Original Research Article

Comparison of efficacy of fentanyl and tramadol as adjuvants to intrathecal hyperbaric bupivacaine 0.5% in elective caesarean section - A prospective randomised double blinded study

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Abstract

Background: Spinal anaesthesia is the technique of choice for elective caesarean section all over the world. It offers excellent operating conditions like dense analgesia and adequate muscle relaxation. However it suffers from certain inherent disadvantages like fixed duration of anaesthesia and haemodynamic instability. **Aim:** To compare the efficacy of intrathecal fentanyl and intrathecal tramadol as adjuvants to hyperbaric bupivacaine 0.5% in elective caesarean section patients in terms of duration of analgesia and intra-operative hemodynamic stability **Materials And Methods**: A single centered randomized, double – blinded study conducted between May 2017 to October 2018 in 60 patients undergoing elective caesarean section with 30 patients in each group. Group I received 0.5% hyperbaric bupivacaine 9 mg (1.8ml) + 0.2 ml i.e. 10 micrograms of fentanyl intrathecally (2ml). Group II received 0.5% hyperbaric bupivacaine 9 mg (1.8 ml) + 10 mg (0.2 ml) of tramadol intrathecally (2ml). **Results:** Duration of analgesia in Fentanyl was 9.47 ± 2.08 hours compared to 6.40 ± 1.25 hours in Tramadol group. Differences between groups are statistically significant with a P value of 0.03. The onset of sensory block in Fentanyl group is 1.37 ± 0.49 minutes compared to 2 ± 0.69 minutes in Tramadol group and the difference is statistically significant with a P – value of 0.001. The onset of motor block in Fentanyl is 1.73 ± 0.45 minutes compared to 2.3 ± 0.65 minutes in Tramadol group and difference is statistically significant with a P – value of 0.001. The time for maximum sensory level in Fentanyl group is 3.7 ± 0.65 minutes compared to 4.3 ± 0.70 minutes in Tramadol group and the difference is statistically significant with a P - value of 0.001. **Conclusion:** Both the groups were effective in providing adequate surgical anaesthesia and hemodynamic stability, but fentanyl is the better alternative to tramadol as an adjuvant to spinal bupivacaine in elective caesarean section.

Key Word: Fentanyl, Tramadol, Spinal anaesthesia, Caesarean section, Analgesia, Muscle relaxation

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INTRODUCTION

Subarachnoid block is the preferred technique for caesarean section. It is easy to perform, rapid onset of action, involves lesser drug doses, produces minimal neonatal depression and gives lesser incidence of chemical pneumonitis.[1] However, it also has disadvantages which include producing only a fixed duration of anaesthesia, causing intra-operative hypotension and difficulty in controlling the height of block.[2] Hyperbaric bupivacaine is the most common drug used in spinal anaesthesia for caesarean section. Bupivacaine belongs to amide group of

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local anaesthetics with high potency, slow onset (5-8 minutes) and long duration of action. For caesarean section intrathecal dose of hyperbaric bupivacaine is 12 to 15 mg.[3] Addition of opioids to local anaesthetics is routinely done in central neuraxial blockade as it provides better intra-operative and early postoperative analgesia.[4] Spinal anaesthesia is often used for both emergency and elective caesarean section. The advantages of spinal anaesthesia are its rapidity in onset, safety and reliability. Caesarean delivery requires traction of peritoneum and handling of intraperitoneal organs, resulting in intraoperative visceral pain. With higher doses of hyperbaric bupivacaine, incidence of intraoperative visceral pain associated with organ manipulation is reduced.[5,6] Although intrathecal bupivacaine alone offers good sensory blockade, a substantial number of patients experience haemodynamic instability, pain and discomfort and may require analgesic supplementation in early postoperative period.[7] To overcome these drawbacks, opioids are administered intrathecally along with bupivacaine. Numerous benefits like stable hemodynamics, denser analgesia, lesser pulmonary complications, earlier ambulation of patients and prompt return of bowel function and reduced stress response. Mixing other drugs with local anaesthetics might help decrease the dosage of local anaesthetics, attenuate adverse effects and increase the duration of anaesthesia.[8] Fentanyl, a lipophilic opioid, has rapid onset of action following intrathecal injection. It is less likely to migrate to the fourth ventricle when administered intrathecally in concentrations significant enough to cause delayed respiratory depression.[9] The addition of fentanyl 10 micrograms to hyperbaric bupivacaine 10.5-12.5 mg enhances the intraoperative and early postoperative quality of subarachnoid block.[10] Intrathecal opioids are prone to cause side effects such as pruritus, nausea, vomiting, respiratory depression. Tramadol is a synthetic analgesic drug which acts centrally having 2 distinct, synergistic mechanisms of action, one being a weak opioid agonist and another as a monoamine neurotransmitter reuptake inhibitor. The racemic mixture of tramadol has 2 enantiomers which compliment each other and enhance the efficacy of analgesia and improve its tolerability profile. Unlike centrally acting opioids, tramadol has a much lesser depressing effect on respiration because it has 6000 fold less affinity for μ receptors compared to morphine. Tramadol can provide effective postoperative pain relief, with almost no risk of respiratory depression when given via central neuraxial route. But, pruritus, nausea, vomiting, urinary retention, activation of herpes labialis and risk of unpredictable respiratory depression compel clinicians to administer lesser dose of tramadol that can be used intrathecally to provide effective and prolonged analgesia without these complications. It also inhibits serotonin and norepinephrine reuptake in the spinal cord providing prolonged post-operative analgesia and does not cause neural toxicity.[11] any studies have been done on the efficacy of either fentanyl with bupivacaine or tramadol with bupivacaine. Very few studies are available on tramadol as the sole adjuvant to bupivacaine. Only few studies are available in the literature, which had tested the same combination of drugs as our study, out of which one study was done in pregnant patients and remaining in non-pregnant patients. Hence the present study.

MATERIALS AND METHODS

This prospective, randomised, double blinded study was done over a period of 18 months. All the patients who underwent elective lower segment caesarean section under subarachnoid block between the age of 18-35yrs, body mass index between 18.5 to 24.9 Kg/m2 and belonging to ASA (American society of Anesthesiologists) Physical status II in Shri Sathya Sai Medical College and Research Institute, Ammapettai were included in the study. Patients who refused spinal anaesthesia, those who belonged to ASA class III and above, allergic to local anaesthetics and adjuvants, infection at needle site, any contraindications to subarachnoid block like bleeding tendencies, gross spinal deformities were excluded from the study. After obtaining institutional ethics committee approval and written informed consent in patient's own language, 60 patients were randomly allocated into two groups (n=30 each) by computer generated list of random numbers and were given adjuvants to 1.8ml of 0.5% hyperbaric Bupivacaine according to the groups: Group I - Fentanyl 0.2ml (10mcg), Group II- Tramadol 0.2ml (10mg). The patients as well as the anaesthetist involved in the assessment of the block were blinded to the drug used for spinal anaesthesia. Separate independent investigator prepared the syringes with drugs and handed them over to the performing anaesthetist. Both drugs were taken in identical 5ml syringes. Patients, anaesthesiologists involved in intra-operative and postoperative care of the patient and investigator collecting the data were unaware of the group allocation. Pre anaesthetic checkup was done for all the patients. Patients were kept nil per oral 8 hours before surgery and given tablet Ranitidine 150mg and tablet Metoclopramide 10mg night before surgery as well as the morning of surgery at 7 AM with small sip of water. Patients were shifted to Operation Theatre (OT). Prior to shifting the patient, the operation theatre underwent routine inspection which included checking of Boyle's machine for any leaks, availability of emergency drugs, all necessary equipment for difficult airway and working standard monitors. Any deficiencies from standard requirements were rectified before shifting patient to the theatre. Standard monitors like pulse oximeter,

electrocardiography and non invasive blood pressure were connected. An IV access was established with 18 gauge intravenous cannula. Patients were preloaded with 15ml/kg of lactated ringer's solution. Patients were positioned in left lateral position. Under strict aseptic precautions, L3-L4 intervertebral space was identified. Skin was infiltrated with 2ml of 2% Lidocaine. 25G Quincke's needle was inserted into the intervertebral space till subarachnoid space was reached which was confirmed by free flow of CSF on removing stylet. The labeled syringe which contained the corresponding drug as per which study group the patient belonged to was attached to the needle, aspirated for CSF and then entire volume of drug was injected. Time of injection of local anaesthetic solution was considered as 0 minutes. Patient was put in supine position and sensory level was checked by pin prick method. Level was checked every 2 minutes in first 20 minutes. Two consecutively same readings of 2 minute intervals were taken as maximum sensory level. Degree of motor blockade was assessed using Bromage scale (0 - able to lift legs, 1 - able to flex knees but not hips, 2 - unable to flex knees but can move ankle, 3 - no movement in legs). It was checked every 2 minutes till grade 3 is reached. Intraoperative parameters such as heart rate, blood pressure, and SpO2 were monitored every 5 minutes for 20 minutes, then every 10 minutes till the end of surgery. Duration of surgery and duration for rescue analgesia (Injection Diclofenac 75mg Intramuscularly on demand when patient complains of pain) was also monitored. Total analgesics required over 24 hours was also noted. Patients were monitored postoperatively for complications like nausea (treated with injection metoclopramide 10mg intravenously), pruritis (treated with injection chlorpheniramine 20mg intravenously), shivering, respiratory depression, hypotension (MAP fall > 20% treated with injection Ephedrine), bradycardia (heart rate < 50 beats/min, treated with Injection Atropine 0.6mg intravenously). Primary outcome of the study was duration of analgesia. Secondary outcomes were onset of sensory and motor block, intra-operative hemodynamic stability.

Sample size calculation: Sample size calculation was done based on previous study with difference of 66 minutes and SD of 61 minutes - 25 patients / each group were taken with 90% of power and 5% significance. So 30 patients were included in each group to avoid possible dropouts.

Statistical methods: Data was analyzed using statistical package for social sciences (SPSS) VERSION 23, Microsoft USA, Armonk, NY: IBM Corporation and its licensors 2015. Continuous variables were expressed in standard deviation and mean. Data was analyzed by independent T-test, Mann Whitney U test or chi square tests whichever is applicable. Demographic parameters were assessed with analysis of variance between the groups and are expressed as Mean and standard deviation (SD). P value < 0.05 was taken as statistically significant.

OBSERVATIONS AND RESULTS

All the 60 patients randomized were analysed for the study and there were no dropouts. The demographic profile were comparable in both the groups in terms of age, height and weight (Table 1). Duration of analgesia in Fentanyl is 9.47 ± 2.08 hours compared to 6.40 ± 2.25 hours in Tramadol group. Difference between groups are statistically significant with a P value of 0.001(Table 2). The onset of sensory blockade in Fentanyl group is 1.37 ± 0.49 minutes compared to 2 ± 0.69 minutes in Tramadol group and the difference is statistically significant with a P – value of 0.001. The onset of motor blockade in Fentanyl group is 1.73 ± 0.45 minutes compared to 2.3 ± 0.65 minutes in Tramadol group and the difference is statistically significant with a P – value of 0.001(Table 3). The time for maximum sensory level in Fentanyl group is 3.7 ± 0.65 minutes compared to 4.3 ± 0.70 minutes in Tramadol group and the difference is statistically significant with a P – value of 0.001. The time for bromage 3 in Fentanyl group is 3.13 ± 0.51 minutes compared to 3.33 ± 0.61 minutes in Tramadol group but the difference is not statistically significant (Table4). The mean and standard deviation of the pulse rate of the fentanyl and tramadol group at various time intervals during the intra operative period was analysed. The statistically significant difference was assessed by using independent 't' test. P-value <0.05 was considered significant. P value for pulse rate at various intervals were insignificant(Table 5). The mean and standard deviation of the mean arterial pressure of the fentanyl and tramadol group at various time intervals during the intra operative period was analysed. The mean arterial pressure in Fentanyl group is 80.06 ± 8.22 mm Hg compared to 69.83 ± 10.76 mm Hg in Tramadol group at 50 minutes and the difference is statistically significant with p value of 0.007(Table 6).

Table 1: Distribution of height, weight and BMI in study population

	GROUP	N	MEAN	STD. DEVIATION	p VALUE BY 't' TEST
Height	Fentanyl	30	158.50	4.19	0.480
	Tramadol	30	157.70	4.51	
Weight	Fentanyl	30	59.43	4.56	0.187
	Tramadol	30	57.97	3.92	
BMI	Fentanyl	30	23.61	0.99	0.246
	Tramadol	30	23.29	1.10	

Table 2: Distribution of time for analgesia duration in the subjects of the study population

	GROUP	N	MEAN	STD. DEVIATION	P VALUE BY 'T' TEST
Analgesia Duration	Fentanyl	30	9.47	7.08	0.001*
	Tramadol	30	6.40	2.25	

Table 3: Distribution of time for onset of sensory and motor blockade in the subjects of the study population study population

	GROUP	N	MEAN	STD. DEVIATION	P VALUE BY 'T' TEST
Onset of Sensory	Fentanyl	30	1.37	0.49	< 0.001*
	Tramadol	30	2.00	0.69	
Onset of Motor	Fentanyl	30	1.73	0.45	< 0.001*
	Tramadol	30	2.30	0.65	

Table 4: Distribution of Time for maximum sensory level and time for bromage 3 of the subjects in the study population

	GROUP	N	MEAN	STD. DEVIATION	p VALUE BY 't' TEST
Time for maximum sensory level	Fentanyl	30	3.70	0.65	0.001*
	Tramadol	30	4.30	0.70	
Time for Bromage 3	Fentanyl	30	3.13	0.51	0.171
	Tramadol	30	3.33	0.61	

Table 5: Pulse rate of the fentanyl and tramadol group at various time intervals during the intra operative period.

PULSE RATE	GROUP	N	MEAN	STD. DEVIATION	p VALUE BY 't' TEST
0 min	Fentanyl	30	93.47	17.51	0.549
	Tramadol	30	90.87	15.85	
5 min	Fentanyl	30	89.37	17.36	0.897
	Tramadol	30	89.93	16.31	
10 min	Fentanyl	30	89.80	15.18	0.885
	Tramadol	30	90.37	14.95	
15 min	Fentanyl	30	88.67	13.62	0.623

20 min	Tramadol	30	90.33	12.48	0.670
	Fentanyl	30	90.07	14.66	
30 min	Tramadol	30	91.53	11.73	0.390
	Fentanyl	30	85.63	13.13	
40 min	Tramadol	30	88.47	12.19	0.364
	Fentanyl	24	80.96	12.86	
50 min	Tramadol	27	84.48	14.40	0.148
	Fentanyl	17	80.94	14.79	
60 min	Tramadol	12	88.67	12.14	0.520
	Fentanyl	7	75.86	16.49	
	Tramadol	9	81.11	15.26	

Table 6: Mean arterial pressure of the fentanyl and tramadol group at various time intervals during the intra-operative period.

MAP	GROUP	N	MEAN	STD. DEVIATION	p VALUE BY 't' TEST
0 min	Fentanyl	30	85.57	11.86	0.480
	Tramadol	30	83.07	15.19	
5 min	Fentanyl	30	76.93	9.70	0.472
	Tramadol	30	79.07	12.89	
10 min	Fentanyl	30	72.43	11.02	0.095
	Tramadol	30	78.80	17.25	
15 min	Fentanyl	30	71.03	10.67	0.085
	Tramadol	30	77.70	17.78	
20 min	Fentanyl	30	72.23	10.82	0.734
	Tramadol	30	71.37	8.74	
30 min	Fentanyl	30	76.63	15.84	0.985
	Tramadol	30	76.57	11.50	
40 min	Fentanyl	23	77.13	12.14	0.987
	Tramadol	27	77.19	11.01	
50 min	Fentanyl	17	80.06	8.22	0.007*
	Tramadol	12	69.83	10.76	
60 min	Fentanyl	6	81.33	12.42	0.131
	Tramadol	9	72.44	9.02	

Adverse effects of opioids like nausea, vomiting, pruritus and shivering were monitored intraoperatively and postoperatively in Fentanyl and Tramadol group. There is no incidence of adverse effects.

DISCUSSION

In this study we have evaluated the efficacy of intrathecal Fentanyl and intrathecal Tramadol as adjuvants to hyperbaric Bupivacaine 0.5% in elective caesarean section patients. We studied the onset of sensory and motor blockade and duration of sensory and motor blockade. We studied the quality of analgesia in terms of pain score and total analgesic requirement, sensory characteristics, motor characteristics in patients receiving Bupivacaine with Tramadol and Bupivacaine with Fentanyl. We also studied the haemodynamic changes, incidence of nausea, vomiting and pruritus in the two groups. The study population had a wide range of age distribution from minimum of 21 years to maximum of 34 years. The mean age of the study population was 26.38 ± 3.54 years with a mode of 24 years. The duration of analgesia for Fentanyl group was 9.47 ± 2.08 hours, compared to 6.40 ± 1.25 hours in Tramadol group which was statistically significant ($P < 0.001$). The onset of sensory blockade in Fentanyl group was 1.73 ± 0.49 min compared to 2 ± 0.69 min in Tramadol group and the difference was statistically significant ($p < 0.001$). The onset of motor blockade in Fentanyl group was 1.73 ± 0.45 min compared to 2.3 ± 0.65 min in Tramadol group and the difference was statistically significant ($p < 0.001$). In this study we compared two easily available agents with good safety profile. There is good analgesia during the most painful duration of post-operative period, but it does not last long enough to avoid the use of rescue analgesics. The limitations of our study included not having a control group which would have provided a better idea of the augmentation of analgesia and motor blockade provided by these adjuvants when compared to bupivacaine alone. Also, we did not include patients that came under ASA physical status higher than 2, which prevents us from learning what sort of outcomes these adjuvants would cause in such patients who have significant systemic illnesses. Alfolayan *et al* studied the same two drugs as adjuvants to bupivacaine in appendicectomies by assessing intra-operative pain and discomfort along with postoperative analgesia and concluded that both provided better analgesia than bupivacaine alone but were equipotent with each other. This may be due to the fact that they used a higher dose of 25mcg Fentanyl and 25mg Tramadol with 3ml of 0.5% Bupivacaine compared to our lower dose of 10mcg, 10mg and 1.8ml respectively.[12] Subedi *et al* performed a similar study with 10mg Tramadol and 10mcg Fentanyl but ended up using 2ml of 0.5% Bupivacaine for the subarachnoid block whereas we only used 1.8ml. Perhaps this difference in volume and dose of local anaesthetic intrathecally might have led to their opposing conclusion of Tramadol providing better postoperative analgesia than Fentanyl as an adjuvant.[13] Chakraborty *et al* studied the effect of adding 20mg of Tramadol intrathecally with 3ml 0.5% Bupivacaine for major gynaecological surgeries in relation to postoperative analgesia and came to the conclusion that it significantly prolonged the postoperative duration of analgesia. This would seem to support our findings of Tramadol providing a good postoperative analgesia duration. However it would be difficult to say for sure since we did not have a control group like they did of Bupivacaine alone to compare with.[14] Sanjul Dandona *et al*, conducted a study consisting of 50 patients belonging to ASA 1 and 2 posted for lower abdominal and lower limb surgeries under subarachnoid block. They compared efficacy of tramadol and fentanyl as adjuvant to local anaesthetics in these patients and concluded that duration of sensory and motor block and duration of postoperative analgesia was significantly prolonged in fentanyl group compared to tramadol group which would concur with the findings of our study.[15] Dalvi *et al* also compared 25mcg Fentanyl and 25mg Tramadol just like Alfolayan *et al*, but concluded favouring our results by proving that intrathecal Fentanyl provided longer duration of sensory and motor blockade than Tramadol.[16] In a study by Manisha Pradhan *et al*, they compared the effect of intrathecal fentanyl with hyperbaric Bupivacaine 0.5% heavy on the quality of subarachnoid block in patients posted for lower segment caesarean section. They found that addition of fentanyl markedly improves the density of intraoperative analgesia with minimal opioid related side effects.[17] Gopichand *et al*, in their study compared the effects of adding fentanyl to intrathecal bupivacaine on the onset and duration of subarachnoid block in 60 parturient patients posted for elective LSCS. The study showed that addition of fentanyl intrathecally prolongs the duration of analgesia, reduces the intra-operative need of analgesic supplement, provides better surgical analgesia, delays time of postoperative rescue analgesia with minimal side effects.[18] Both the previous mentioned studies concluded in favour of Fentanyl like our study. The former based it on intraoperative analgesia whereas the latter would also stress upon postoperative analgesia duration. Choi DH *et al* compared the efficacy of different doses of 0.5% heavy bupivacaine with different dose combination of 0.5% bupivacaine plus fentanyl in patients posted for caesarean section. They concluded that high dose of local anaesthetics are required to produce surgical anaesthesia compared to local anaesthesia with fentanyl group. They inferred that adding opioid to local anaesthetics reduces the dose local anaesthetic agent by increasing the block density.[19] Combination of adjuvants with local anaesthetics allows for a reduction in doses of both classes of drugs, thus lessening the likelihood of side effects attributable to each.[20] Future scope of this study would be to overcome all the limitations that we had encountered while we

performed ours, such as not being able to compare different doses of adjuvants, small sample size and performing the block only in lateral position. So if the same study could be done in a larger sample size, using different doses of both drugs and performed in both sitting and lateral position, we would have a better idea of the various other factors affecting the outcome of our primary and secondary objectives.

CONCLUSION

Both the groups were effective in providing adequate surgical anaesthesia and hemodynamic stability, but fentanyl seems to be a better alternative to tramadol as an adjuvant to spinal bupivacaine in elective caesarean surgeries

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REFERENCES

1. Gauchan S, Thapa C, Prasai A, Pyakurel K, Joshi I, Tulachan J. Effects of intrathecal fentanyl as an adjunct to hyperbaric bupivacaine in spinal anesthesia for elective caesarean section. Nepal Med Coll J. 2014 Sep;16(1):5-8.
2. Caplan RA, Ward RJ, Posner K, Cheney FW. Unexpected cardiac arrest during spinal anesthesia: a closed claims analysis of predisposing factors. Anesthesiology. 1988 Jan;68(1):5-11
3. Srivastava U, Kumar A, Gandhi NK, Saxena S, Dutta D, Chandra P, Singh S. Hyperbaric or plain bupivacaine combined with fentanyl for spinal anaesthesia during caesarean delivery. Indian J Anaesth. 2004 Jan 1;48(1):44-6.
4. Bogra J, Arora N, Srivastava P. Synergistic effect of intrathecal fentanyl and bupivacaine in spinal anesthesia for cesarean section. BMC anesthesiology. 2005 Dec;5(1):5.
5. Pedersen H, Santos AC, Steinberg ES, Schapiro HM, Harmon TW, Finster M. Incidence of visceral pain during cesarean section: the effect of varying doses of spinal bupivacaine. Anesthesia and analgesia. 1989 Jul;69(1):46-9.
6. De Simone CA, Leighton BL, Norris MC. Spinal anesthesia for cesarean delivery: a comparison of two doses of hyperbaric bupivacaine. Reg Anesth Pain Med. 1995 Mar 1;20(2):90-4.
7. Chavan G, Chavan A, Ghosh A. Effect of Intrathecal Fentanyl on subarachnoid block with 0.5% hyperbaric bupivacaine. Int J Health Biomed Res. 2014 Jul; 2: 67-76
8. Upadya M, Neeta S, Manissery JJ, Kuriakose N, Singh RR. A randomized controlled study comparing intrathecal hyperbaric bupivacaine-fentanyl mixture and isobaric bupivacaine-fentanyl mixture in common urological procedures. Indian journal of anaesthesia. 2016 Jan;60(1):44 - 9.
9. Etches RC, Sandler AN, Daley MD. Respiratory depression and spinal opioids. Canadian journal of anaesthesia. 1989 Mar 1;36(2):165-85.
10. Dahlgren G, Hultstrand C, Jakobsson J, Norman M, Eriksson EW, Martin H. Intrathecal sufentanil, fentanyl, or placebo added to bupivacaine for cesarean section. Anesthesia and Analgesia. 1997 Dec 1;85(6):1288-93.
11. Scott LJ, Perry CM. Tramadol. Drugs. 2000 Jul 1;60(1):139-76.
12. Afolayan JM, Olajumoke TO, Amadasun FE, Edomwonyi NP. Intrathecal tramadol versus intrathecal fentanyl for visceral pain control during bupivacaine subarachnoid block for open appendicectomy. Nigerian journal of clinical practice. 2014;17(3):324-30
13. Subedi A, Biswas BK, Tripathi M, Bhattarai BK, Pokharel K. Analgesic effects of intrathecal tramadol in patients undergoing caesarean section: a randomised, double-blind study. International journal of obstetric anesthesia. 2013 Nov 1;22(4):316-21.
14. Chakraborty S, Chakrabarti J, Bhattacharya D. Intrathecal tramadol added to bupivacaine as spinal anesthetic increases analgesic effect of the spinal blockade after major gynecological surgeries. Indian journal of pharmacology. 2008 Aug;40(4):180-2.
15. Sanjul Dandona , Neha Batra SS . Comparison of Intrathecal tramadol and fentanyl as adjuvant in abdominal and lower limb surgeries: A randomized clinical study. Int J Med Heal Res.2017;3(2):46-9.
16. Dalvi NP, Patil N. Comparison of effect of intrathecal fentanyl bupivacaine and tramadol-bupivacaine combination on postoperative analgesia in lower abdominal surgeries. Research and Innovation in Anesthesia. 2016;1(2):35-40.
17. Pradhan M, Amatya SP, Shrestha A, Piya R, Hirachan N. To compare the effect of intrathecal Fentanyl with hyperbaric Bupivacaine on the quality of subarachnoid blockade in cesarean section. Journal of Advanced Medical and Dental Sciences Research. 2017 Aug 1;5(8):4-7.
18. Gopichand AK, Author Suresh Assistant CT. Effects Fentanyl on Hyperbaric Bupivacaine in Spinal Anaesthesia for Caesarean Section. J Med Sci Clin Res [Internet]. 2016 [cited 2018 Sep 14];4(8):11714–9. Available from: http://dx.doi.org/10.18535/jmscr/v4i8.06
19. Choi DH, Ahn HJ, Kim MH. Bupivacaine-sparing effect of fentanyl in spinal anesthesia for cesarean delivery. Regional anesthesia and pain medicine. 2000 May 1;25(3):240-5.
20. Yahya M, Sriramamurthy K, Farhat S, Kumari S. Effect of addition of fentanyl to low dose bupivacaine in cesarean section under spinal anesthesia. Eur J Pharm Med Res. 2017 Feb 4(2):568–72.

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