European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 09, Issue 03, 2022

ORIGINAL RESEARCH

Comparison of Adjuvant Intrathecal Dexmedetomidine or Fentanyl to Hyperbaric Bupivacaine for Postoperative Analgesia - A Randomized, Double-Blind Controlled Study

Nishigandha Mahajan[1], Shilpa Sharda[2], Krishan Gopal Jangir[3], Swati Sharma[4]

[1]Assistant Professor Department of Anesthesiology, Pacific Medical College and Hospital, Udaipur, Rajasthan, India.

[2]Assistant Professor, Department of Anesthesiology, Pacific Medical College and Hospital, Udaipur, Rajasthan, India

[3]Assistant Professor, Department of Anesthesiology, Pacific Medical College and Hospital, Udaipur, Rajasthan, India.

[4]Assistant Professor, Department of Anesthesiology, Pacific Medical College and Hospital, Udaipur, Rajasthan, India

ABSTRACT

Background: Various adjuvants have been used with local anaesthetics in spinal anaesthesia to prolong postoperative analgesia. Dexmedetomidine, the new highly selective α2-agonist drug, is now being used as a neuraxial adjuvant. The aim of this study was to evaluate the onset and duration of sensory and motor block, hemodynamic effect, postoperative analgesia, and adverse effects of dexmedetomidine, or fentanyl when given intrathecally with hyperbaric 0.5% bupivacaine.

Materials and Methods: Ninety patients classified in American Society of Anaesthesiologists classes I and II scheduled for lower abdominal surgeries requiring spinal anaesthesia were studied. Patients were randomly allocated to receive either 12.5 mg hyperbaric bupivacaine plus 10 µg dexmedetomidine (group D, n=30) or 12.5 mg hyperbaric bupivacaine plus 25 µg fentanyl (group F, n=30) intrathecal. The control group received 12.5 mg hyperbaric bupivacaine intrathecally (n=30).

Results: Patients in the dexmedetomidine group (D) had a significantly longer sensory and motor block time than patients in the fentanyl group (F) and control group (B). VAS score at rescue analgesia was significantly higher in the control group. Duration of analgesia was significantly more in the dexmedetomidine, and fentanyl group as compared to control. The total duration of analgesia was longer with dexmedetomidine than fentanyl. Sedation scores were significantly higher in the Dexmedetomidine group. No hemodynamic changes were noted in any group.

Conclusion: Intrathecal dexmedetomidine and fentanyl as adjuvants to hyperbaric bupivacaine prolong sensory and motor block with minimal hemodynamic instability and reduced demand for rescue analgesia. Intrathecal dexmedetomidine has a longer duration of analgesia than fentanyl.

Keywords: Intrathecal, Fentanyl, Dexmedetomidine, spinal anaesthesia, bupivacaine.

Corresponding Author: Dr Swati Sharma, Assistant Professor, Department of Anesthesiology, Pacific Medical College and Hospital, Udaipur, Rajasthan, India.

INTRODUCTION

The majority of patients experience postoperative pain following surgical procedures which most of the time is reported as moderate, severe, or extreme.[1,2] Pain that is inadequately

controlled negatively affects the quality of life, recovery and increases the risk of complications.[3] Thus preoperative, intraoperative, and postoperative interventions and management strategies including multimodal analgesia or use of a variety of analgesics or techniques are devised to reduce and mitigate postoperative pain. Randomized trials have shown that multimodal analgesia offers additive or synergistic effects by exhibiting different mechanisms of action and is effective in relieving pain compared with single-modality interventions.[4-6]

Spinal anaesthesia is a technique of choice for below diaphragm surgeries.[7] A common problem during lower abdominal surgeries under spinal anaesthesia is visceral pain, nausea, and vomiting.[8] Spinal anaesthesia with 0.5% bupivacaine is the most commonly used technique for sub umbilical surgeries. Bupivacaine is an amide local anaesthetic with a prolonged duration of action and lower incidence of transient radicular symptoms.[9] Intrathecal hyperbaric bupivacaine had a more rapid onset of the sensory blockade at the 4ththoracic vertebra (T4) level than isobaric bupivacaine.[10] However, high doses of intrathecal bupivacaine may lead to myocardial depression, arrhythmias, and heart block.[11]

To maximize the quality and duration of anaesthesia as well as postoperative analgesia, several adjuvants are added to bupivacaine.[12] The addition of fentanyl to hyperbaric bupivacaine improves the quality of intraoperative and early postoperative subarachnoid blocks.[13] However, the use of opioids with bupivacaine has associated disadvantages of pruritus and respiratory depression.[13]

Dexmedetomidine, a highly selective α2-agonist, is under evaluation as a neuraxial adjuvant since it gives good quality of intraoperative and prolonged postoperative analgesia with minimal side effects providing stable hemodynamic conditions.[12,14,15] Dexmedetomidine is approved by the Food and Drug Administration (FDA) as a short-term sedative for ventilated intensive care unit (ICU) patients. Hyperbaric bupivacaine in spinal anaesthesia with intrathecal 5 μg dexmedetomidine produces a favourable postoperative analgesic effect with minimal side effects.[8,12,14,16]

Although various studies have compared dexmedetomidine and fentanyl with isobaric bupivacaine, there are fewer studies comparing the addition of dexmedetomidine to hyperbaric bupivacaine with fentanyl to hyperbaric bupivacaine.[8,12,14] Thus, this study was undertaken to compare fentanyl and dexmedetomidine as an adjuvant to hyperbaric bupivacaine in lower abdominal surgeries, with an aim to study and compare the changes in characteristics of spinal blockade, degree and duration of post-operative analgesia, duration and degree of motor and sensory blockade and hemodynamic and associated adverse effects.

MATERIALS & METHODS

Study Population

A prospective, randomized, double-blind, single centre study was conducted in patients presenting for elective lower abdominal surgeries under spinal anaesthesia. Following study approval from the institutional ethics committee the study was initiated. All patients gave a written informed consent prior to study participation. Study inclusion criteria were as per American Society of Anaesthesiologists (ASA)-physical status I or II of either sex, aged between 18–65 years.[17] Exclusion criteria were: patients allergic to drug, with heart block/dysrhythmia, or those on therapy with adrenergic receptor antagonists, calcium channel blockers, and/or angiotensin converting enzyme inhibitors. Patients with local skin infection on the back, with severe spinal deformities and coagulation abnormalities, were also excluded.

Study Investigations

All the patients were evaluated and assessed preoperatively for history of medical and surgical illness. Investigations included haemoglobin, total and differential leucocyte count,

platelet count, blood sugar level, blood urea, serum creatinine, coagulation profile and electrocardiogram. Specific additional investigations were done whenever necessary.

Treatment

Before induction of anaesthesia, ninety patients were randomly divided (1:1:1) in one of the three groups. Patients in group B received 12.5 mg of 0.5% hyperbaric bupivacaine plus 0.5 ml NS, group F received 12.5 mg of 0.5% hyperbaric bupivacaine plus inj. fentanyl 25 µg, and group D received 12.5 mg of 0.5% hyperbaric bupivacaine plus inj. dexmedetomidine 10 µg and 0.4 ml NS. The total volume of injectate administered intrathecally was 3 ml in all three groups.

Anaesthesia Procedure

All patients received alprazolam 0.25 mg and omeprazole 20 mg on the night before surgery and were fasted for 6 hours preoperatively. As a premedication, all patients received injection glycopyrrolate 0.004 mg/kg intramuscularly. Patients were continuously monitored with automated non-invasive blood pressure, pulse oximetry, and electrocardiogram. A 20G peripheral venous access was secured and the patients were preloaded with intravenous crystalloid infusion, prior to subarachnoid block.

Subarachnoid block was given in the sitting position under due aseptic precautions. 25G Quincke tip spinal needles were introduced through L3–L4 interspaces in sitting position using aseptic precautions. Once free and clear flow of cerebrospinal fluid was obtained, the drug was injected. Patients were then made supine, and the operation table was kept straight in neutral position. All patients received oxygen by mask at the rate of 4 lit/min. No intraoperative sedation or other analgesic was given to any of the patients.

Study Assessments

Intraoperatively vitals were monitored. Onset of highest level of sensory block and regression of sensory level by 2 segments was assessed by pinching the skin with a forcep in the midclavicular line bilaterally in the cephalad direction every 2 min for the first 20 min and then every 5-10 min. Duration of motor blockade and surgery was noted in minutes. Post-operative pain was assessed by Visual Analogue Scale (VAS) at 0 min, 2 hr, 4hr, 6hr, 8 hr, 10hr and 12hr. Time of first post-operative pain (VAS >4) complained by patients was noted wherein rescue analgesia was provided with inj. diclofenac sodium 75 mg intramuscularly. Pain assessment with VAS was determined before rescue analgesia was administered. Modified Ramasay sedation scale was used for assessing the degree of sedation.[18]

All patients were monitored for adverse effects like restlessness, nausea, vomiting, pruritus, respiratory depression, sedation, and hypotension, which if observed were treated accordingly.

Statistical Analysis

Statistical analysis was done using the Statistical Package for Social Science (SPSS15.0 Evaluation version). Data are expressed as either mean and standard deviation or numbers and percentages.[19] Continuous covariates were compared using analysis of variance (ANOVA). The comparison was studied using the Mann-Whitney U test or Chi-square test or Fisher's exact test or Kruscal Wallis as appropriate, with the p value <0.05 considered statistically significant.

RESULTS

A total of 90 patients were included in the study and randomized to the either treatment groups (n=30 each). The treatment groups were comparable with respect to age, gender and

ASA distribution, and duration of surgery status [Table 1]. There was no significant difference (p>0.001) in the groups baseline characteristics. [Table 1].

Table 1:Baseline characteristics

Parameter	Group B (n=30)	Group F (n=30)	Group DI (n=30)	p-value
Age (years), mean ± SD	45.50 ± 15.26	46.63 ± 15.28	44.30 ± 15.53	0.841
Gender, n (%)				
Male	21 (70)	22 (73.3)	21 (70)	0.999
Female	9 (30)	10 (33.3)	9 (30)	
ASA (I:II)	17:13	19:11	15:15	0.623
Duration of surgery (min), mean ± SD	60.33 ± 16.34	62.33 ± 14.06	65.17 ± 13.23	0.44

ASA, American Society of Anaesthesiologist; SD, standard deviation.

Sensory and Motor block

The characteristics of sensory and motor block are summarized in Table 2. There was no difference between the groups B, F and D in the highest level of block achieved amongst them (T6, T7 and T8, respectively). However, the time required to achieve highest level of spinal anaesthesia was significantly less in groups F and D as compared to group B. Block regression was slower with addition of fentanyl and dexmedetomidine as compared to hyperbaric bupivacaine alone [Table 2]. Block regression was much slower with intrathecal dexmedetomidine when compared with fentanyl group. Time to two segment regressions were significantly more with intrathecal dexmedetomidine when compared to bupivacaine and fentanyl [Table 2]. Duration of motor blockade was significantly highest with intrathecal dexmedetomidine as compared to intrathecal fentanyl which was higher than bupivacaine. The time to receive rescue analgesic was significantly longer in group D as compared to group F which in turn was greater than group B.

Table 2: Sensory and motor block and rescue analgesic requirement

Parameter	Group B (n=30)	Group F (n=30)	Group D (n=30)	p-value
Highest level of spinal blockade (T6:T7: T8)	7:4:19	7:4:19	5:5:20	0.97
Time required for highest spinal level (min)	5.73 ± 1.36	4.40 ± 0.93*	4.50 ± 0.82*	*< 0.001
Time to 2 segment regression of sensory level (min)	72.36 ± 7.04	82.83 ± 8.48	114.17 ± 6.31	< 0.001
Duration of motor blockade (min)	134.33 ± 8.98	166.50 ± 8.72	423.00 ± 12.50	< 0.001
Time to rescue analgesia (min)	124.33 ± 19.06	232.33 ± 12.02	310.00 ± 10.99	< 0.001

Visual Analog Scale Score

At two hours the median VAS score was least in subjects receiving intrathecal dexmedetomidine when compared with intrathecal fentanyl, which was less than bupivacaine alone. This trend was also maintained at four hours also [Table 3].

Table 3: VAS scores

Parameter	Group B (n=30)	Group F (n=30)	Group D (n=30)	p-value
Median VAS score				
At 120 mins	3	2	0.5	< 0.001
At 240 mins	-	3	2	< 0.001
VAS score at rescue analgesia				
Median	5.5	4	4	< 0.001
4, n (%)	5(16.66)	16(53.3)	16(53.3)	-
5, n (%)	10(33.33)	10(33.3)	13(43.33)	-
6, n (%)	9(30)	4(13.33)	1(3.33)	-
7, n (%)	4(13.33)	0	0	-
8, n (%)	2(6.66)	0	0	-

VAS, visual analog scale.

The VAS scores were also compared when first rescue analgesia was administered. Half of the patients had a VAS score of 4 in group D and F at rescue analgesia time. None of the patients in group F and D had a VAS score above 7 when rescue analgesia was given as compared to group B wherein 6 patients (20%) had a VAS score >7. Only one patient had a VAS score of 6 in comparison to 4 patients in group F and 9 patients in group B, inferring a lower VAS score at rescue analgesic requirement time for group receiving dexmedetomidine.

Haemodynamic and Sedation Score

All patients of all groups remained hemodynamically stable intraoperatively as determined by measurement of pulse rate and mean arterial pressure as measured every 5 min up to 30 min (data not shown). The sedation score was higher in group D patients. The mean sedation score was 3.3±0.59 in group D as compared to 2.5±0.63 in group F and 1.9 ± 0.30 in group B which was statistically significant ($p<0.001$). [Figure 1] presents the details of proportion of patients with sedation scores in each group.

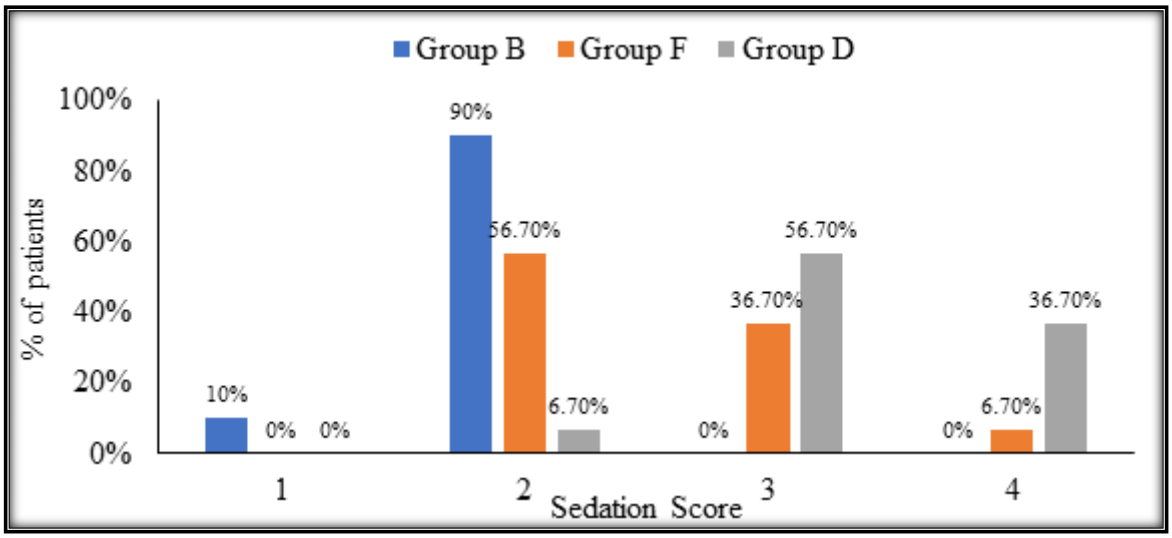

Figure 1: Comparative sedation score

Adverse Effects

Group B patients did not have any side effects while 3 patients experienced itching in group F and 1 patient had hypotension in group D.

DISCUSSION

Central nervous system (CNS) sensitization occurs following surgical incision resulting in amplification of post-operative pain. Prevention of altered central processing reduces post-operative pain and accelerates recovery.[20] Subarachnoid block is routinely administered for lower abdominal procedures to optimize and prolong the quality and duration of postoperative pain relief.[21]

Use of adjuvants with local anaesthetics in the subarachnoid space has several advantages like ease of administration, prolonged pain relief after a single dose, minimal chances of systemic overdoses along with reduced number of painful intramuscular injections required post-operatively as rescue analgesia. They are also safe to be used in patients where NSAID's are contraindicated.[21-23]

Intrathecal α2-adrenoceptor agonists prolong the motor and sensory block of local anaesthetics by binding to presynaptic C-fibres and postsynaptic dorsal horn neurons.[12] Intrathecal α2-receptor agonists have been found to have antinociceptive action for both somatic and visceral pain.[24,25] Fentanyl is a lipophilic μ-receptor agonist opioid. Intrathecally, fentanyl exerts its effect by combining with opioid receptors in the dorsal horn of spinal cord and may have a supraspinal spread and action.[26]

Studies comparing combination of local anaesthetics and intrathecal dexmedetomidine versus intrathecal fentanyl are lacking. This randomised double blind controlled study was done to compare the efficacy and safety of intrathecal fentanyl and intrathecal dexmedetomidine for post-operative analgesia in combination with bupivacaine. It was performed on ninety patients presenting for elective lower abdominal surgeries under spinal anaesthesia with ASA physical status I or II. These patients before induction of anaesthesia were randomised to three groups, with 30 patients in each group. Group b received 12.5 mg of 0.5% hyperbaric bupivacaine +0.5ml NS; group F received 12.5 mg of 0.5% hyperbaric bupivacaine + inj. fentanyl 25 μg while group D received 12.5 mg of 0.5% hyperbaric bupivacaine + inj. dexmedetomidine 10 μg+ 0.4 ml ns. A number of animal studies conducted using intrathecal dexmedetomidine at a dose range of 2.5–100 μg did not report any neurologic deficits with its use.[27-29] In our study, the intrathecal dose of dexmedetomidine selected was based on previous animal studies.[30]

All groups had similar baseline characteristics including duration of surgery. Also, the maximum sensory levels achieved in all three groups were comparable (T6-T8), a result like the study conducted by Gupta et al.[8] The time required to achieve peak sensory level was less with intrathecal dexmedetomidine and fentanyl when compared to the control group although onset of sensory blockade was comparable with fentanyl and dexmedetomidine. Similar results were observed by Gupta et al.[8]

In the present study, duration of sensory block was longer with intrathecal fentanyl and dexmedetomidine when compared to control group. These results are like those observed by Al Mustafa et al.[14] wherein a study on 66 patients undergoing urological procedures reported regression of sensory level by two segments which was significantly prolonged in the group receiving intrathecal dexmedetomidine 10 μgas compared to the groups receiving plain bupivacaine and dexmedetomidine 5 μg.

In the present study, intrathecal dexmedetomidine provides longest duration of motor block than fentanyl, which in turn is longer than the control arm with bupivacaine alone. Kuusniemi et al., also reported longer duration of motor block with fentanyl when added as an adjuvant when compared to bupivacaine alone while study of Ghanem et al., concluded that bupivacaine supplemented with 5 μg dexmedetomidine showed prolonged motor and sensory block compared with 25 μg fentanyl.[12,15,31]

In the present study, degree of analgesia was better with fentanyl and dexmedetomidine in the post-operative period at 2 hrs as compared to the control group. At 4 hrs median VAS score was higher in fentanyl group when compared to dexmedetomidine group inferring that dexmedetomidine provides better degree of pain relief for a longer duration of time. Also, at the time of rescue analgesia the VAS score was low with use of dexmedetomidine and fentanyl. A study comparing bupivacaine with and without fentanyl as adjuvant also concluded that intrathecal 20 µg fentanyl significantly improved the quality of analgesia; prolonged the duration of bupivacaine in spinal anaesthesia and delayed the analgesic requirement in the early post-operative period. Number of studies concluded that pain scores were significantly lower with intrathecal dexmedetomidine at rest, at 8 and 12 hrs and on movement at 4, 8 and 12 hrs.[32,33]

The sedation score was higher with the use of intrathecal dexmedetomidine when compared to fentanyl and control arm; a finding in line with the study of Guptal et al.[8] At a lower dose (3 µg) possibly the observations would have been different as reported by Kanazi et al.[34]

There were no instances of bradycardia or hemodynamic changes in any of the three groups. As far as adverse effects were observed, only one patient receiving dexmedetomidine developed hypotension which was treated with boluses of 6 mg of mephentermine and i.v fluids. Three patients of fentanyl group complained of itching. None of the patients had respiratory depression, episodes of desaturation, urinary retention, headache, nausea, vomiting, shivering or high /total spinal.

The study included a single centre small study with patient pool of ASA I/II only. VAS, a subjective tool was used for assessment of analgesia, which may have led to measurement bias.

CONCLUSION

Dexmedetomidine 12.5 µg seems to be an attractive alternative to 25 µg fentanyl as an adjuvant to spinal hyperbaric bupivacaine in surgical procedures. It provides good quality of intraoperative analgesia, hemodynamically stable conditions, minimal side effects, and excellent quality of postoperative analgesia.

REFERENCES

1. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesthesia and analgesia 2003; 97: 534-40.
2. Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. Current medical research and opinion 2014; 30: 149-60.
3. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet 2006; 367: 1618-25.
4. Elia N, Lysakowski C, Tramèr MR. Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. Anesthesiology 2005; 103: 1296-304.
5. Maund E, McDaid C, Rice S, Wright K, Jenkins B, Woolacott N. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after major surgery: a systematic review. British journal of anaesthesia 2011; 106: 292-7.
6. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the

American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. The Journal of Pain 2016; 17: 131-57.
7. das Neves JF, Monteiro GA, de Almeida JR, Brun A, Cazarin N, Sant'Anna RS, et al. Spinal anesthesia for cesarean section: comparative study between isobaric and hyperbaric bupivacaine associated to morphine. Revista brasileira de anestesiologia 2003; 53: 573-8.
8. Gupta R, Verma R, Bogra J, Kohli M, Raman R, Kushwaha JK. A Comparative study of intrathecal dexmedetomidine and fentanyl as adjuvants to Bupivacaine. Journal of anaesthesiology, clinical pharmacology 2011; 27: 339-43.
9. Shafiei FT, McAllister RK, Lopez J. Bupivacaine. [Updated 2021 Aug 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532883/.
10. Sng BL, Siddiqui FJ, Leong WL, Assam PN, Chan ES, Tan KH, et al. Hyperbaric versus isobaric bupivacaine for spinal anaesthesia for caesarean section. The Cochrane database of systematic reviews 2016; 9: Cd005143.
11. Ryu HY, Kim JY, Lim HK, Yoon J, Yoo BS, Choe KH, et al. Bupivacaine induced cardiac toxicity mimicking an acute non-ST segment elevation myocardial infarction. Yonsei medical journal 2007; 48: 331-6.
12. Al-Ghanem SM, Massad IM, Al-Mustafa MM, Al-Zaben KR, Qudaisat IY, Qatawneh AM, et al. Effect of adding dexmedetomidine versus fentanyl to intrathecal bupivacaine on spinal block characteristics in gynecological procedures: A double blind controlled study. American journal of applied sciences 2009; 6: 882.
13. Hunt CO, Naulty JS, Bader AM, Hauch MA, Vartikar JV, Datta S, et al. Perioperative analgesia with subarachnoid fentanyl-bupivacaine for cesarean delivery. Anesthesiology 1989; 71: 535-40.
14. Al-Mustafa MM, Abu-Halaweh SA, Aloweidi AS, Murshidi MM, Ammari BA, Awwad ZM, et al. Effect of dexmedetomidine added to spinal bupivacaine for urological procedures. Saudi medical journal 2009; 30: 365-70.
15. Kanazi GE, Aouad MT, Jabbour-Khoury SI, Al Jazzar MD, Alameddine MM, Al-Yaman R, et al. Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. Acta anaesthesiologica Scandinavica 2006; 50: 222-7.
16. Gupta R, Verma R, Bogra J, Kohli M, Raman R, Kushwaha JK. A Comparative study of intrathecal dexmedetomidine and fentanyl as adjuvants to Bupivacaine. Journal of anaesthesiology, clinical pharmacology 2011; 27: 339-43.
17. Haynes S, Lawler P. An assessment of the consistency of ASA physical status classification allocation. Anaesthesia 1995; 50: 195-9.
18. Sheahan CG, Mathews DM. Monitoring and delivery of sedation. BJA: British Journal of Anaesthesia 2014; 113: ii37-ii47.
19. Barde MP, Barde PJ. What to use to express the variability of data: Standard deviation or standard error of mean? Perspectives in clinical research 2012; 3: 113-6.
20. Pogatzki-Zahn EM, Segelcke D, Schug SA. Postoperative pain-from mechanisms to treatment. Pain reports 2017; 2: e588.
21. Swain A, Nag DS, Sahu S, Samaddar DP. Adjuvants to local anesthetics: Current understanding and future trends. World J Clin Cases 2017; 5: 307-23.
22. Nersesyan H, Slavin KV. Current aproach to cancer pain management: Availability and implications of different treatment options. Ther Clin Risk Manag 2007; 3: 381-400.
23. Sullivan D, Lyons M, Montgomery R, Quinlan-Colwell A. Exploring Opioid-Sparing Multimodal Analgesia Options in Trauma: A Nursing Perspective. Journal of Trauma Nursing | JTN 2016; 23: 361-75.

24. Eisenach JC, De Kock M, Klimscha W. alpha(2)-adrenergic agonists for regional anesthesia. A clinical review of clonidine (1984-1995). Anesthesiology 1996; 85: 655-74.
25. Kalso EA, Pöyhiä R, Rosenberg PH. Spinal antinociception by dexmedetomidine, a highly selective alpha 2-adrenergic agonist. Pharmacology & toxicology 1991; 68: 140-3.
26. Bujedo BM, Santos SG, Azpiazu AU. A review of epidural and intrathecal opioids used in the management of postoperative pain. Journal of opioid management 2012; 8: 177-92.
27. Talke P, Xu M, Paloheimo M, Kalso E. Effects of intrathecally administered dexmedetomidine, MPV-2426 and tizanidine on EMG in rats. Acta anaesthesiologica Scandinavica 2003; 47: 347-54.
28. Xu M, Kontinen VK, Kalso E. Effects of radolmidine, a novel alpha2 -adrenergic agonist compared with dexmedetomidine in different pain models in the rat. Anesthesiology 2000; 93: 473-81.
29. Horvath G, Joo G, Dobos I, Klimscha W, Toth G, Benedek G. The synergistic antinociceptive interactions of endomorphin-1 with dexmedetomidine and/or S(+)-ketamine in rats. Anesthesia and analgesia 2001; 93: 1018-24.
30. Lo WC, Harris J, Clarke RW. Endogenous opioids support the spinal inhibitory action of an alpha 2-adrenoceptor agonist in the decerebrated, spinalised rabbit. Neuroscience letters 2003; 340: 95-8.
31. Subhi MA-G, Islam MM, Mahmoud MA-M, Khaled RA-Z, Ibrahim YQ, Ayman MQ, et al. Effect of Adding Dexmedetomidine versus Fentanyl to Intrathecal Bupivacaine on Spinal Block Characteristics in Gynecological Procedures: A Double Blind Controlled Study. American Journal of Applied Sciences 2009; 6:
32. Eid H, Shafie MA, Youssef H. Dose-related prolongation of hyperbaric bupivacaine spinal anesthesia by dexmedetomidine. Ain Shams J Anesthesiol 2011; 4: 83-95.
33. Techanivate A, Urusopone P, Kiatgungwanglia P, Kosawiboonpol R. Intrathecal fentanyl in spinal anesthesia for appendectomy. Journal of the Medical Association of Thailand= Chotmaihet thangphaet 2004; 87: 525-30.
34. Srinivasan R. A Study of clinical effects of Intra Thecal Ropivacaine and Ropivacaine with Dexmedetomidine in Inguinal Hernia Cases: A Study of 60 cases. 2013, Tirunelveli Medical College, Tirunelveli.