that directly compare them regarding their efficacy prompted us to compare both drugs as an adjuvant to intrathecal bupivacaine for spinal anaesthesia and postoperative analgesia in patients undergoing caesarian section.

Methods and Material
In a prospective, randomized, study forty parturients between 18 to 35 years of age, of ASA grade I or II, awaiting caesarian section were randomly distributed into two equal groups. Patients were given 2.0 ml of hyperbaric bupivacaine 0.5% with either 60µg of clonidine or 25µg of fentanyl intrathecally. Duration of effective analgesia (primary outcome measure), onset peak and duration of sensory and motor blockade, level of sedation, maternal haemodynamic parameters and foetal parameters (secondary outcome measures) were compared.

Results
Both groups were comparable with respect to demographic profile, onset, peak and duration of sensory and motor block and overall haemodynamic stability. Duration of analgesia was significantly higher in bupivacaine with clonidine 60µg group (BC60 group) than in bupivacaine with fentanyl 25µg group (BF25 group). Sedation was more prevalent in BC60 group.

Conclusion
Intrathecal addition of 25µg fentanyl to bupivacaine provides good analgesia with less sedation and is a better option when sedation is not desirable. However intrathecal addition of 60µg clonidine to bupivacaine provides longer duration of postoperative analgesia than 25µg of fentanyl and is a preferred option when sedation is acceptable or required.

Key words: intrathecal; clonidine; bupivacaine; postoperative analgesia; spinal anaesthesia

Introduction
Spinal anaesthesia and postoperative analgesia can be prolonged by using adjuvants to local anaesthetics like adrenaline, midazolam, opioids, neostigmine and clonidine1,2,6. Administration of opioids as adjuvants to local anaesthetics intrathecally results in both synergistic and multimodal analgesia7. The successful use of intrathecal morphine in human beings was first described by Wang et al8 in 1979. Since then almost all opioids have been used via this route. Fentanyl citrate, a µ-1 and µ-2 agonist is a very potent drug because of its high lipophilicity. It is preferred as an adjuvant in spinal anaesthesia because of its rapid onset and short duration of action with lesser incidence of respiratory depression2,9. However pruritus, nausea, vomiting, activation of herpes labialis, urinary retention and late and especially unpredictable, respiratory depression of other opioids have directed pain research towards non-opioids10. Clinical studies
have suggested that intrathecal clonidine prolongs sensory and motor block of spinal anaesthesia. It decreases local anaesthetic requirements, and provides prolonged postoperative analgesia. Other beneficial effects are antiemesis, reduced post spinal shivering, anxiolysis and sedation. Unlike spinal opioids, clonidine does not produce pruritus or respiratory depression. In this study we have compared intrathecal clonidine with fentanyl in regard to their efficacy and safety as an adjuvant to intrathecal bupivacaine for spinal anaesthesia and postoperative analgesia in patients undergoing caesarian section.

**Method**
A prospective, randomized, study design with two parallel groups was used. After prior approval from Institutional Ethics Committee, study was conducted on 40 parturients of age group between 18 – 35 years and of ASA grade I or II booked for elective as well as emergency Lower Segment Caesarian Section. Informed consent was obtained from all the parturients. Exclusion criteria were complicated pregnancy including pregnancy-induced hypertension, placenta praevia, abruptio placentae, severe systemic disorders like diabetes mellitus, hypertension, heart disease changing ASA grade to more than II, allergy to bupivacaine, fentanyl or clonidine and all known contraindications for spinal anaesthesia, such as spine deformity, increased intracranial pressure, neurological disorders, haemorrhagic diathesis, or infection at the puncture site. Parturients were randomly divided by blocked randomization method into two groups of 20 patients each and randomization was concealed.

**GROUP BF 25 (n=20)**
In this group, each patient was given 2.0ml (10 mg) of hyperbaric bupivacaine 0.5% with 25µg of fentanyl, intrathecally.

**GROUP BC 60 (n=20)**
In this group, each patient was given 2.0ml (10mg) of hyperbaric bupivacaine 0.5% with 60µg of clonidine, intrathecally.

The sample size could not be calculated before the start of the study due to paucity of similar studies. Post-hoc power analysis was carried out keeping its limitations in mind for duration of effective analgesia measured by time in minutes for requirement of rescue analgesia. This study had 99.53% power to detect effect size of 180.95 minutes between two groups assuming alpha error 0.05(two-sided). Sedatives and hypnotics were avoided in premedication, as well as intraoperatively. All these patients were premedicated with intravenous ondansetron (4 mg) and routine acid aspiration prophylaxis per orally. Patients were preloaded with Ringer Lactate (RL) 10-15 ml/kg. Pre-operative parameters like pulse rate, oxygen saturation and blood pressure were recorded. Spinal anaesthesia was given with 25G Quincke needle in sitting position with aseptic precautions. Depending upon the groups, respective agents were injected intrathecally. Each group had a total volume of 2.5ml made by addition of normal saline. Both the patient and anaesthesiologist were blinded to the study solutions. Syringes were prepared just before the spinal injection ensuring the volumes of 2.5ml by a third person knowing the code to blind the anaesthesiologist administering the drug and later on making the observations. Pulse and blood pressure were measured every 5 minutes for first 30 minutes and thereafter every 10 minutes. Number of occasions for pulse rate and blood pressure variations more than 20% of baseline were noted in both groups. Bradycardia was treated with i.v. atropine 0.6mg if persistent for a long time and was symptomatic. Sensory block was tested by pinprick method. Degree of motor blockade was assessed by modified Bromage scale used by Breen et al. Observations were made at T₀ = Time of spinal anaesthesia, T₁ = Time of onset of sensory block, T₂ = Time of onset of motor block, T₃ = Time of peak sensory block, T₄ = Time to two segment regression of sensory level, T₅ = Time of wearing off of motor block, T₆ = Time to first dose of post-operative rescue analgesia. Apgar score of the newborn was monitored at 1, 5, and 10 minutes. In the intra operative period, patient was closely monitored for pulse rate, SpO₂, blood pressure and blood loss. Oxytocin 10U was added to RL infusion after delivery of the anterior shoulder. Any side effects such as nausea, vomiting, pain, shivering, pruritus, sedation, hypotension, bradycardia, and respiratory discomfort were noted. Patients were assessed for degree of sedation and scoring was done with Campbell Sedation Score as 1) wide awake 2)
awake and comfortable 3) drowsy and difficult to aroused 4) not rousable. Residual sensory blockade was monitored and its wearing off time was noted (when sensation to pin-prick gets 2 dermatomal segments regression). Residual motor blockade was monitored and its wearing off time was noted when patient started to lift legs against gravity. Patients were monitored for degree of pain with the Visual Analogue Scale (VAS). Postoperative rescue analgesia (intramuscular diclofenac 75mg) was given when the VAS score was > 7 and the time of injection of first analgesic drug was noted. This was taken as the time of wearing off of analgesia.

Statistical analysis was carried out with Stata 10. Demographic characteristics, haemodynamic parameters, onset, peak and duration of sensory and motor block and duration of postoperative analgesia, level of sedation and foetal parameters were compared between two groups and data was analyzed. For continuous variables descriptive statistics (mean and standard deviations) were computed. Comparison of means in group BF 25 and group BC 60 was done using unpaired t-test. For categorical data chi-square test was applied. P < 0.05 was considered significant.

Results
Both groups were comparable with respect to their demographic profile as shown in Table I. There was no significant difference in them regarding age, ASA status, height, weight, parity, duration of pregnancy and duration of labour.

Table 1 Demographic characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BF 25 Group (n =20)</th>
<th>BC 60 Group (n =20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>23.1 ± 2.55 (19-28)</td>
<td>24.7 ± 3.15 (19-30)</td>
<td>0.09</td>
</tr>
<tr>
<td>Height in cm.</td>
<td>153.65 ± 5.21 (146-167)</td>
<td>153.25 ± 6.09 (142-167)</td>
<td>0.82</td>
</tr>
<tr>
<td>Weight in kg</td>
<td>57.6 ± 7.92 (40-72)</td>
<td>59.65 ± 8.73 (42-78)</td>
<td>0.44</td>
</tr>
<tr>
<td>Duration of pregnancy in weeks</td>
<td>38.72 ± 1.36 (36-40.3)</td>
<td>38.68 ± 1.77 (34.6-42.4)</td>
<td>0.94</td>
</tr>
<tr>
<td>Duration of labour in hours</td>
<td>3.65 ± 2.87 (1-10)</td>
<td>4.55 ± 4.01 (1-18)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Parity
- Primipara: 7
- Second para: 11
- Multipara: 2

BF 25 Group: Intrathecal 2.0ml of hyperbaric bupivacaine 0.5% with 25µg of fentanyl.
BC 60 Group: Intrathecal 2.0 ml of hyperbaric bupivacaine 0.5% with 60µg of clonidine.
* p-value> 0.05

They were also comparable with respect to their baseline haemodynamic parameters like pulse rate (87.85 ± 8.55: 89±12.08), systolic blood pressure (119.15 ±8.53: 119.85±7.09), diastolic blood pressure (74.9 ±9.71: 77.55±8.09). Patients from both groups were comparable with haemodynamic parameters as shown in Table 2. No significant difference was found in them regarding average pulse rate (87.84 ±12.54: 88.41±13.60), average systolic blood pressure (112.29 ±12.28:111.05±10.26), average diastolic blood pressure (64.43± 8.71: 63.25±9.38). No significant difference was found regarding pulse variation (21:28) and incidence of hypotension (11: 17). Bradycardia< 60 beats/minute was observed only in two patients and both belonged to BC 60 group. Only one of them showed pulse rate drop up to the level of 50 beats/minutes needing intervention and responded well to i.v. atropine 0.6 mg.

Table 2 Comparison of maternal haemodynamic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BF 25 group (n =20)</th>
<th>BC 60 group (n =20)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline pulse rate per minute</td>
<td>87.85±8.55</td>
<td>89±12.08</td>
<td>0.73</td>
</tr>
<tr>
<td>Baseline systolic blood pressure mmHg</td>
<td>119.15±8.53</td>
<td>119.85±7.09</td>
<td>0.78</td>
</tr>
<tr>
<td>Baseline diastolic blood pressure mmHg</td>
<td>74.9±9.71</td>
<td>77.55±8.09</td>
<td>0.35</td>
</tr>
<tr>
<td>Average pulse rate per minute</td>
<td>87.84±12.54</td>
<td>88.41±3.60</td>
<td>0.89</td>
</tr>
<tr>
<td>Average systolic BP mmHg</td>
<td>112.29±12.28</td>
<td>111.05±10.26</td>
<td>0.73</td>
</tr>
<tr>
<td>Average diastolic BP mmHg</td>
<td>64.43±8.71</td>
<td>63.25±9.38</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Haemodynamic variability

- Number of occasions of pulse rate fall< 80% of baseline: 11
- Number of occasions of pulse rate rise>120% of baseline: 10
- Number of occasions of fall in BP < 80% of baseline: 8
- Number of occasions of rise in BP > 120% of baseline: 3
- Total number of occasions of haemodynamic variability: 32 45 77
Table 3 compares onset, peak and duration of sensory and motor block and duration of postoperative analgesia. There was no difference in onset of sensory block (0.90 ± 0.21: 0.91±0.17 min) (p>0.05), onset of motor block (1.59 ± 0.48:1.71 ± 0.51 min) (p>0.05), onset of peak sensory block (7.55 ± 0.94 : 7.54 ±1.80 min) (p > 0.05), two segment regression of sensory block (131 ± 14.83 : 135.2 ± 12.45 min) (p>0.05) and wearing of motor block (189.5 ±18.06 : 182.1±10.08 min) (p>0.05). Duration of analgesia was significantly higher in BC60 group (598.7±140.47 min) than in BF25 (417.75 ±108.76) group. (p<0.01).

Table 3 Comparison of sensory, motor blockade and duration of analgesia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BF25 Group (n =20)</th>
<th>BC60 Group (n =20)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time in minutes for onset of sensory blockade</td>
<td>0.90±0.21</td>
<td>0.91 ± 0.17</td>
<td>0.87</td>
</tr>
<tr>
<td>Time in minutes for onset of motor blockade</td>
<td>1.59±0.48</td>
<td>1.71 ± 0.51</td>
<td>0.44</td>
</tr>
<tr>
<td>Time in minutes for peak of sensory blockade</td>
<td>7.55 ± 0.94</td>
<td>7.54 ± 1.80</td>
<td>0.98</td>
</tr>
<tr>
<td>Two segment regression time in minutes for sensory blockade</td>
<td>131 ± 14.83</td>
<td>135.2 ± 12.45</td>
<td>0.34</td>
</tr>
<tr>
<td>Time in minutes for wearing off of motor block</td>
<td>189.5 ± 18.06</td>
<td>182.1±10.08</td>
<td>0.12</td>
</tr>
<tr>
<td>Time in minutes for first rescue analgesia</td>
<td>417.75 ±108.76</td>
<td>598.7±140.47</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Sedation score 4 was observed in none of the patients from both groups as per shown in Table 4. More patients from group BC 60 showed sedation score of 2 or 3 implying more sedation with clonidine than with fentanyl. (p<0.01).

Table 4 Sedation score
(Number of patients having sedation score in each group)

<table>
<thead>
<tr>
<th>Sedation score</th>
<th>Group BF 25</th>
<th>Group BC 60</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Wide awake</td>
<td>19 (95 %)</td>
<td>1 (5 %)</td>
<td>20</td>
</tr>
<tr>
<td>2 Awake and comfortable</td>
<td>1 (5 %)</td>
<td>14 (70 %)</td>
<td>15</td>
</tr>
<tr>
<td>3 Drowsy and difficult to arouse</td>
<td>0</td>
<td>5 (25 %)</td>
<td>5</td>
</tr>
<tr>
<td>4 Not rousable</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>20</td>
<td>40</td>
</tr>
</tbody>
</table>

Pearson chi2(2) =32.4500  Pr = 0.000 p< 0.01

The other side effects observed for were not seen in both groups.

Table 5 shows overall foetal wellbeing in both groups. APGAR scores at one minute, 5 minutes and 10 minutes after birth were comparable in both groups. (p>0.05)

Table 5 Comparison of foetal parameters

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BF25 Group (n =20)</th>
<th>BC60 Group (n =20)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APGAR Score at 1 minute</td>
<td>7.2 ± 0.41</td>
<td>7.35 ± 0.49 *</td>
<td>0.30</td>
</tr>
<tr>
<td>APGAR Score at 5 minute</td>
<td>8.4 ± 0.50</td>
<td>8.35 ± 0.49 *</td>
<td>0.75</td>
</tr>
<tr>
<td>APGAR Score at 10 minutes</td>
<td>9.5 ± 0.51</td>
<td>9.4 ± 0.50 *</td>
<td>0.54</td>
</tr>
</tbody>
</table>

* p-value> 0.05

Discussion

Both fentanyl and clonidine if used in low doses are safe and prolong postoperative analgesia of intrathecal bupivacaine. Thorough literature search revealed paucity of studies directly comparing these two drugs for their efficacy and safety. Present study was designed to directly compare these two drugs. To compare the efficacy we used the duration of effective analgesia measured by time in minutes for requirement of rescue analgesia. In consistency to results of several other studies\textsuperscript{2,4,6,15,16} we found both drugs to be effective as adjuvants to intrathecal bupivacaine prolonging the duration of analgesia. Duration of analgesia was significantly higher in BC60 group (598.7±140.47 min) than in BF25 (417.75 ±108.76) group. (p<0.01). Prolonged duration of analgesia due to fentanyl in our study was different to other studies\textsuperscript{15,16}. Similarly prolonged...
duration of analgesia due to clonidine in our study was also different to other studies. This was expected considering the different doses of clonidine, fentanyl or bupivacaine used. A small dose of intrathecal clonidine as well as fentanyl is not usually associated with systemic side effects such as bradycardia, hypotension, or sedation. The overall haemodynamic stability observed in both groups throughout the surgical procedure in our study confirms to this. Only two patients had significant bradycardia one of which got corrected on its own. Bradycardia requiring treatment was observed only in one patient who responded well to i.v. atropine 0.6mg. Kothari N et al found the incidence of both hypotension and bradycardia more in bupivacaine group than in bupivacaine with clonidine group. Bajwa SJ who used 9mg of bupivacaine also did not observe bradycardia by addition of clonidine even up to 45µg. Shah BB and Sethi BS who used 1mcg/kg of intrathecal clonidine for non-obstetric surgeries had also very few incidences of hypotension and bradycardia requiring intervention. Biswas et al and Agrawal A et al observed similar haemodynamic stability with 12.5µg and 25µg of intrathecal fentanyl. Our findings regarding haemodynamic stability with use of fentanyl were in agreement to their findings and our findings with use of clonidine were in agreement to several other studies. We could not appreciate any difference in both groups regarding onset, peak and duration of sensory and motor block. We found duration of analgesia significantly higher in BC60 group than in BF25 group (p<0.05). This implies that both fentanyl and clonidine prolong the duration of postoperative analgesia and it is more with clonidine than fentanyl. We observed a similar difference in sedation scores. We observed more sedation scores in BC 60 group than in BF 25 group (p<0.05). Kothari N et al also found 35 to 45% of patients drowsy by addition of 50µg of clonidine to bupivacaine; but Bajwa SJ et al did not find any sedation by addition of up to 45µg of clonidine to bupivacaine. Thus the sedation with clonidine is dose dependent. In our study we could not observe sedation with intrathecal fentanyl added to bupivacaine similar to Biswas BN et al. Dahlgren G et al and Hunt CO et al. In conclusion, intrathecal addition of 60µg clonidine to bupivacaine gives longer duration of postoperative analgesia than 25µg of fentanyl but with higher degree of sedation. Fairly good analgesia is observed with less sedation with 25µg fentanyl and it may be recommended as a better option when sedation is not desirable. When some amount of sedation is acceptable or required addition of 60µg of clonidine which gives excellent analgesia with negligible haemodynamic complications may be recommended.

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