Comparative Study between The Addition of Pethidine Vs Fentanyl to Hyperbaric Bupivacaine for Spinal Anesthesia in Caesarean Section
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ABSTRACT
Background: cesarean section is the most common obstetric surgery in the world. Spinal anesthesia is a preferred technique for cesarean delivery for its distinct advantages over general anesthesia as the simplicity of the technique, reliability, minimal fetal exposure to drugs, patients’ awareness and minimization of the hazards of aspiration.
Aim of the Work: to define first time require analgesia in postoperative among two groups.
Patients and Methods: this prospective comparative study was carried on fifty patients, ASA physical status II, aged from 18 to 45 years. These patients were scheduled for elective caesarean delivery under spinal anesthesia and divided to two groups. This protocol was approved by Research Ethical Committee of Ain Shams University. Written informed and verbal consent was obtained from each patient before being included in this procedure.
Results: the addition intrathecal 25mg pethidine make the total duration of analgesia 169.20 ± 7.59 minute but adding 25µg fentanyl intrathecal extended the period of effective analgesia up to 178.40 ± 6.25 min with high significant P-value (0.000). The rapid onset of sensory and motor blocks in (F) group than (P) group with P value=0.000, also increased duration of sensory and motor blocks in (F) group than (P) group with P value 0.000.
Conclusion: intrathecal opioid is a good technique of labor analgesia, although pethidine was the most widely used opioid for obstetric analgesia, it has character of local anesthetics so adding pethidine intrathecal in dose 25mg enhanced effect of local anesthetics but associated with more complications as nausea, vomiting and hypotension.
Keywords: Pethidine, Fentanyl, Hyperbaric Bupivacaine, Spinal Anesthesia, Caesarean Section.

INTRODUCTION
Intrathecal opioids are quite commonly used as adjunct to local anesthetics in regional anesthesia with multiple advantages. The most common causes of mortality in regional anesthesia are high spinal and local anesthetic toxicity. Hence, reduction in the doses of local anesthetics and better management of local anesthetic toxicity is possible in this way. Opioids intrathecally decrease nociceptive inputs form A delta and C fibers without affecting dorsal root axons or somatosensory evoked potentials (1).

Fentanyl is a potent synthetic μ receptor-stimulating opioid, was first synthesized by Dr. Paul Janssen in December 1960. The drug was first used as an intravenous analgesic clinically in Europe in 1963 and in the United States in 1968 and since then has become one of the most important and frequently used opioid analgesics in the world (2).

Fentanyl was discovered to identify an improvement in human health analgesic over morphine, an opioid frequently associated with histamine-release, bradycardia, hyper- or hypotension, and prolonged postoperative respiratory depression.

Historically, the pharmacological features of fentanyl have been described primarily through the study of the human approved fentanyl citrate formulation. Fentanyl has a wide margin of safety, minimum effects on the cardiovascular and respiratory systems, and is readily reversible. Other pharmacological features include sedation, mild reductions in body temperature, and dose-dependent reduction in food intake (3).

As for Pethidine, it is a lipophilic opioid analgesic with local anesthetic effects when administered intrathecally. It can be used as a sole agent for spinal anesthesia. However, it is not as widely used as bupivacaine for this purpose (4).

Although pethidine continues to be the most commonly administered opioid in obstetrics, it is no longer the preferred option for most care settings. Newer opioid derivatives such as fentanyl are favored, because of the short onset time for pain relief and clearance. In particular, fentanyl has been shown to have a similar safety profile for children and adults in both the pre-hospital and hospital settings (5).

Pethidine is the only member of the opioid family that has clinically important local anesthetic activity in the dose range which is normally used for analgesia. Pethidine is unique as the only opioid in current use, which is effective as the sole agent for spinal anesthesia. In lower doses, intrathecal pethidine is also an effective analgesic for treating pain during labor (6). Apart from axonal block its prolonged postoperative analgesic actions were because of its action on nociceptive synaptic junctions in spinal cord, Pethidine, a μ-receptor and κ-receptor agonist, has a more prominent effect in the prevention and

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treatment of postoperative shivering than other opioids, may be because of stimulation of the κ-receptor apart from its non-opioid anti shivering effects such as monoamine reuptake inhibition, N-methyl-d-aspartate receptor antagonism, and stimulation of α-2 receptors (7).

AIM OF THE WORK
To define first time require analgesia in postoperative among two groups.

PATIENTS AND METHODS
This prospective comparative study was carried out on fifty patients, ASA physical status II, aged from 18 to 45 years. These patients were scheduled for elective cesarean delivery under spinal anesthesia.

This protocol was approved by Research Ethical Committee of Ain Shams University. Written informed and verbal consent was obtained from each patient before being included in this procedure.

Inclusion criteria:
Any parturien aged 18 to 45 years of ASA II, who were scheduled for elective cesarean section under spinal anesthesia at gestational age >36 weeks.

Exclusion criteria:
- Any contraindication to regional anesthesia as patient refusal.
- Allergy to applied drugs.
- Obstetrical causes such as preeclampsia, placenta pravia.
- Emergency cesarean section due to maternal or fetal causes like placenta previa or fetal distress.
- Multiple pregnancy.
- History of bleeding diathesis, hepato-renal disease.
- Long term opioid use.

Randomization:
Fifty patients were divided randomly into two groups of twenty-five patients in each one.

Group P: received hyperbaric bupivacaine 0.5%+25mg of pethidine (0.5ml).

Group F: received hyperbaric bupivacaine 0.5%+25μg fentanyl (0.5ml).

Preoperative evaluation:
1) Preoperative changes in mean arterial blood pressure and HR were recorded at the following times: basal (immediately before spinal anesthesia), every 1 min for the first 10min after spinal anesthesia, every 2 min for the second 10 min, and every 5 min till the end of surgery.

2) Block characteristics include: onset of sensory block (define as the time from the intrathecal injection of the study drug till reach peak sensory dermatome level), duration of sensory block (time from onset of block till first analgesia need), onset of motor block (time taken to reach Bromage 3), time of motor blockade (time from complete block to Bromage 0).

Postoperative evaluation:
1) At the end of surgery, patient was assessed for pain intensity based on visual analogue scale (VAG) (where 0= no pain, 10=the worst pain) immediately after surgery, 1h, 2h, 6h, 12h, 24h after surgery. Analgesia was given when VAS still >4.

2) The duration of spinal anesthesia was recorded (the period from spinal injection to the time of administration of first analgesic in postoperative period). The time to full motor recovery (the time to recover a Bromage of 0) were also reported.

3) The incidence of adverse effect including: hypotension, bradycardia, nausea, vomiting, shivering, pruritus were also reported.

4) Incidence of hypotension, bradycardia, nausea, vomiting, shivering, pruritus.

5) The level of consciousness was determined by the Ramsay Sedation Scale.

6) Neonatal outcome detected by APGAR score.

Statistical Analysis
Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations (SD) and ranges when their distribution found parametric and median with inter-quartile range (IQR) when their distribution found non-parametric. Also qualitative variables were presented as number and percentages. P-value of 0.05 or less was considered statistically significant.

RESULTS
Table (1): Difference between Fentanyl group and Pethidine group in first time require analgesia in first 24-hour post-operative.

<table>
<thead>
<tr>
<th></th>
<th>Fentanyl group</th>
<th>Pethidine group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. = 25</td>
<td>No. = 25</td>
</tr>
<tr>
<td>First time need analgesia in first 24 hrs. post-operative (min)</td>
<td>Mean±SD</td>
<td>Mean±SD</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>178.40 ± 6.25</td>
<td>169.20 ± 7.59</td>
</tr>
<tr>
<td></td>
<td>170 – 190</td>
<td>150 – 180</td>
</tr>
</tbody>
</table>

P-value = 0.001, Sig. = HS

HS: Highly Significant *: Chi-square test; •: Independent t-test

Result show difference in time of effective analgesia post-operative between Fentanyl group (178.40 min) and Pethidine group (169.20 min) with significant P-value (0.000).
Table (2): Average Changes in mean Arterial blood pressure in surgery.

<table>
<thead>
<tr>
<th>Average MABP</th>
<th>Fentanyl group</th>
<th>Pethidine group</th>
<th>P-value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average MABP 1st 10 min</td>
<td>85.03 ± 5.57</td>
<td>80.95 ± 6.00</td>
<td>0.016</td>
<td>S</td>
</tr>
<tr>
<td>Average MABP 2nd 10 min</td>
<td>119.64 ± 6.10</td>
<td>118.10 ± 6.27</td>
<td>0.384</td>
<td>NS</td>
</tr>
<tr>
<td>Average MABP till end of surgery</td>
<td>88.86 ± 4.63</td>
<td>88.87 ± 3.98</td>
<td>0.995</td>
<td>NS</td>
</tr>
</tbody>
</table>

> 0.05 NS: Non significant; < 0.05 S: Significant; < 0.01 HS: Highly significant; •: Independent t-test

This table shows significance decrease in MABP in Pethidine group than Fentanyl group in 1st 10 min and non significance changes between the group in 2nd 10 min and till end of surgery.

Table (3): Heart rate (HR) basal and HR changes every 1min in first 10min of surgery.

<table>
<thead>
<tr>
<th>HR every 1 min in 1st 10 min</th>
<th>Fentanyl group</th>
<th>Pethidine group</th>
<th>P-value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. = 25</td>
<td></td>
<td>No. = 25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal HR</td>
<td>70.00 ± 7.46</td>
<td>69.84 ± 6.12</td>
<td>0.934</td>
<td>NS</td>
</tr>
<tr>
<td>HR 1 min</td>
<td>76.36 ± 7.95</td>
<td>73.52 ± 6.77</td>
<td>0.180</td>
<td>NS</td>
</tr>
<tr>
<td>HR 2 min</td>
<td>77.08 ± 8.04</td>
<td>76.20 ± 7.12</td>
<td>0.684</td>
<td>NS</td>
</tr>
<tr>
<td>HR 3 min</td>
<td>75.00 ± 9.66</td>
<td>77.40 ± 12.28</td>
<td>0.446</td>
<td>NS</td>
</tr>
<tr>
<td>HR 4 min</td>
<td>72.04 ± 10.83</td>
<td>79.76 ± 15.03</td>
<td>0.043</td>
<td>S</td>
</tr>
<tr>
<td>HR 5 min</td>
<td>73.04 ± 14.06</td>
<td>79.60 ± 14.20</td>
<td>0.107</td>
<td>NS</td>
</tr>
<tr>
<td>HR 6 min</td>
<td>72.20 ± 15.62</td>
<td>81.60 ± 13.74</td>
<td>0.028</td>
<td>S</td>
</tr>
<tr>
<td>HR 7 min</td>
<td>72.92 ± 14.05</td>
<td>83.96 ± 12.54</td>
<td>0.005</td>
<td>HS</td>
</tr>
<tr>
<td>HR 8 min</td>
<td>75.08 ± 12.39</td>
<td>87.00 ± 11.44</td>
<td>0.001</td>
<td>HS</td>
</tr>
<tr>
<td>HR 9 min</td>
<td>75.48 ± 9.19</td>
<td>89.04 ± 9.09</td>
<td>0.001</td>
<td>HS</td>
</tr>
<tr>
<td>HR 10 min</td>
<td>77.72 ± 8.43</td>
<td>88.96 ± 4.91</td>
<td>0.001</td>
<td>HS</td>
</tr>
</tbody>
</table>

> 0.05 NS: Non significant; < 0.05 S: Significant; < 0.01 HS: Highly significant; •: Independent t-test

This table shows significance increase in heart rate in pethidine group more than fentanyl group.

Table (4): HR changes every 2 min in second 10 min of surgery.

<table>
<thead>
<tr>
<th>HR every 2 min in 2nd 10 min</th>
<th>Fentanyl group</th>
<th>Pethidine group</th>
<th>P-value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. = 25</td>
<td></td>
<td>No. = 25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR 2 min</td>
<td>77.76 ± 18.52</td>
<td>88.28 ± 7.84</td>
<td>0.012</td>
<td>S</td>
</tr>
<tr>
<td>HR 4 min</td>
<td>81.48 ± 11.48</td>
<td>88.04 ± 6.12</td>
<td>0.015</td>
<td>S</td>
</tr>
<tr>
<td>HR 6 min</td>
<td>81.92 ± 12.31</td>
<td>86.88 ± 5.63</td>
<td>0.073</td>
<td>NS</td>
</tr>
<tr>
<td>HR 8 min</td>
<td>81.36 ± 11.22</td>
<td>86.96 ± 5.88</td>
<td>0.032</td>
<td>S</td>
</tr>
<tr>
<td>HR 10 min</td>
<td>81.12 ± 11.88</td>
<td>86.80 ± 5.69</td>
<td>0.036</td>
<td>S</td>
</tr>
</tbody>
</table>

> 0.05 NS: Non significant; < 0.05 S: Significant; < 0.01 HS: Highly significant; •: Independent t-test

This table shows significance increase in heart rate in pethidine group more than fentanyl group.

**DISCUSSION**

Result show that addition intrathecal 25mg pethidine make the total duration of analgesia 169.20 ± 7.59 hours but adding 25μg fentanyl intrathecal extended the period of effective analgesia up to 178.40 ± 6.25 min with high significant P-value (0.001). Result show rapid onset of sensory and motor blocks in (F) group than (P) group with P value=0.000, also increased duration of sensory and motor blocks in (F) group than (P) group with P value 0.000. The baseline hemodynamic parameters heart rate, blood pressure in two study groups were recorded and statistically insignificant. Following spinal anesthesia there was hemodynamical stability between two groups.

In our study there is difference between (P) group and (F) group in incidence of nausea and vomiting which was 40% for fentanyl and 60% for pethidine with non-significant P-value (0.157). Purities between two groups have no statically significance difference with P-value =0.123. Level of consciousness between two groups have no statically significance with P-value =0.384. Also no clinically important hemodynamic changes were noted during the intraoperative and postoperative period, and neonatal APGAR scores did not differ significantly.
Karaman et al. (8) found that dose 25μg intrathecal fentanyl used in spinal anesthesia in C.S which is the same dose we use in our study, has been in agreement, and a prolongation of effective analgesia (197.7 ± 60.0) to (252) minutes.

Akanmu et al. (9) found that intrathecally administered 25μg Fentanyl in spinal anaesthesia for lower limb surgery increased effective analgesic time to 239.97 min.

In contrast with our study, Biswas et al. (10) who add intrathecal fentanyl with bupivacaine in elective C.S and found that period of effective analgesia was only 150 min.as he use dose 12.5μg but in our study we use 25μg fentanyl.

Gomaa et al. (11) found that there no significant changes in BP when adding 25 μg fentanyl intrathecally with bupivacaine in spinal anesthesia in patients undergoing elective cesarean sections.

Honarmand et al. (12) add 20μg fentanyl and 0.2mg pethidine intrathecal in other group and found that pethidine reduce incidence of shivering intraoperative and post operative with Pvalue=0.01

Salmah and Choy (13) noticed that no patient have purities intraoperative and a small number had afterward in after adding 10 mg pethidine intrathecally who made a review in intrathecal pethidine.

Bakhsha and Behnampour (14) found that 16 % of the patients had mild itching after adding 30mg pethidine intrathecally in saddle block in patients undergoing perineal surgery. The common sites of excoriation due to their scratching were the face, the neck and the chest, and it started 10 min after injection with pethidine. The itching lasted till 2 hours after the end of the surgery.

Chun et al. (15) used a dose of 0.2 mg/kg intrathecal pethidine in spinal anesthesia for transurethral prostatectomy in elderly patients and found that was effective in decreasing the incidence of postspinal shivering.

In contrast, Shami et al. (16) concluded that using a minidose of intrathecal pethidine (10 mg) can decrease the incidence and intensity of shivering during cesarean section under spinal anesthesia without having major side effects.

Sadegh et al. (17) found that intrathecal fentanyl decrease intraoperative incidence of shivering when add 25 μg fentanyl in spinal anesthesia in patients undergo elective C.S 10% of patient have shivering while in patients not receive fentanyl have incidence of 75% with significant p-value p<0.0001.

There is no effect on neonatal outcome in (P) group and (F) group APGAR score was not affected in our study.

Khan et al. (18) had same result with different doses of pethidine intrathecal.

CONCLUSION

Intrathecal opioid is a good technique of labor analgesia, so adding pethidine intrathecal in dose 25mg enhanced effect of local anesthetics but associated with more complications as nausea, vomiting and hypotension. Fentanyl is widely used as 25μg fentanyl intrathecal has more effective post-operative analgesia, safe, and more hemodynamical stable.

REFERENCES


10. Biswas BN, Rudra A, Bose BK et al. (2002): Intrathecal fentanyl with hyperbaric bupivacaine improves analgesia during caesarean delivery and in


