Original Article

A Comparison of Dexmedetomidine and Fentanyl as an Adjuvant to Intrathecal Hyperbaric Bupivacaine in Elective Lower Limb Surgeries

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ABSTRACT

Background: Spinal block is a popular modality for lower limbs surgery. Various adjuvant is being use to improve the quality and duration of anesthesia and analgesia. So, we compare the efficacy of fentanyl and dexmedetomidine added to intrathecal bupivacaine in spinal block**.**

Methods: In this prospective observational study, 30 patients undergoing elective lower limb surgeries in the age group 18-60 years belonging to both sexes, patients were allocated into two groups. Via intrathecal approach, the patients received injection bupivacaine heavy (0.5%) 3.0 ml plus injection dexmedetomidine 10μg in Group D (n=15), injection fentanyl 25μg in Group F (n=15) respectively. Time to reach modified Bromage 3 motor block, the highest sensory level and regression from block, rescue analgesic request and duration of the drug effect, hemodynamic changes and side effects were compared between the groups.

Result: The onset times to reach T10 dermatome and complete motor block were not significantly different between the groups. But Group D had significantly longer sensory and motor block times than patients in Group F. Dexmedetomidine group showed significantly less and delayed requirement of rescue analgesic. The heart rate (HR) and mean arterial pressure (MAP) were comparable between the groups.

Conclusions: Using highly selective α_2 adrenergic agonist dexmedetomidine 10 micrograms is a valuable adjuvant to bupivacaine for spinal block lower limb surgeries which augments quality of spinal block and provides intraoperative sedation and hemodynamic stability.

Key words: Dexmedetomidine, Fentanyl, Hyperbaric Bupivacaine, Spinal block.

INTRODUCTION

Spinal block is a popular modality for lower abdominal and lower limb surgery. It has the benefit of simple procedure, quicker onset of action and dependability in generating generalized sensory and motor blockade. Its demerit is shorter duration and hence devoid of long-lasting postoperative analgesia.

To surpass this issue, administration of local anesthetics in permutation with different adjuvant is a fair method which provides early commencement and prolonged duration of sensory and motor blockade of subarachnoid block and hence acts as synergistic to local anesthetics with lower local anesthetic requirement, reduced side effects and excellent postoperative analgesia. Good pain control has the potential to allow earlier hospital discharge and may improve the patient's ability to tolerate physical therapy.[1]

Different agents, like opioids, α_2-agonists, vasoconstrictors, adenosine and magnesium sulfate, have been used as adjuncts to local anesthesia for prolonging the duration of spinal analgesia via the intrathecal route.[2]

Dexmedetomidine is highly selective α_2-adrenoceptor agonist activity, especially for the $\alpha_{2\Lambda}$ receptor subtype, making it a more effective analgesic, sedative, anti-anxiety, hypnotic, neuroprotective and anesthetic-sparing effects than clonidine and free of undesirable cardiovascular effects related to α_1 receptor activation.[3,4] Dexmedetomidine along with other drugs have been used to increase the duration of analgesia in subarachnoid, epidural and caudal blocks.[5,6] Most of the clinical studies about the intrathecal α_2-adrenergic agonist are related to clonidine.[7] There is little in the literature about the use of intrathecal dexmedetomidine with local anesthesia in humans.

Fentanyl is a μ receptor agonist centrally acting synthetic opioid, which is used widely for pain control. Intrathecal fentanyl is usually added to other local anesthetics to increase anesthesia and analgesia.[8] It has improved spinal anesthesia and reduces visceral and somatic pain.[9] However, their addition may have side effects like pruritus, respiratory depression, urinary retention, postoperative nausea and vomiting which limits their use.[10]

Dexmedetomidine and fentanyl have been used as adjuvant to local anesthetics in different surgeries to provide superior analgesia and to improve the duration of the block.[11,12] Based on earlier human studies, it was hypothesized, dexmedetomidine 5μg added to 0.5% bupivacaine heavy produces profound postoperative analgesia with minimal side effects.[13,14]

So, we compare the efficacy of dexmedetomidine 10μg versus fentanyl 25μg on intraoperative analgesia and the duration of sensory and motor block when added to 15mg intrathecal hyperbaric bupivacaine in spinal block**.**

METHOD

After obtaining approval from the Institutional Ethic Committee (IEC) along with written informed consent from patients, present study was carried out in the Department of Anesthesiology between July 2021 and September 2021 at orthopedic operating room in SMIMER Hospital, Surat (Guj.), India. This was a prospective, observational study.

Study population: Thirty ASA I, II patients of both sex and aged between 18-60 years posted for elective lower limb orthopedic surgery under spinal block were enrolled in the study. A thorough pre-anesthetic evaluation and necessary investigations were carried out. All patients were examined and investigated a day prior to surgery, and were familiarized with visual analogue scale[15] (VAS) and its use for measuring the postoperative pain. They were advised fasting for 6 hours before the surgery.

Exclusion criteria: Patients who had contraindications for spinal anesthesia like patient refusal, coagulation disorders, on anticoagulants, infection at the site of injection, spinal deformity, allergic to amide local anesthetics and a significant history of drug or alcohol abuse, morbid obesity (body mass index >29 kg/m^2), cardiovascular, neurologic, or other systemic illness, ASA grade III or more, musculoskeletal and psychiatric diseases that could make our technique difficult were excluded.

Basis of sample size: Based on previous study (Divya VS, et al 2021),[1] sample size of total 30 (**n=15** cases per each group) was calculated by using Open EPI software considering, Time from injection to achieve sensory level T10 (min) of **Group F:** Fentanyl is (03.38±0.83) & **Group D:** Dexmedetomidine is (02.62±0.56) at a power of 80% and confidence interval of 95%, a minimum sample size of 14 patients in each group was required. We enrolled 15 (Sample size = 30; n_F= 15, n_D= 15) patients in each group to compensate for dropouts.

Randomization and group allocation: Thirty study patients were randomized using sealed envelope technique into two groups of 15 each, depending on the drug regime used for spinal block as follows:

Table 1: Grouping for The Study

Group F, (n=15)	Intrathecal 0.5% hyperbaric bupivacaine 15mg (3.0ml) plus Fentanyl 25µg (0.5ml)
Group D, (n=15)	Intrathecal 0.5% hyperbaric bupivacaine 15mg (3.0ml) plus Dexmedetomidine 10µg (0.1ml)

Spinal anesthesia technique: Following arrival in the pre-anesthetic room, peripheral venous access was secured on hand with 18G cannula and pre-loading with Inj. Ringer Lactate 10-15 ml/kg was initiated. All patients were premedicated with Inj. Glycopyrrolate 0.2mg and Ondensetron 4mg IV in operation theatre. Standard monitoring was used throughout the operation with the help of a multipara-monitor having Heart Rate (HR), Noninvasive blood pressure (NIBP), Electrocardiography (ECG) and Pulse Oximetry (SpO2). Baseline blood pressure, heart rate and SpO2 were recorded.

Patients were placed in sitting position and after taking full aseptic precautions, spinal block was performed in L3-L4 inter-vertebral space in midline or Para median approach by a 25G Quincke spinal needle. Correct needle placement was identified by free flow of clear cerebrospinal fluid (CSF). Then study drug was injected in subarachnoid space according to group allocation as 3ml of 0.5% hyperbaric bupivacaine (15mg) plus Fentanyl 25µg (0.5ml) in group F and 3ml of 0.5% hyperbaric bupivacaine (15mg) plus Dexmedetomidine 10µg (0.1ml) in group D. After the injection patient was placed supine. The end of intrathecal injection of study drug was termed as **"Time Zero"** for the purpose of subsequent patient assessment. Parameters observed & compared included 1) Onset of sensory and motor block; 2) Duration of sensory and motor block; 3) Hemodynamic changes during intra & post operatively (SBP, DBP, MAP and HR); 4) Duration of analgesia and Rescue Analgesia; and 5) Side effects and complications during intra & post operatively (if any).

Data recording: All data were recorded in a Performa, The onset of sensory block was defined as the time between injection of intrathecal anesthetic and the absence of pain at the T10 dermatome assessed by sterile pinprick test[16] using 24 gauge hypodermic needle at every 2 min till T10 dermatome was achieved. The highest level of sensory block was evaluated by pinprick at mid-clavicular line anteriorly every 2 min for 10 min after the injection, thereafter every 15 min. The duration of sensory block was defined as the time of regression of two segments in the maximum block height, evaluated by pinprick. The motor level was assessed according to Modified Bromage score as per.[16,17] [Table 2]

Table 2: Modified Bromage Score

Bromage 0 (none)	The patient is able to move the hip, knee, and ankle
Bromage 1 (Partial)	The patient is unable to move the hip, but is able to move the knee & ankle
Bromage 2 (Almost complete)	The patient is unable to move hip & knee, but is able to move the ankle
Bromage 3 (Complete)	The patient is unable to move the hip, knee, and ankle

Time for motor block onset was defined as modified Bromage score of 3. Complete motor block recovery was assumed when modified Bromage score was 0. The duration of spinal anesthesia was defined as the period from spinal injection to the first occasion when the patient complained of pain in the postoperative period. All durations were calculated considering the time of spinal injection as **"Time Zero".**

Surgery was allowed to commence on achieving adequate sensory block height (T10). Vitals were recorded at every 2 min for 10 min after the injection, thereafter every 15 minutes. Intraoperative fluid and blood transfusion were given as per losses and maintenance required.

Hypotension was described as > 20% fall of baseline blood pressure, treated with crystalloid fluids and 6mg mephenteremine IV, Bradycardia defined as HR < 50 beats/min, treated with 0.5mg atropine IV, Respiratory depression was defined as respiratory rate < 9 breaths/min and SpO2 <90% on room air, incidence of pruritus, nausea, vomiting, and sedation were also recorded.

In postoperative phase, for recovery characteristics, sensory and motor block regression were assessed every 15min after completion of surgery till the time of regression of two segments in maximum block and modified bromage score returns to zero (complete motor recovery) in the Post Anesthesia Care Unit (PACU) along with the vital signs and VAS scores. Any patient showing VAS more than or equal to 3 was administered a supplemental dose of Inj. Tramadol 50mg IV. The amount required by the patients in the next 24 hours was recorded in all the groups.

Statistical analysis: Data was analyzed and expressed as Mean ± standard deviation or percentage as applicable. Comparison between two groups was done using independent t test for quantitative data and chi-square test for qualitative data. P value < 0.05 is considered significant.

Statistical methods: Data were collected; tabulated, coded then analyzed using Statistical Package for Social Science SPSS @ version 20.0 software. Numerical variables were presented as Mean ± standard deviation, while categorical variables were presented as percentage. As regard numerical variables, independent t test was done. [Table-3]

Table 3: P Value interpretation

P value > 0.05	Non-Significant
P value < 0.05	Significant
P value < 0.001	Highly Significant

RESULTS

All patients (n=30) completed the study; there was no statistical difference in patients' demographics or duration of surgery as shown in Table 4.

Table 5 shows the number of patients in each group undergoing different types of lower limb surgeries. The numbers of patients under each type of surgery performed on the lower limb were similar amongst the groups thereby keeping the comparison unbiased.

When compared the time of onset of both, sensory and motor block was statistically insignificant in both groups. (P > 0.05) [Table 6] T8 was the highest level of sensory block attained at 9.6 ± 2.9 min & 10.3 ± 3.3 min after injection in group F and D; respectively. However; 80.0% and 70.0% of patients in groups F and D had sensory block to a level of T10 at 8.6 ± 1.5min & 8.3 ± 2.4min after the injection (statistically insignificant). T10 sensory level was achieved in all patients. However, there were patients with level progressing further to the highest sensory level of T8.

The duration of sensory block, duration of motor block and duration of spinal anesthesia was significantly prolonged in group D as compared to group F (P < 0.0001) [Table 6].

Table 4: Patients Demographics

Variable Group	Group F (n=15)	Group D (n=15)	P value
Age (years)	38.1±13.5	37.8±15.6	0.59
Sex (M:F)	9:6	7:8	0.44
ASA (I:II)	7:8	10:5	0.22
Height (cm)	168.2±6.0	169.6±5.5	0.51
Weight (kg)	63.6±11.2	66.6±7.9	0.40
Duration of surgery (min)	101.6±36.3	110.8±33.7	0.47

*__ASA__=American society of anesthesiology, **M**=Male, **F**=Female, Values are Mean ± Standard Deviation (SD)

Table 5: Type of Lower Limb Surgeries Performed

Type of lower limb surgeries performed	Group F (n=15)	Group D (n=15)
Tibia ORIF	7	5
Shaft of femur ORIF	5	7
Anteriorcruciate ligament reconstruction	3	3

*** ORIF:** Open reduction internal fixation, Values are in number of patients.

The mean values of mean arterial pressure (MAP) and heart rate (HR) were comparable between the two groups throughout the intraoperative and postoperative periods [Figures 1 and 2]. None of the patients experienced respiratory distress at any point of time. All patients had peripheral oxygen saturation (SpO2) greater than 96% at all the times and did not require additional oxygen in Post Anesthesia Care Unit (PACU). No significant difference was observed in the sedation score with patients in all groups having score of 1.

In Figure 1: Heart Rate (HR) values are mean ± standard deviation (SD). No significant differences were noted between the groups. In Figure 2: Mean arterial pressure (MAP) values are mean ± SD. No significant differences were noted between the groups.

Pruritus was observed only in group F in one patient (6.7 %) at different intervals of time, Bradycardia was observed in both the group one-one patients (6.7 %), but there were no significant differences between two groups regarding the side effects. [Table 7]

Lower visual analogue scale (VAS <3) were observed in all the groups during the whole duration of the surgery and none of the patients required additional analgesics intra-operatively. Postoperative VAS scores and total analgesic requirement in 24 h were minimal in group D (P value < 0.001) [Table-8].

Table 6: Characteristics Of Spinal Block

Variable (Min)	Group F (n=15)	Group D (n=15)	P Value
Time of onset of sensory block (T10)	8.6±1.5	8.3±2.4	**0.684**
Time of onset of motor block	9.0±3.0	9.7±3.2	**0.541**
Time to reach maximum sensory level (T8)	9.6±2.9	10.3±3.3	**0.542**
Duration of sensory block	119.5±22.7	146.7±20.5	**0.001**
Duration of motor block	196.0±26.8	273.3±24.6	**0.001**
Duration of spinal anaesthesia	235.5±38.3	295.5±44.3	**0.001**

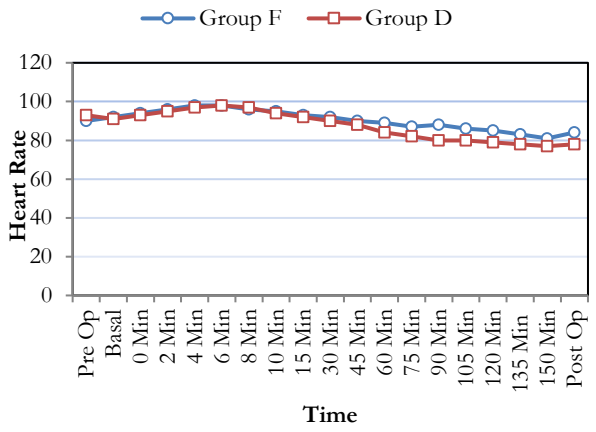

Figure 1: Comparison of Heart Rate between two groups

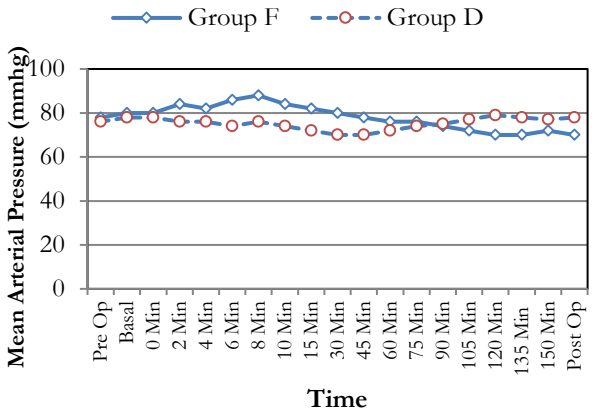

Figure 2: Comparison of Mean arterial pressure between two groups

Table 7: Side Effects between Groups

Side effects	Group F (n=15)	Group D (n=15)
Nausea	0	0
Vomiting	0	0
Chilling	0	0
Pruritus	1 (6.7 %)	0
Hypotension	0	0
Bradycardia	1 (6.7 %)	1 (6.7 %)

Table 8: Comparison of visual analogue scale

VAS	Group F (n=15)	Group D (n=15)	P Value
6 hours	3.00±0.31	0.00±0.00	**0.001**
12 hours	4.90±0.87	2.50±0.51	**0.001**
18 hours	5.28±0.64	3.52±0.25	**0.001**
24 hours	5.24±0.96	4.62±0.69	**0.051**

DISCUSSION

Present results in this study showed that the supplementation of spinal bupivacaine with 10µg dexmedetomidine significantly prolonged both sensory and motor block compared with intrathecal 25µg fentanyl and bupivacaine in elective lower limb surgery.

Both fentanyl and dexmedetomidine improved the quality of intraoperative analgesia and diminished the risk of supplementation of general anesthesia. Fentanyl is a lipophillic µ-receptors agonist opioid. Intrathecally, fentanyl exerts its effect by combining with opioid receptors in the dorsal horn of spinal cord and may have a supra spinal spread and action.[18,19] Intrathecal fentanyl prolongs the duration of spinal anesthesia produced by bupivacaine and lignocaine and this effect has been shown in various surgeries.[20,21] The prolongation of the duration of spinal analgesia produced by intrathecal fentanyl is not a dose related.

Dexmedetomidine is a highly selective α_2-adrenoreceptor agonist approved as intravenous sedative and adjuvant to anesthesia. Dexmedetomidine when used intravenously during anesthesia reduces opioid and inhalational anesthetics requirements.[22,23] Intrathecal dexmedetomidine when combined with spinal bupivacaine prolongs the sensory block by depressing the release of C-fibers transmitters and by hyperpolarization of post-synaptic dorsal horn neurons. Motor block prolongation by α_2-adrenoreceptor agonists may result from binding these agonists to motor neurons in the dorsal horn of the spinal cord. Intrathecal α_2-adrenoreceptor agonists have been found to have antinoniceptive action for both visceral and somatic pain.[24-27]

In our study, we also found that time taken for sensory & motor block did not change significantly, but duration of sensory block & motor block was significantly longer in dexmedetomidine group (146.7 ± 20.5 min & 273.3 ± 24.6 min) than in the fentanyl group (119.5 ± 22.7 min & 196.0 ± 26.8 min) respectively. Even the mean time for postoperative analgesia was significantly longer in dexmedetomidine group (10.6 hours) than in the fentanyl group (5.55 hours).

Subhi M Al-Ghanem et al.,[28] study also winded up that 5µg dexmedetomidine seems to be a suitable adjuvant to spinal bupivacaine in surgical procedures especially in long surgeries with minimal side effect and excellent quality of analgesia. Al Mustafa et al.,[29] Abdullah et al.[30] & Wu HH et al.,[31] also found similar increase in the duration of spinal block after adding dexmedetomidine as a neuraxial adjuvant, facilitating better anesthesia and analgesia. Kanazi et al.[2] & Jung et al.,[32] also did their studies on dexmedetomidine and found quite similar results to our studies. In 2006, Kanazi et al.,[2] found that intrathecal dose of dexmedetomidine (3µg) used with bupivacaine for spinal anesthesia have been shown to produce a rapid onset of motor blockade and a prolongation in the duration of sensory and motor blockade with hemodynamic stability and lack of sedation.

Various other studies such as Shani et al.,[33] who compared magnesium sulphate to dexmedetomidine also pointed out the importance of adding low dose dexmedetomidine as adjuvant. Solanki et al.[34] & Reddy et al.,[35] compared dexmedetomidine with clonidine & found out dexmedetomidine to be a better adjuvant for subarachnoid block than clonidine. R Gupta et al.,[22] who compared dexmedetomidine & fentanyl as adjustments to bupivacaine & Halder et al.,[36] studied different doses of dexmedetomidine.

In Rajani Gupta et al.,[22] have done comparative study of intrathecal fentanyl and dexmedetomidine as adjuvant to bupivacaine. 60 patients classified in ASA I & II scheduled for lower abdominal surgeries were studied. Patients randomly allocated to receive 12.5mg hyperbaric bupivacaine

(2.5ml) plus 5µg dexmedetomidine (group D) or 12.5 mg hyperbaric bupivacaine (2.5ml) plus 25µg fentanyl (group F) intrathecal. They found that patients in group Dexmedetomidine had a significantly longer sensory and motor block time than patients in group Fentanyl. The mean time of sensory and motor regression is longer in dexmedetomidine than fentanyl.

Hanoura at al.,[37] compared dexmedetomidine with fentanyl in terms of intraoperative condition & quality of postoperative analgesia in caesarian sections and found results similar to our studies.

CONCLUSION

Using highly selective α_2-adrenergic agonist dexmedetomidine 10µg is good alternative to fentanyl 25µg as an valuable adjuvant to 0.5% hyperbaric bupivacaine for spinal block lower limb surgeries which augments quality of spinal block and provides a better quality of perioperative / intraoperative analgesia, intraoperative sedation, hemodynamic stability, minimal side effects and reduced demand for rescue analgesics in 24 hours as compared to fentanyl. Hence, Dexmedetomidine seems to be a good choice as Intrathecal adjuvant with hyperbaric Bupivacaine.

The findings of our study are limited by several limitations:

First, our study was limited to patients scheduled for elective surgery and results of this study are applicable to these (young and healthy) patients only. **Second,** the effects in older patients with cardiovascular and others co-morbidities are yet to be investigated. **Third,** this study also lacks an active control for systemic effects of dexmedetomidine.

RECOMMENDATIONS

Further studies that compare effect of systemic versus intrathecal dexmedetomidine on spinal Bupivacaine may also be warranted.

REFERENCES

1. Divya VS, Raghu R, Indira P, Roy S. Comparison of dexmedetomidine and fentanyl as adjuvants to 0.5% hyperbaric bupivacaine in spinal anesthesia in elective lower abdominal surgeries. Indian J Clin Anaesth 2021;8(2):257-264.
2. Kanazi GE, Aouad MT, Jabbour-Khoury SI, Al Jazzar MD, Alameddine MM, Al-Yaman R, Bulbul M, Baraka AS. Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block.ActaAnaesthesiol Scand. 2006 Feb;50(2):222-7.
3. Kalso EA, Pöyhiä R, Rosenberg PH. Spinal antinociception by dexmedetomidine, a highly selective alpha 2-adrenergic agonist. Pharmacol Toxicol 1991; 68:140-143.
4. Panzer O, Moitra V, Sladen RN. Pharmacology of sedative-analgesic agents: Dexmedetomidine, remifentanil, ketamine, volatile anesthetics, and the role of peripheral mu antagonists. Crit Care Clin. 2009;25(3):451–69. Vii
5. Bekker A, Sturaitis M, Bloom M, Moric M, Golfinos J, Parker E, Babu R, Pitti A. The effect of dexmedetomidine on preoperative hemodynamics in patients undergoing craniotomy. Anesth Analg. 2008;107(4):1340–7.
6. Sudheesh K, Harsoor S. Dexmedetomidine in anaesthesia practice: a wonder drug? Indian J Anaesth. 2011;55(4):323–4.
7. Elia N, Culebras X, Mazza C, Schiffer E, Tramer MR. Clonidine as an adjuvant to intrathecal local anesthetics for surgery: Systematic review of randomized trials. Reg Anesth Pain Med 2008;33:159-67.
8. Liu SS, McDonald SB. Current issues in spinal anesthesia. Anesthesiology. 2001;94(5):888–906.
9. Ummenhofer WC, Arends RH, Danny SD. Comparative spinal distribution and Clearance Kinetics of Intrathecally administered Morphine, Fentanyl, Al Fentanyl and Sufentanil. Anesthesiology. 2000;92:739–53.
10. Bogra J, Arora N, Srivastava P. Synergistic effect of intrathecal fentanyl and bupivacaine in spinal anesthesia for cesar.
11. Mohamed T, Susheela I, Balakrishnan BP, Kaniyil S. Dexmedetomidine as adjuvant to lower doses of intrathecal bupivacaine for lower limb orthopedic surgeries. Anesth Essays Res. 2017;11(3):681–5.
12. Farooq N, Singh RB, Sarkar A, Rasheed MA, Choubey S. To evaluate the efficacy of fentanyl and Dexmedetomidine as adjuvant to Ropivacaine in brachial plexus block: a double-blind, prospective. Randomized Study Anesth Essays Res. 2017;11(3):730–9.
13. Khan ZP, Ferguson CN, Jones RM. Alpha-2 and imidazoline receptor agonists Their pharmacology and therapeutic role. Anaesthesia. 1999; 54(2): 146–65. doi:10.1046/j.1365-2044. 1999.00659.x.
14. Abu-Halaweh AMM, Aloweidi SA, Murshidi AS, Ammari MM, Awwad BA, M Z. Effect of dexmedetomidine added to spinal.
15. Katz J, Melzack R. Measurement of pain. Surg Clin North Am 1999;79:231-52.
16. Vanna O, Chumsang L, Thongmee S. levobupivacaine and bupivacaine in spinal anesthesia for transurethral endoscopic surgery. J Med Assoc Thai 2006; 89 : 1133-9.
17. Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. Acta Anaesthesiol Scand Suppl 1965;16:55-69.
18. Shende D, Cooper GM, Bowden MI. The influence of intrathecal fentanyl on the characteristics of subarachnoid block for caesarean section. Anaesthesia 1998; 79: 702-710. DOI : 10.1046/j.1365-2044.1998.329-az0482.x.
19. Choi Dw, Ahn HJ, Kim MH. Bupivacaine-sparing effect of fentanyl in spinal anesthesia for Cesarean delivery. Reg Anesth Pain Med 2000; 25: 240-245. http://www.ncbi.nlm.nih.gov /pubmed/10834777.
20. Kuusniemi KS, Pihlajamaki KK, Pitkanen MT, Helenius HY, Kirvela OA. The use of bupivacaine and fentanyl for spinal anesthesia for urologic surgery. Anesth Analg 2000; 91: 1452-1456. http://www.ncbi.nlm.nih.gov/pubmed/11093999.
21. Palmer CM, Voulgaropoulos D, ASlves D. Subarachnoid fentanyl augments lidocaine spinal anesthesia for Cesarean delivery. Region Anesth Pain Med 1995; 20: 389-394. http://www.ncbi.nlm.nih.gov/pubmed/8519715.
22. Rajani Gupta, Reetu Verma, Jaishi Bogra, Monica Kohli, Rajesh Raman, Jitendra Kumar Kushwaha, et alA comparative study of intrathecal dexmedetomidine and fentanyl as adjuvants to bupivacaine.JOACP2011;27:339-343.

23. Ibrahim F. A. Khalifa. A comparative study of adding intrathecal dexmedetomidine versus sufentanil to heavy bupivacaine for postoperative analgesia in patients undergoing inguinal herniarepair. Benha medical journal2009; 26:3:207-19.

24. Lawhead RG, Blaxall HS, Bylund BD. Alpha2A is the predominant -2 adrenergic receptor subtype in human spinal cord. Anesthesiology 1992;77:983-91. http://www.ncbi.nlm.nih.gov/pubmed/1359811 7-30. Smith MS, Schumbra UB, Wilson KH et al. Alpha 2 adrenergic receptor in human spinal cord: specific localized expression of mRNA encoding alpha-2 adrenergic receptor subtypes at four distinct levels. Brain Res 1995; 34: 109-17 http://www.ncbi.nlm.nih.gov/pubmed/8750866.

25. Yaksh TL. Pharmacology of spinal adrenergic systems which modulate spinal nociceptive processing. Pharmacol Biochem Behav 1985; 22:845-58 http://www.ncbi.nlm.nih.gov/pubmed/2861606.

26. Harada Y, Nishioka K, Kitahata LM, et al. Visceral antinociceptive effects of spinal clonidine combined with morphine, enkephalin, or U50, 488H. Anesthesiology 1995;83:344-52 http://www.ncbi.nlm.nih.gov/pubmed/7631957.

27. Yaksh TL, Reddy SVR. Studies in primate on the analgesic effects associated with intrathecal actions of opiates, -adrenergic agonists, and baclofen. Anesthesiology 1981; 54:451-67 http://www.ncbi.nlm.nih.gov/pubmed/6112935.

28. Subhi M. Al-Ghanem, Islam M. massad, Mohamoud M. Al-Mustafa, khaled R. Al-Zaben, Ibrahim Y Qudaisat, Ayman m Qatanweh et al.Effect of addingDexmedetomidine versus Fentanyl to Intrathecal Bupivacaine on spinal block characteristics in gynecological procedures: A double blind controlled study. American journal of applied sciences 2009; 6:882-87.

29. Al-Mustafa MM, Abu-Halaweh SA, Aloweidi AS, Murshidi MM, Ammari BA, Awwad ZM, Al-Edwan GM, Ramsay MA. Effect of dexmedetomidine added to spinal bupivacaine for urological procedures. Saudi medical journal. 2009;30(3):365-70.

30. Abdallah FW, Abrishami A, Brull R. The facilitatory effects of intravenous dexmedetomidine on the duration of spinal anesthesia: a systematic review and meta-analysis. Anesthesia & Analgesia. 2013 Jul 1;117(1):271-8.

31. Wu HH, Wang HT, Jin JJ, Cui GB, Zhou KC, Chen Y, Chen GZ, Dong YL, Wang W. Does dexmedetomidine as a neuraxial adjuvant facilitate better anesthesia and analgesia? A systematic review and meta-analysis.PLoS One. 2014 Mar 26;9(3):e93114. doi: 10.1371/journal. pone.0093114. eCollection 2014.

32. Jung SH, Lee SK, Lim KJ, Park EY, Kang MH, Lee JM, Lee JJ, Hwang SM, Hong SJ. The effects of singledose intravenous dexmedetomidine on hyperbaric bupivacaine spinal anesthesia.J Anesth. 2013 Jun;27(3):380-4. doi: 10.1007/s00540-012-1541-0. Epub 2013 Jan 10.

33. Shahi V, Verma AK, Agarwal A, Singh CS. A comparative study of magnesium sulfate vsdexmedetomidine as an adjunct to epidural bupivacaine.Journal of Anaesthesiology Clinical Pharmacology. 2014 Oct 1;30(4):538.

34. Solanki SL, Bharti NA, Batra YK, Jain A, Kumar P, Nikhar S. The analgesic effect of intrathecaldexmedetomidine or clonidine, with bupivacaine, in trauma patients undergoing lower limb surgery: a randomised, double-blind study. Anaesthesia and intensive care. 2013 Jan 1;41(1):51.

35. Reddy VS, Shaik NA, Donthu B, Sannala VK, Jangam V. Intravenous dexmedetomidine versus clonidine for prolongation of bupivacaine spinal anesthesia and analgesia: A randomized double-blind study. Journal of Anaesthesiology Clinical Pharmacology. 2013 Jul 1;29(3):342.

36. Halder S, Das A, Mandal D, Chandra M, Ray S, Biswas MR, Mandal P, Das T. Effect of different doses of dexmedetomidine as adjuvant in bupivacaineinduced subarachnoid block for traumatized lower limb orthopaedic surgery: A prospective, double-blinded and randomized controlled study. J ClinDiagn Res. 2014 Nov 1;8.

37. Hanoura SE, Hassanin R, Singh R. Intraoperative conditions and quality of postoperative analgesia after adding dexmedetomidine to epidural bupivacaine and fentanyl in elective cesarean section using combined spinal-epidural anesthesia. Anesthesia, essays and researches. 2012 Dec;7(2):168-72.