e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(11); 1182-1188

Original Research Article

A Comparative Study of Block Characteristics and Side Effects of Intrathecal versus Intravenous Fentanyl for Supplementation of Subarachnoid Block in Patients Undergoing Total Abdominal Hysterectomy

Ashiq Kalam[1], Harini Priyadarshini M.S.[2], Pooja N.[3], Shivashankar M.[4]

[1]Junior Consultant, Department of Anaesthesiology, Cura Hospital, Kammanahalli, Bangalore, Karnataka, India

[2]HOD & Senior Consultant, Department of Anaesthesiology, K. C. General Hospital, Malleshwaram, Bangalore, Karnataka, India

[3]Consultant, Department of Anaesthesiology, Motherhood Hospital, Hebbal, Bangalore, Karnataka, India

[4]Professor, Department of Anaesthesiology, Sri Siddhartha Institute of Medical Sciences and Research Center, T. Begur, Bangalore Rural, Karnataka, India

Received: 25-08-2024 / Revised: 23-09-2024 / Accepted: 25-10-2024

Corresponding Author: Dr. Harini Priyadarshini M.S.

Conflict of interest: Nil

Abstract:

Introduction: Although there are studies comparing various opioids and various dosages of fentanyl, studies comparing the two routes of administration, especially for total abdominal hysterectomy are very few.

Methods: Inj. fentanyl 25µg (0.25ml) intrathecally and Inj. fentanyl 1µg/kg intravenously were compared.15 mg of 0.5% hyperbaric bupivacaine was used for spinal anaesthesia in both groups. Onset of sensory blockade, maximum level of sensory blockade attained, and the time taken for the same were noted. Time taken for onset of motor blockade, i.e., Bromage 6, and time taken to achieve maximum motor block, i.e., Bromage 1, were noted. Time for two-segment sensory regression, time for sensory regression to T12, time for motor regression to Bromage 6, and the level of sedation by using the Ramsay sedation score were also recorded. Time for rescue analgesia using 75 mg diclofenac intramuscularly when patient complained of mild pain or VAS > 5 was also noted.

Results: The mean onset of sensory blockade in minutes was 1.94±0.85 in IT fentanyl and 1.59±0.71 in IV fentanyl, p <0.008. The mean onset of motor blockade in minutes was 3.16±1.06 in IT fentanyl and 2.71±0.84 in IV fentanyl, p <0.007. The mean time for maximum sensory blockade in minutes was 17.50±4.76 in IT fentanyl and 19.44±4.43 in IV fentanyl, p <0.014. The mean time for maximum motor blockade in minutes was 5.44±1.53 in IT fentanyl and 4.91±1.02 in IV fentanyl, p <0.017. The mean regression of sensory blockade to T12 in minutes was 192.84±32.80 in IT fentanyl and 176.23±19.81 in IV fentanyl, p <0.001. The mean regression of motor blockade to T12 in minutes was 163.76±37.40 in IT fentanyl and 152.16±22.39 in IV fentanyl, p <0.028. The time to rescue analgesia in minutes was 216.81±38.79 in IT fentanyl and 184.43±16.91 in IV fentanyl, p <0.001. About 87% of patients had an RSS score of 2, and 13% had an RSS score of 3 in IT fentanyl. 74% of patients had an RSS score of 2, and 26% had an RSS score of 3 in IV fentanyl. About 4% of patients had nausea and vomiting and about 13% had hypotension in the IT fentanyl group, whereas the IV fentanyl group had about 14% of patients with nausea and vomiting, 16% with hypotension, and 4% with pruritus.

Conclusion: Intrathecal fentanyl 25µg compared to intravenous fentanyl 1µg/kg administered with 0.5% hyperbaric bupivacaine for subarachnoid block in total abdominal hysterectomies, prolonged sensory and motor block, increased the duration of analgesia with fewer adverse effects.

Keywords: Intrathecal, Intravenous, Fentanyl, Subarachnoid Block.

Introduction

Subarachnoid block with Bupivacaine alone is most often used as the anaesthetic technique for gynaecological procedures like total abdominal hysterectomy. Patients, however, experience varying degrees of pain and discomfort when the procedure is prolonged. [1] Increasing the dose of Bupivacaine may increase the level of block and duration, but it also increases the risk of hypotension and bradycardia. [2] This led to the study of the use of adjuvants like opioids with

subarachnoid blocks to reduce the dose of bupivacaine and to increase the effectiveness of the block. [2-8]

The local anesthetic-mediated block may be significantly enhanced by low doses of fentanyl to reduce nociceptive activation. It provides efficient intraoperative and prolonged postoperative analgesia. The incidence of perioperative adverse reactions like nausea and vomiting is also reduced. [9,10] According to research, opioids that are used in addition to spinal anaesthesia may not entirely act in the spinal cord. According to an experimental study, a sizable portion of a lipophilic opioid, like fentanyl, that is administered intrathecally is lost through diffusion into the epidural space and then into the plasma. [11] This suggests that fentanyl may cause analgesia through a systemic mechanism rather than a spinal one. We reasoned that if intrathecal fentanyl causes analgesia by bloodstream absorption instead of spinal action, then an intravenous injection might have the same effect. Hence, our study compared the effect of intrathecal versus intravenous fentanyl for supplementation of subarachnoid block in patients undergoing total abdominal hysterectomy.

Methods

This was a prospective randomized study involving 140 (70 patients in group IT (Intrathecal) and 70 patients in group IV (Intravenous)) patients of age group 40-60 years, belonging to ASA grade I and grade II, posted for elective total abdominal hysterectomy. Patients who belonged to the IT (Intrathecal) group were given 15 mg of 0.5% hyperbaric bupivacaine and Inj. fentanyl 25µg (0.25 ml) intrathecally. Patients who belonged to the IV (Intravenous) group were given 15 mg of 0.5% hyperbaric Bupivacaine and 0.25 mL of distilled water intrathecally, followed by Inj. Fentanyl 1 µg/kg intravenously. Using a 27G blunt-tip hypodermic needle inserted into the midclavicular line every 30 seconds for the first two minutes, every minute for the next five, every five minutes for the following fifteen, and every ten minutes for the next thirty, the pin prick method was used to evaluate the onset of sensory blockage. It was noted how long it took to reach the maximum level of sensory blockage.

Time taken for onset of motor blockade, i.e., Bromage 6, and time taken to achieve maximum motor block, i.e., Bromage 1, were noted. Time for two-segment sensory regression, time for sensory regression to T12, time for motor regression to Bromage 6, and the level of sedation by using the Ramsay sedation score were also recorded. Time for rescue analgesia using 75 mg diclofenac intramuscularly when patient complained of mild pain or VAS > 5 was also noted.

Mean± SD was used to display findings for continuous data, while number (%) was used to display results for categorical measurements. The 5% level of significance was used to evaluate significance. The significance of research parameters on a continuous scale between two groups (intergroup analysis) on metric parameters was determined using the two-tailed, independent student t test. In order to evaluate the homogeneity of variance, Leven's test was conducted. The significance of research parameters on a categorical scale between two or more groups was determined using the chi-square/Fisher Exact test.

Results

The mean age distribution of subjects in intrathecal fentanyl (IT fentanyl) group was 46.37±5.14 and that of intravenous fentanyl (IV fentanyl) 46.87±5.52. There was no significant difference in mean age as evidenced by a p-value of 0.580.

Table 1: Age Distribution Samples are Age Matched with P=0.580, Student T-Test

Age (in years)	IT Fentanyl	IV Fentanyl	Total
40-49	48(68.6%)	47(67.1%)	95(67.9%)
50-59	22(31.4%)	23(32.9%)	45(32.1%)
Total	70(100%)	70(100%)	140(100%)
Mean ± SD	46.37±5.14	46.87±5.52	6.62±5.32

There was no difference between the two groups with respect to height (p = 0.197) and weight (p = 0.166) and hence were comparable. The onset of sensory block in minutes for subjects on IT fentanyl was 1.94±0.85 and that of IV fentanyl was 1.59±0.71. The p-value of 0.008, which was statistically significant, suggests that intravenous fentanyl has a faster onset of action than intrathecally administered fentanyl. The p-value of 0.014 for maximum sensory blockade and p-value less than 0.001 for regression of sensory blockade suggested that intrathecally administered fentanyl attains peak action quicker and regresses slower than intravenous fentanyl. The onset of motor block in minutes for subjects on IT fentanyl was 3.16±1.06 and that of IV fentanyl was 2.71±0.84. The p-value of 0.007 suggested that intravenously administered fentanyl has quicker action on motor blockade than intrathecally administered fentanyl. The p-value of 0.017 for maximum motor blockade and p-value less than 0.028 for regression of motor blockade suggested that intravenously administered

fentanyl has a faster onset of motor blockade, attains peak action quicker and regresses faster than intrathecally administered fentanyl.

Table 2: A Comparison of Block Characteristics among the Two Groups

Variables (in minutes)	IT Fentanyl	IV Fentanyl	Total	P-Value
Onset Sensory Block	1.94±0.85	1.59±0.71	1.76±0.80	0.008**
Onset Motor Block	3.16±1.06	2.71±0.84	2.94±0.98	0.007**
Time Max Sensory Block	17.50±4.76	19.44±4.43	18.47±4.68	0.014*
Time Max Motor Block	5.44±1.53	4.91±1.02	5.18±1.32	0.017*
Regression Sensory Block	192.84±32.80	176.23±19.81	184.54±28.25	<0.001**
Regression Motor Block	163.76±37.40	152.16±22.39	157.96±31.26	0.028*
Time for Rescue Analgesia	216.81±38.79	184.43±16.91	200.62±33.95	<0.001**

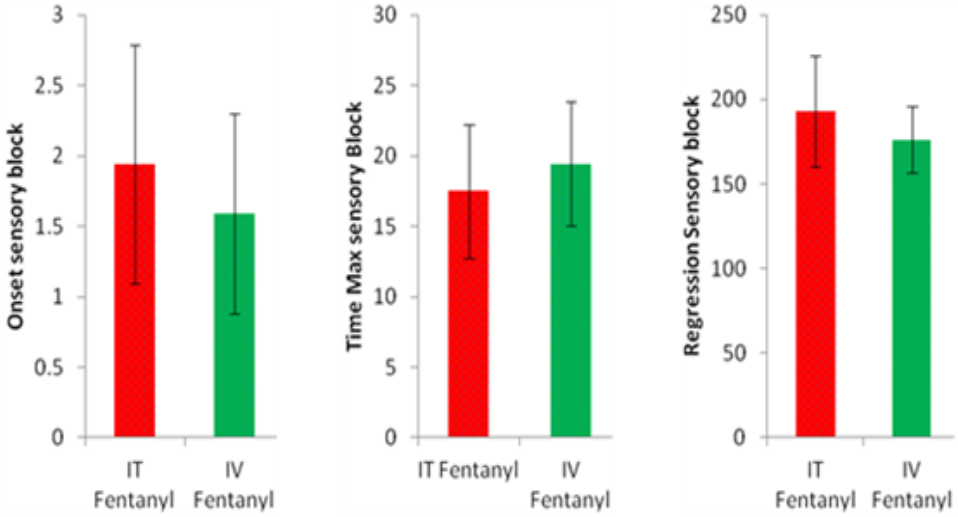

Figure 1: Onset of Sensory Block

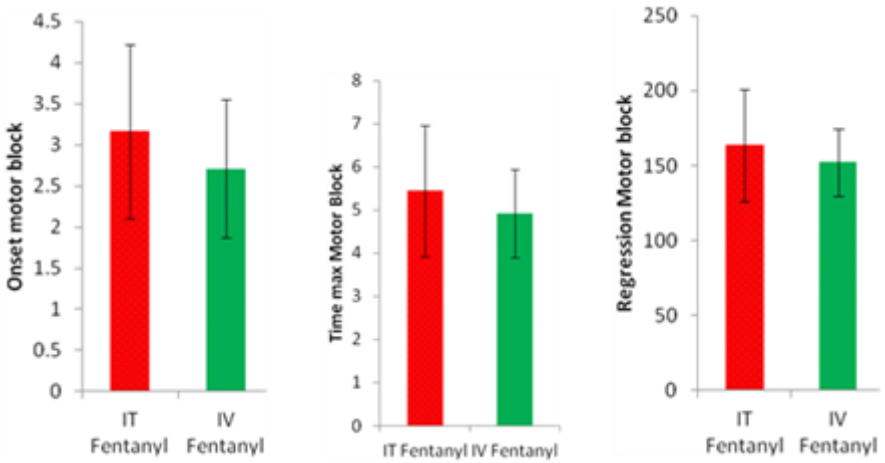

Figure 2: Onset of Motor Block

Patients in IV fentanyl group had higher sedation scores than IT fentanyl, although the difference was not statistically significant but suggestive.

Table 3: RSS Sedation Score

RSS Score	IT Fentanyl	IV Fentanyl	Total
1	0 (0%)	0 (0%)	0 (0%)
2	61 (87.1%)	52 (74.3%)	113 (80.7%)
3	9 (12.9%)	18 (25.7%)	27 (19.3%)
Total	70 (100%)	70 (100%)	140 (100%)
P=0.054+, Significant, Fisher Exact Test			

The time for rescue analgesia in minutes in the IT fentanyl group was 216.81±38.79 and that of the IV fentanyl group was 184.43±16.91 with a p-value of <0.001. The value was statistically significant by virtue of the fact that subjects given intrathecal fentanyl required rescue analgesia much later than those given fentanyl intravenously.

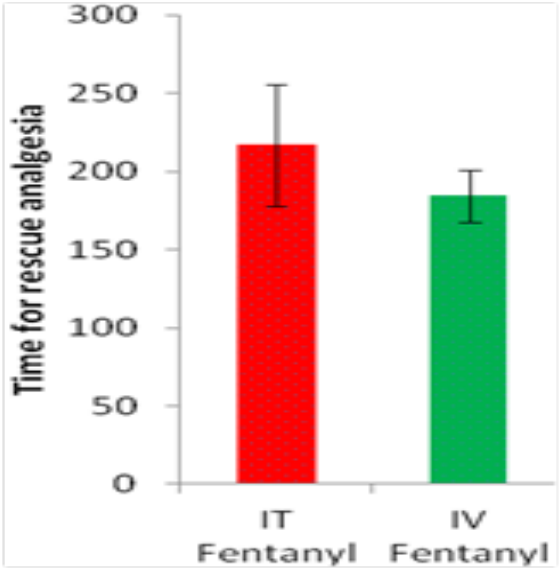

Figure 3: Time for Rescue Analgesia

Patients in the IV fentanyl group had more adverse effects, such as bradycardia, hypotension, nausea and vomiting, and pruritus, than the patients in the IT fentanyl group. With a p-value of 0.020, the difference was statistically significant.

Table 4: Side Effects Distribution in Two Groups

Side Effects	IT Fentanyl (N = 70)	IV Fentanyl (N = 70)	Total (N = 140)
Nil	58(82.9%)	46(65.7%)	104(74.3%)
Yes	12(17.1%)	24(34.3%)	36(25.7%)
Hypotension	9(12.9%)	14(20.0%)	23(16.4%)
Nausea and Vomiting	3(4.3%)	10(14.3%)	13(9.3%)
Pruritus	0	3(4.3%)	3(4.3%)
P=0.020*, Significant, Chi-Square test			

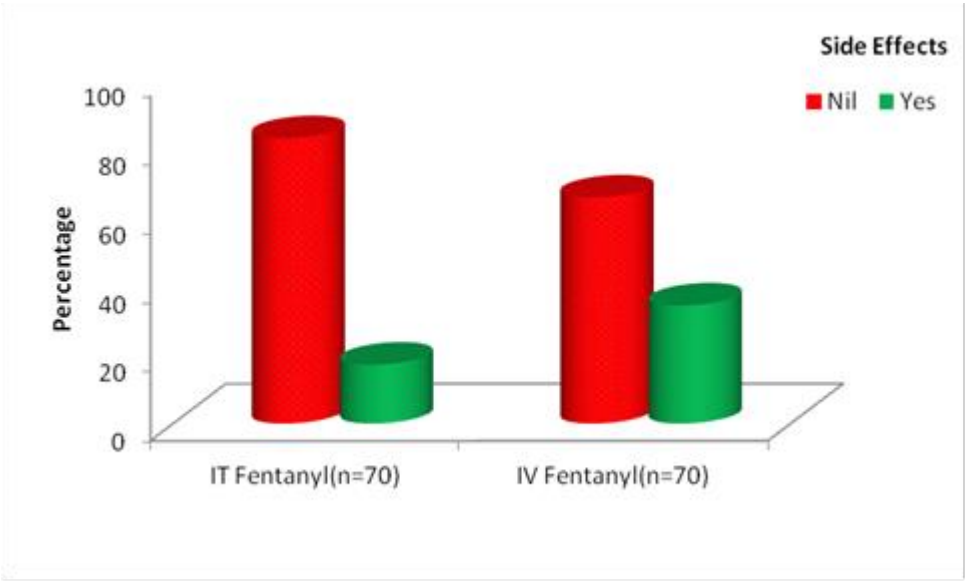

Figure 4: Side Effects

Discussion

The present study was carried out to compare the efficacy of intrathecal fentanyl with intravenous fentanyl as a supplementation to 0.5% hyperbaric bupivacaine in subarachnoid block with respect to onset of sensory and motor blockade, duration of sensory and motor blockade, time for rescue analgesia, hemodynamic profile, degree of sedation, and side effects. Both groups were comparable with regards to age, weight, height distribution, and ASA grading. The patients in the intrathecal fentanyl group had slower onset but longer duration of sensory and motor blockade. Although there was no statistically significant difference between the groups with respect to the level of sedation, the incidence of side effects such as hypotension, nausea, and pruritus was higher in the intravenous group. Literature on the topic is very sparse. Although there are studies comparing various opioids and also various dosages of fentanyl, studies comparing the two routes of administration, especially for total abdominal hysterectomy, are very few. The following discussion is based on available literature.

Spinal and systemic μ-opioid agonists can have a synergistic antinociceptive effect when administered together, according to several animal studies. [12,13] Systemic fentanyl was shown in earlier research to promote the spread of lidocaine-induced spinal anaesthesia. [14,15] Nevertheless, it was impossible to identify the fundamental process behind this improvement.

Intrathecal (i.t.) opioids block the spinal transmission of nociception, whereas systemic opioids, at small dosages, primarily affect the brain. When fentanyl is delivered spinally, the μ-agonist activity at the supraspinal level may interact in a supra-additive way. I.V. morphine and fentanyl stimulate the release of spinal norepinephrine and acetylcholine, as shown by Bouaziz et al. [16] As an inhibitory transmitter, norepinephrine lessens the dorsal horn neurones' sensitivity to unpleasant stimulus. [17] The synergistic impact between intravenous and intrathermal fentanyl may possibly be attributed to this mechanism.

Fentanyl 50μg i.v. and 20μg i.t. similarly increased the spread of spinal anaesthesia, according to research by A. Kararmaz et al. [18] Contrary to what we observed, the co-administration of intravenous and intrathermal fentanyl did not exhibit extended analgesia, even though it prolonged the regression of spinal anaesthesia. They proposed that greater intravenous fentanyl dosages might be able to provide extended post-operative analgesia. They came to the conclusion that fentanyl could be given intravenously as well as intrathecal to increase the distribution of bupivacaine-induced spinal analgesia. Concurrent administration of fentanyl via the spinal and supraspinal routes, however, results in a longer duration of anaesthesia and a larger distribution of spinal analgesia without causing additional side effects.

Systemic fentanyl and nalbuphine, as shown by Fassoulaki et al., [19] increase the distribution of spinal analgesia caused by intrathecal lidocaine in a dose-dependent manner. Additionally, it was demonstrated that when given simultaneously via the spinal and supraspinal routes, μ-opioid agonists could have a synergistic and long-lasting antinociceptive effect. [20] However, when fentanyl is given intravenously as a component of a spinal anaesthetic solution, the impact of fentanyl on the distribution of spinal analgesia has not been investigated. The purpose of this study was to test the hypothesis that when bupivacaine and fentanyl are used together for spinal anaesthesia, systemic fentanyl results in a larger enhancement of the level of spinal analgesia.

Philip W. H. Peng and Alan N. Sandler [21] conducted a study about a review of the use of fentanyl analgesia in the management of acute pain in adults. The study concluded that subarachnoid use provides the most intense, complete analgesia, although intravenous PCA, with its more convenient format, is also effective.

Jayendra Makwana et al., [22] found that time to achieve sensory block up to T6 in minutes was 6.74±0.84 in bupivacaine and fentanyl group (group BF) and 6.69 ± 0.92 when bupivacaine was used alone (group B). The onset of motor blockade to Bromage 3 in minutes was found to be 5.74±0.46 in group BF and 4.70 ± 0.86 in group B. In the study, regression of sensory blockade to T12 in minutes was found to be 192.00±29.05 in group BF and 165.98±25.07 in group B with a p-value = 0.0004. The regression of motor block to Bromage scale 0 in minutes was 165.32 ± 29.69 in Group BF and 162.00 ± 26.83 in group B with a p-value = >0.05. The first demand of analgesic in minutes was 310.44±41.53 in group BF whereas it was 213.20±21.46 in group B with a p value<0.01. According to the study's findings, using intrathecal fentanyl as a bupivacaine adjuvant enhanced the quality of the block by extending the duration of both the sensory block and the effective analgesia.

Siddik-Sayyid et al., [1] conducted a study with 23 patients supplemented with intrathecal fentanyl and 25 patients supplemented with intravenous fentanyl with bupivacaine for subarachnoid block. The study found that time to maximum sensory block onset in minutes was 12.19±4.5 in the IT fentanyl group, whereas it was 11.54±5.2 in the IV fentanyl group. The time for regression of sensory block to T12 in minutes was 148.39±43.06 in IT fentanyl

group and 133.64±44.37 in IV fentanyl group. In the study, it was noted that time to full motor recovery in minutes was 169.13±48.13 in the IT fentanyl group and 167.39±43.35 in the IV fentanyl group. It was also found that the time to first postoperative analgesic request in minutes was 159.38±39.02 in IT fentanyl group and 119.12±44.9 in IV fentanyl group. The study also found that the side effects such as nausea (p-value = 0.02), systolic BP<90 (p-value = 0.01), ephedrine requirements (p-value = 0.01), itching (p-value = 0.09), and shivering (p-value = 0.08) were more common in the IV fentanyl group when compared to the IT fentanyl group.

The study found that adding intrathecal fentanyl to bupivacaine-spinal block during caesarean delivery resulted in higher-quality spinal anaesthesia than adding the same amount of IV fentanyl. Although the study groups were different, the findings and conclusions of the Siddik-Sayyid et al., study were very similar to our observations.

Conclusion

Intrathecal fentanyl 25µg compared to intravenous fentanyl 1µg/kg administered with 0.5% hyperbaric bupivacaine for subarachnoid block in total abdominal hysterectomies, prolonged sensory and motor block, increased the duration of analgesia with fewer adverse effects. Since the literature comparing intrathecal and intravenous fentanyl is limited, further research into the findings is required.

References

1. Siddik-Sayyid SM, Aouad MT, Jalbout MI, Zalaket MI, Berzina CE, Baraka AS. Intrathecal versus intravenous fentanyl for supplementation of subarachnoid block during cesarean delivery. Anesth Analg 2002;95(1):209–13.
2. Chung CJ, Bae SH, Chae KY, Chin YJ. Spinal anaesthesia with 0.25% hyperbaric bupivacaine for Caesarean section: effects of volume. British Journal of Anaesthesia 1996;77(2):145–9.
3. Bhar D, RoyBasunia S, Das A, Kundu SB, Mondal RC, Halder PS, et al. A comparison between intrathecal clonidine and neostigmine as an adjuvant to bupivacaine in the subarachnoid block for elective abdominal hysterectomy operations: A prospective, double-blind and randomized controlled study. Saudi J Anaesth 2016;10(2):121.
4. Ahmed F, Khandelwal M, Sharma A. A comparative study of the effect of clonidine, fentanyl, and the combination of both as adjuvant to intrathecal bupivacaine for postoperative analgesia in total abdominal hysterectomy. J Anaesthesiol Clin Pharmacol 2017;33(1):102.
5. Bhavsar M, Chauhan D, Parmar M, Upadhyaya R. A study on combined use of intrathecal fentanyl and neostigmine as an adjunct to bupivacaine for postoperative analgesia after abdominal hysterectomy. Gujarat Medical Journal 2014;69(2):68-71.
6. Gurunath BB, Madhusudhana R. Postoperative analgesic efficacy of intrathecal fentanyl compared to nalbuphine with bupivacaine in spinal anesthesia for lower abdominal surgeries. Anesth Essays Res 2018;12(2):535.
7. Chattopadhyay S, Datta M, Biswas B. A study on perioperative effects of intrathecal clonidine and fentanyl with hyperbaric bupivacaine in spinal anesthesia for vaginal hysterectomy, Asian Journal of Pharmaceutical and Clinical Research 2016;9(5):245-8.
8. Thada B, Khare A, Sethi SK, Meena S, Verma M. Comparison of dexmedetomidine and fentanyl as intrathecal adjuvants to 0.5% hyperbaric bupivacaine for total abdominal hysterectomy under subarachnoid block: a prospective randomized double-blind study. Anaesthesia, Pain & Intensive Care 2019;21(1):65–72.
9. Makwana JC, Shivraj TN, Khade A, Bansal S, Mandal N, Goswami S, et al. Comparison between hyperbaric bupivacaine and hyperbaric bupivacaine plus fentanyl intrathecally in major gynecological surgeries. Int J Med Sci Public Health 2014; 3:319–23.
10. Peng PW, Sandler AN. A review of the use of fentanyl analgesia in the management of acute pain in adults. Anesthesiology: The Journal of the American Society of Anesthesiologists 1999;90(2):576–99.
11. Ummenhofer WC, Arends RH, Shen DD, Bernards CM. Comparative spinal distribution and clearance kinetics of intrathecally administered morphine, fentanyl, alfentanil, and sufentanil. Anesthesiology: The Journal of the American Society of Anesthesiologists 2000;92(3):739–53.
12. Roerig SC, Fujimoto JM. Multiplicative interaction between intrathecally and intracerebroventricularly administered mu opioid agonists but limited interactions between delta and kappa agonists for antinociception in mice. J Pharmacol Exp Ther 1989; 249:762-8.
13. Niv D, Nemirovsky A, Rudick V, Geller E, Urca G. Antinociception induced by simultaneous intrathecal and intraperitoneal administration of low doses of morphine. Anesth Analg 1995; 80:886-9.
14. Fassoulaki A, Sarantopoulos C, Chondreli S. Systemic fentanyl enhances the spread of spinal analgesia produced by lignocaine. Br J Anaesth 1991; 67:437-9.
15. Sarantopoulos C, Fassoulaki A. Systemic opioids enhance the spread of sensory analgesia produced by intrathecal lidocaine. Anesth Analg 1994; 79:94-7.

16. Bouaziz H, Tong C, Yoon Y, Hood DD, Eisenach JC. Intravenous opioids stimulate norepinephrine and acetylcholine release in spinal cord dorsal horn. Systematic studies in sheep and an observation in a human. Anesthesiology 1996; 84:143-54.
17. Headley PM, Duggan AW, Griersmith BT. Selective reduction by noradrenaline and 5-hydroxytryptamine of nociceptive responses of cat dorsal horn neurones. Brain Res 1978;21: 185-9.
18. Kararmaz A, Kaya S. Which administration route of fentanyl better enhances the spread of spinal anaesthesia: intravenous, intrathecal or both? Acta Anaesthesiol Scand 2003; 47:1096-100.
19. Sarantopoulos C, Fassoulaki A. Systemic opioids enhance the spread of sensory analgesia produced by intrathecal lidocaine. Anesth Analg 1994; 79:94-7.
20. Niv D, Nemirovsky A, Metzner J, Rudick V, Jurna I, Urca G. Antinociceptive effect induced by the combined administration of spinal morphine and systemic buprenorphine. Anesth Analg 1998; 87:583-6.
21. Peng PW, Sandler AN. A review of the use of fentanyl analgesia in the managemt of acute pain in adults. Anesthesiology: The Journal of the American Society of Anesthesiologists 19 99;90(2):576-99.
22. Makwana JC, Shivraj TN, Khade A, Bansal S, Mandal N, Goswami S, et al. Comparison between hyperbaric bupivacaine and hyperbaric bupivacaine plus fentanyl intrathecally in major gynecological surgeries. Int J Med Sci Public Health 2014; 3:319–23.