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Comparison of Premixed Versus Sequential Administration of Fentanyl as an Adjuvant to Intrathecal Hyperbaric Bupivacaine in Infra-Umbilical Surgeries: A Randomized Controlled Study

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Abstract

Opioids and local anaesthetics administered together intra-thecally have potent synergistic analgesia. *Aims and Objectives:* To compare the efficacy of premixed versus sequential administration of fentanyl as an adjuvant to intrathecal hyperbaric bupivacaine following spinal anaesthesia in infra-umbilical surgeries. *Methodology*: This study was carried out in a tertiary care center where 140 orthopaedic, urology and general surgery patients scheduled for elective infra umbilical surgery under spinal anaesthesia were enrolled. All the patients were randomly divided into two groups with 70 patients in each group. Patients in group A received intrathecal hyperbaric bupivacaine 12.5 mg premixed with fentanyl 25 mcg. The drugs were mixed together in a single syringe just before intrathecal injection. Those in group B received fentanyl 25mcg followed by sequential administration of hyperbaric bupivacaine 12.5mg in a separate syringe intrathecally. The vitals were monitored and recorded, progression of spinal block was assessed and all data collected were analysed using appropriate statistical methods. *Results*: More patients in group A achieved a higher level of intrathecal block than in group B. However, time to regress L1 spinal level was significantly less in group B compared with group A (p-value 0.001). Also, patients in group B achieved maximum sensory level earlier than group A. Time to regression of motor block to Modified Bromage I was also significantly more in group B than in group A. Haemodynamically, there was no significant difference in the baseline heart rate and blood pressure between both the groups. After spinal anesthesia, heart rate and blood pressure (both systolic and diastolic) decreased in both groups minimally without statistical significance. Postoperatively, in both the groups very few patients required rescue analgesics. The incidence of adverse effects was comparable in both the groups without statistical significance. *Conclusions*: Fentanyl given sequentially in a separate syringe as adjuvant to intrathecal hyperbaric bupivacaine can result in faster onset of both sensory and motor block and prolongs the duration of spinal anaesthesia. Also, it minimises clinically significant side effects and reduces the postoperative analgesic requirements.

Keywords: Opioids; Intrathecal; Spinal Blockade.

Introduction

Spinal anaesthesia is the most common procedure of choice for infra umbilical surgeries - the reasons being simpler technique, higher patient acceptance and early recovery. Duration of spinal anaesthesia mainly depends on the local anaesthetic agent used and is an important limiting factor of this technique. Bupivacaine is an amide local anesthetic, which is used commonly and that has a prolonged duration of action and lower incidence of transient radicular symptoms [2], but when high doses of intrathecal bupivacaine is used, it may lead to myocardial depression, dysrhythmias, and heart block [3].

Thus, to enhance the duration of action, to provide stable hemodynamics and at the same time to minimize the adverse effects of local anaesthetics, various adjuvants are used [4].There are various factors that havebeen shown to influence the

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intrathecal spread of local anaesthetic like temperature and pH of the drug, baricity, height of the patient and patient position after the injection [1].

Opioids and local anaesthetics administered together intrathecally have found to produce a potent synergistic analgesia.By improving the quality of intraoperative analgesia we can provide postoperative pain relief for longer duration without complications. Intrathecal opioids like fentanyl, enhance analgesia even from sub therapeutic doses of local anaesthetics and make it possible to achieve successful spinal anaesthesia which otherwise will have inadequate effect.

The clinical efficacy of fentanyl has been well documented to relieve the visceral pain. Intrathecal opioids also do not cause any further depression of efferent sympathetic activity either alone or in combination with the bupivacaine. Intrathecal opioids enhances the sensory blockade without altering the degree of sympathetic blockade which inturn results in less adverse hemodynamic effects [5,6].

However, the anaesthetic effect of premixing fentanyl with bupivacaine and using the two drugs sequentially has not been evaluated in a detailed manner so far. The studies are lacking to elucidate the anaesthetic effect and adverse effects of using the mixed drugs and sequential use of the drugs. Hence, this study was undertaken in order to find out if the effect of these two drugs could vary by altering their mode of administration.

Materials and Methods

This study was conducted in a tertiary care centre, where 140 orthopaedic, urology and general surgery patients scheduled for elective infra umbilical surgeries under spinal anaesthesia were enrolled. All the patients were ASA class1 and 2, aged between 18 and 65 yearswith no significant comorbidities. Patients with ASA grade higher than 2, age less than 18 years or more than 65 years, and history of allergy to fentanyl or bupivacaine were excluded from this study.

All patients had undergone pre-anaesthetic check-up before surgery. Patients were kept nil per orally for six hours before surgery. Patients were taken into the preoperative room and vitals were recorded including heart rate, ECG, oxygen saturation and non-invasive blood pressure. Patients were then taken into the operating theatre.

In the operating room, intravenous access was secured with 18G intravenous cannula and the standard monitors were attached. All the patients were randomly divided into two groups using computer generated random numbers, with 70 patients in each group. Patients in group A received intrathecal hyperbaric bupivacaine 12.5 mg premixed with fentanyl 25 mcg. The drugs were mixed together in a single syringe just before intrathecal injection.

Those in group B received fentanyl 25mcg followed by sequential administration of hyperbaric bupivacaine 12.5mg in a separate syringe intrathecally. Spinal anaesthesia was administered using a 25G Quincke needle with patients in sitting position. After spinal anaesthesia all patients were made to lie supine to achieve the desired sensory level. No manoeuvres like tilting of table, asking the patient to cough etc., were done to adjust the spinal level. All patients were co loaded with 10 ml / kg of intravenous Ringer's lactate solution during the intraoperative period followed by 2 ml / kg /hr infusion of Ringer's lactate solution.

Haemodynamic parameters, i.e. heart rate, blood pressure, respiratory rate and oxygen saturation, were recorded every 2 minutes for the first 10 minutes and every 5 minutes subsequently till completion of surgery. An episode of hypotension was defined as a fall in blood pressure by more than 20% of baseline values and bradycardia as heart rate < 50 beats/min or if there was less than 20% of fall from baseline heart rate and if there were associated clinical signs and symptoms. For hypotension, the patient received a rapid infusion of crystalloids (200 ml of normal saline or ringer lactate) and intravenous injection of ephedrine 6 mg intravenously if hypotension persisted. For bradycardia, the patient received injection of atropine 0.6 mg intravenously.

The progression of spinal block was assessed using ice cube every 2 minutes until the maximum level was reached. Surgery was started only after sensory level up to T10 or higher was achieved. Time to achieve T6 level as well as sensory level at 30mins and maximum height of block was noted and compared. At the same time a modified Bromage scale was used to assess the motor block as: I— no block with full flexion possible at knees and feet; II— partial block, with patient just able to flex knees with full flexion possible at feet; III— almost complete, with patient unable to flex knees but flexion of feet possible; and IV— complete block, i.e. inability to move legs and feet. Time to achieve Bromage IV was recorded.

Postoperatively patients were observed for a period of six hours following intrathecal injection either in PACU or in the ward. Time of regression of sensory block four dermatomes below the maximum block height and time to regress to L1 Level were assessed. Also time of demand of first rescue analgesic was also noted. All patients received injection of fentanyl 1mcg/kg on demand if they complained of pain. Any side effects such as itching, shivering, nausea, vomiting, excessive sedation or respiratory depression and if any changes in ECG during the intraoperative period were noted.

The primary outcome was to study the effect of sequential administration of intrathecal fentanyl on characteristics of spinal block (onset, maximum height of block and duration) as compared with when administered premixed in the same syringe. A secondary outcome was to compare clinically significant side effects noticed among patients in both groups as well as postoperative analgesic requirement.

Statistical Analysis

Based on similar studies in the past, sample size estimation was done based on onset of sensory and motor block and time for four segment regression and time to regress L1 level. To achieve a level of significance of 0.05 and a power of 80% a sample size of 70 patients was required per group. So, 140 patients in total were considered for this study. Data were entered into a Microsoft excel spreadsheet and analysed using statistical package for social sciences version 11.5. Qualitative data were expressed as ratio and proportion and analysed using a chi-square test, while quantitative data were analysed with an unpaired t-test. A p-value <0.05 was considered statistically significant.

Results

Seventy patients were studied in each group. Patients in both groups were comparable in terms of age, gender, height, weight and ASA physical status. All patients underwent infra umbilical surgeries under spinal anaesthesia and duration of surgery was comparable. There was no incidence of failed spinal block in any patient.

Both the group A and group B were similar with respect to age of the patients. Mean age in group A was 42.79 years with SD of 12.9. In group B mean age was 40.3 years with SD of 11.93. p-value of 0.23 and was statistically insignificant. The mean height and standard deviation were 164.09cm and 7.18 in group A and 162.09cm and 6.55 in Group B respectively. The p value of 0.08 was statistically not significant. In group A the mean weight was 66.84 kg and SD 11. In group B mean weight was 65.85 kg and SD 8.22, p-value of 0.54 was not significant. The heart rate, systolic blood pressure, diastolic blood pressure, SpO_2, respiratory rate were observed every 2 minutes for the first 10 minutes and every 5 minutes subsequently till completion of surgery there was no statistical significance was observed among the two groups.

The mean time to achieve sensory level T6 after SA in Group A is 8.93±7.264 minutes whereas in Group B is 5.64±2.14 minutes and is statistically significant (Table 1).

The mean time of onset of motor blockade after SA in Group A is 2.63±0.82 minutes whereas in Group B is 2.29±0.54 minutes and is statistically significant (Table 2).

The mean time to 4 segment regression time after SA in Group A is 145.94±27.33 minutes whereas in Group B is 140±19.07 minutes and is statistically not significant (Table 3).

Table 1: Time to achieve sensory level T6

Parameter	Mean ± SD		Mean difference	P*value
	Group A	Group B		
Sensory level T6 (mins)	8.93±7.264	5.64±2.144	3.284	0.001

Table 2: Time of onset of motor blockade

Parameter	Mean ± SD		Mean difference	P*value
	Group A	Group B		
Motor blockade (mins)	2.63±0.82	2.29±0.542	0.343	0.004

Table 3: 4 Segment regression time

Parameter	Mean ± SD		Mean difference	P*value
	Group A	Group B		
4 segment regression time(mins)	145.94±27.33	140±19.07	5.84	.145

Table 4: Time to regress L1 level

Parameter	Mean ± SD		Mean difference	P*value
	Group A	Group B		
Time to regress L1 level (mins)	215.89±30	200±23.28	15.88	0.001

More patients in group A achieved a higher level of intrathecal block than in group B. However, time to regress L1 spinal level was significantly less in group B compared with group A (p-value 0.001). (Table 4). Also, patients in group B achieved maximum sensory earlier than group A. Time to regression of motor block to Modified Bromag I was also significantly more in group B than in group A.

Haemodynamically, there was no significant difference in the baseline heart rate and blood pressure between two groups. After spinal injection, though heart rate and blood pressure (both systolic and diastolic) decreased in both groups minimally.

Postoperatively, in both group very few patients required rescue analgesic. The incidence of adverse effects like nausea, vomiting and shivering were comparable in both the groups.

Discussion

The current study aims to compare the effect of premixed versus sequential administration of fentanyl as an adjuvant to intrathecal hyperbaric bupivacaine in infra-umbilical surgeries.

In our study, We found that separate intrathecal injection of fentanyl and hyperbaric bupivacaine provided significant improvement in the quality of sensory and motor block and duration of analgesia compared to injection of mixed medications.

Understanding the mechanisms of intrathecal drug spread can explain our results. When the patients are turned supine immediately after injection in the lumbar region, a hyperbaric solution will spread under the influence of gravity down the slope created by lumbar spinal curvature. However, plain solution being less viscous, mixes rather freely with CSF, and thus moves easily through compressed subarachnoid space and will not have gravity dependent spread. Similar observation were made by upadya et al. [7].

In our study, The onset time of sensory and motor block was significantly more ($p<0.04$) in sequential (Group B) than premixed group (A) but the time taken for highest level of sensory and motor block achieved was significantly less ($p<0.05$) in sequential (Group B) than other group (A). The time to reach maximum sensory block height and maximum motor block was significantly less in Group B (sequential drugs) than in Group A (mixed drugs) in this study. This difference might have existed because of the preferential cephalad spread of fentanyl by administering it through a separate syringe. Also the hyperbaric nature of bupivacaine is lost when the drugs are premixed leading to more cephalad spread limiting the gravitational spread. Desai et al. [8] also observed that the time to reach highest level of block was less when morphine and Fentanyl were administered sequentially with spinal anaesthesia than when given as a mixture.

Sensory regression was high in Group B than Group A. Complete motor blockade was achieved earlier in Group B than in Group A and the resolution time of motor block was significantly prolonged in Group B than in Group A. Our study also revealed that total duration of analgesia lasted significantly slightly longer in Group B as compared to Group A. It depicted significant prolongation of analgesic effect in the group receiving drugs in a sequential fashion. Analgesic requirement was almost same whether fentanyl is given in sequential or in mixture with hyperbaric bupivacaine. This difference might be due to the fact that injecting fentanyl and Bupivacaine as a mixture dilutes fentanyl and receptor occupancy might decrease leading to less pronounced effect. And if fentanyl is administered separately, a greater spread and therefore formation of stronger bonds with the receptor leading to a denser and prolonged block may occurred which was supported by observations of Desai et al. [1]. Gray et al. [9], also found that duration of analgesia is increased when IT morphine is administered with normal saline (hypobaric) than with dextrose saline (hyperbaric). Similar to present study, observations were made by Jyoti P et al. [10] and Thakur A et al. [11] also who reported that sequential Clonidine significantly increase the duration of analgesia than when it is given in mixture with hyperbaric Bupivacaine in other surgery like lower limb surgery (Jyoti P et al. [10]) and inguinal herniorrhaphy (Thakur A et al. [11]).

There are various similar studies with the above findings. Amr Aly Ismail Keera and Ali Mohamed [12] in their study on124 parturient scheduled for elective caesarean section, who were randomly allocated into two groups, one group received 10mg

bupivacaine 0.5% premixed with 25mcg fentanyl in the same syringe and other group received in two separate syringe. Patients with intraoperative pain that was controllable without the need for a shift to general anaesthesia was significantly lower in sequential than in premixed group. Separate intrathecal injection of fentanyl and hyperbaric bupivacaine provided a significant improvement in the quality of sensory block and significant reduction of the frequency of hypotension compared to injection of mixed medications.

Gunjan Chaudhry et al. [13] in their study on 60 orthopaedic patients scheduled for elective lower limb surgery who were divided into two groups to receive either intrathecal hyperbaric bupivacaine 12.5mg premixed (group P) with dexmeditomidine 10mcg (diluted to 0.5ml with normal saline) or by sequential administration in separate syringes (group S). Dexmeditomidine given sequentially as adjuvant can result in faster onset of both sensory and motor block and prolongs the duration of spinal anaesthesia, minimises clinically significant side effects and reduces the postoperative analgesic requirement.

Dr.S.K. Sharma et al. [14] in their study where 60 patients undergoing elective caesarean sections were divided into two groups. Group A is given mixture of clonidine (75mcg) and hyperbaric bupivacaine 0.5% (10mg) intrathecally, whereas other Group B received sequentially in two separate syringes. It was found that duration of analgesia was significantly longer in group B than in group A. Time to achieve highest sensory and complete motor block was significantly less in group B than group A. So it can be depicted that administering clonidine and hyperbaric bupivacaine in a sequential manner is better than mixing of the two drugs.

Dr. Sachan P et al [15] in their study, 60 full-term parturients scheduled for elective Caesarean Sections were divided into two groups. Group M received mixture of clonidine (75mcg) and hyperbaric bupivacaine 0.5% (10mg) intrathecally, whereas group B received sequentially in separate syringes. Duration of analgesia was significantly longer in group B than in group M. Time to achieve highest sensory block and complete motor block was significantly less in group B without any major hemodynamic instability and neonatal outcome.

It was also observed in our study that adverse side effects like Hypotension, Bradycardia, nausea and vomiting, shivering were also not found with significant variation (P>0.05) in both the groups.

So it can be depicted that sequential administration of fentanyl reduces the time to achieve complete sensory and motor block and significantly prolongs the total duration of analgesia without any significant side effects.

Conclusion

In conclusion, fentanyl given sequentially in a separate syringe as adjuvant to intrathecal hyperbaric bupivacaine results in faster onset of both sensory and motor block and prolongs the duration of spinal anaesthesia. Also, it minimises clinically significant side effects and reduces the postoperative analgesic requirements. Hence it is advisable to use sequential administration of fentanyl with bupivacaine than premixed administration of fentanyl with bupivacaine.

Recommendations

1. Intrathecal administration of Bupivacaine after fentanyl sequentially is advisable as it has better hemodynamic and analgesic profile than pre mixed intrathecal administration.

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