ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 11, Issue, 08, pp.5972-5976, August, 2019

DOI: https://doi.org/10.24941/ijcr.36309.08.2019

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

A COMPARATIVE STUDY OF INTRATHECAL BUPIVACAINE ALONE AND WITH FENTANYL AND DEXMEDETOMIDINE AS ADJUVANTS FOR POST-OPERATIVE ANALGESIA UNDER SPINAL ANAESTHESIA

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ARTICLE INFO

Article History:
Received 28th May, 2019
Received in revised form
20th June, 2019
Accepted 24th July, 2019
Published online 31st August, 2019

Key Words:

Post-op Analgesia, Fentanyl, Dexmedetomidine, Bupivacaine

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ABSTRACT

Background: Postoperative pain occurs due to the peripheral tissue injury which provokes peripheral and central sensitization. Several modalities have been developed, using analgesics and adjuvant drugs, to assure complete pain relief in perioperative period. Spinal anaesthesia, is a popular and common technique used worldwide, for lower limb and lower extremity surgeries. However, post-operative pain control is a major problem with using local anesthetics alone in subarachnoid block, because of relatively short duration of action. Regional techniques with adjuvant drugs are effective in control of post-operative pain. **Objectives:** This study is aimed at evaluating and comparing the efficacy of Fentanyl and Dexmedetomidine as adjuvants to 0.5% Bupivacaine, for post-operative analgesia in terms of- a. Onset and duration of sensory and motor block. b. Duration of post-operative analgesia. c. Observe side effects if any. **Material & methods:** This prospective, randomized, comparative, double-blind clinical study was conducted at St. Stephen's Hospital, Delhi, on 90 patients between the age group of 15-70 years, belonging to ASA class I and II, who were to undergo any lower abdominal or lower limb surgery under subarachnoid block. The patients were randomly allocated into 3 groups of 30 each: Group B: Bupivacaine 0.5% 3.0ml + 0.5ml saline. Group F: Bupivacaine 0.5% 3.0ml + 0.5ml Fentanyl (25ug). Group D: Bupivacaine 0.5% 3.0ml + Dexmedetomidine (5ug) **Results:** 1. The mean duration of complete analgesia for group B was 150± 26 minutes, 215.3 ± 30.9 for group F and 252.2 ± 33.4 for group D. This was found to be stastically significant (p Value=0.00). 2. The mean duration of 1st analgesic medication requirement for group B was 182.03± 31.99 minutes, 255.1 ± 36.15 minutes for group F and 310.5± 38.6 minutes for group D. This was found to be stastically significant (p Value=0.00). 3. The incidence of Hypotension and Bradycardia was significantly higher in Group D as compared to group B and group F (P=0.002 and 0.002 respectively). 4. The incidence of Pruritus was significantly higher in group F as compared to group D and Group B (P=0.005). **Conclusion:** The conclusions that were drawn from the study can be summarized as follows: The addition of Dexmedetomidine may benefit patients undergoing lower limb surgery or lower abdominal surgeries under spinal anaesthesia in terms of prolongation of analgesic-time and reduction of analgesic dose without any major side effect.

Citation: MohitArora, Kanika Gupta and Vaibhav Tewari, **2019.** "A comparative study of intrathecal bupivacaine alone and with fentanyl and dexmedetomidine as adjuvants for post-operative analgesia under spinal anaesthesia", *International Journal of Current Research*, 11, (08), 5972-5976.

INTRODUCTION

Pain is among the most concerning ailments for the patient as well as the doctor. In words of John Milton *"pain is the perfect misery*". No analgesic has been ideal for management of post-operative pain and search for a better alternative continues. Post-operative analgesic modalities include oral/parenteral analgesics, peripheral nerve blocks, intra-spinal opioids and non- opioid adjuvants in neuraxial blocks. Spinal Anesthesia was first introduced by Karl August Bier in 1898 performed with 3ml of 0.5% cocaine intrathecally (Bier, 1962). Spinal Anesthesia offers many advantages like an awake patient, simplicity of administration, rapid action, cost-effective and fewer side effects. Bupivacaine and Tetracaine are the most commonly used agents for spinal anesthesia. However, post-operative pain control is a major problem with using local anesthetics alone because of relatively short duration of action. Various adjuvants have been tried to prolong the effect of spinal anesthesia. Traditionally intrathecal opioids are used to augment local anesthetics. Fentanyl is the preferred opioid because it has rapid onset of action. It is a pure mu agonist. Dexmedetomidine, a new highly selective alpha-2 agonist, which was first introduced as a sedative, is under evaluation as a neuraxial adjuvant. It exerts analgesic, sedative and anxiolytic effects. It provides stable and predictable hemodynamic conditions, good quality of intra-operative and prolonged post-operative analgesia. Adverse effects are minimal and include hypotension & bradycardia (due to sympatholytic action) (Bhana, 2009; Taiji, 2004).

MATERIALS AND METHODS

After approval from the Hospital Ethical Committee, this prospective, randomized, comparative, double-blind clinical study was conducted at St. Stephen's Hospital, Delhi, on 90 patients who were to undergo any lower abdominal or lower limb surgery under subarachnoid block. Informed consent was taken for the anaesthetic procedure.

The *Inclusion criteria* were

- Age between 15-70 years.
- Belonging to ASA Class I and II
- Weighing between 30-90 kg.
- Elective surgery duration less than or equal to 120 minutes.

The *Exclusion criteria* were

- Lack of patient consent.
- Patients with Coagulation disorders.
- Patients with Uncontrolled Hypertension, Arrhythmias, Angina, H/O MI.
- Patients with focus of infection near the site of block.
- Patients with history of hypersensitivity to any of the drugs under study.
- Patient with psychiatric disorder.

SAMPLE SIZE*:* The sample size was calculated using the formula

$$X = \frac{(Z_1 - \alpha/2\ \sqrt{2P(1-P)} + Z_{1-\beta}\sqrt{(P_1(1-P_1) + (P_2(1-P_2))^2}}{(P_1-P_2)^2}$$

Where,

$Z\alpha = 1.96$ normal deviate for α level of significance (5%)
$Z\beta = 0.842$ normal deviate value for power (80%)
P_1 = % pain relief in Group I
P_2 = % pain relief in Group II
$P = P_1+P_2/2$

The calculated sample size is 79 patients in each group. However due to constraints of time, 30 patients were taken in each group. 90 patients were divided into three groups of thirty each, depending on the drug combination used for analgesia. Patients were allocated into the three study groups using computed generated randomization tables (Dallal, 2007).

Group 1(B): These 30 patients received subarachnoid block with 3ml of 0.5% (H) Bupivacaine plus 0.5ml saline. A total of 3.5ml of drug was injected intrathecally.

Group 2(F): These thirty patients received subarachnoid block with 3ml of 0.5% (H) Bupivacaine plus 25ug fentanyl (0.5ml). A total of 3.5ml of drug was injected intrathecally.
Group 3(D): These thirty patients received subarachnoid block with 3ml of 0.5% (H) Bupivacaine plus 5ug Dexmedetomidine (0.5ml). A total of 3.5 ml drug was injected intrathecally.

Procedure: A detailed pre-anaesthetic evaluation was done including history as well as clinical examination. After ascertaining that patient was fit to undergo procedure and after proper explanation of the anaesthetic technique, a written informed consent was obtained from each patient selected for the study. Once inside the operating room, baseline readings of Blood Pressure, pulse rate, oxygen saturation and grade of pain experienced (by VAS score) were recorded. An intravenous line with an 18G cannula was secured. All patients were preloaded with Ringer Lactate 10ml/kg starting 30min before the anaesthesia.

The patient was then randomly allocated to one of the three study groups making sure that the patient and the anaesthetist administering the drug combination were blinded. The patient was placed in sitting position with neck flexed. After cleaning and draping, lumbar puncture was performed in L2-L3/L3-L4 interspace using a 25G Quincke's spinal needle. After checking for clear and free flow of CSF, drug combination from the preloaded syringe was administered intrathecally. The time of injection was noted. Patient was immediately placed in supine position. All patients received oxygen @ 4l/min via mask intraoperatively.

The parameters evaluated intra-operatively and postoperatively include

Vital parameters like Pulse rate, Systolic Blood Pressure, Diastolic Blood Pressure, Oxygen saturation were recorded prior to block, at 1,5,10 minutes after the block. Then they were recorded every 10min till end of surgery. In postop period they were recorded hourly till the patient complained of pain. Quality of Analgesia- was assessed using Visual Analogue Score (VAS) from 0-100, with 0 denoting.

The patients marked on the line the point that they felt represented their perception of their state of pain. The VAS Score was determined by measuring in millimeters from the left hand end of the line to the point that the patient marked. VAS was assessed prior to block and then at 1min, 2min, 5min, 10min and every 10min till end of surgery. In post-op period VAS was recorded hourly till patient complained of pain.

- Onset of Sensory Block- was assessed by pinprick and was recorded in minutes.
- Onset of Motor Block- was assessed using modified Bromage score; where

0= No paralysis with full range of motion
1= Inability to raise extended leg
2= Inability to flex the knee
3= Inability to flex the ankle (complete motor block).

- Total duration of Analgesia- was recorded as time from subarachnoid injection to first report of pain.
- Rescue analgesia- Was given in the form of Inj. Diclofenac Sodium 75mg intramuscularly.
- Adverse effects- Hypotension- A fall in systolic blood pressure below 90mm Hg or more was considered significant. It was treated with inj. Ephedrine 6mg I/V bolus.
- Bradycardia- A fall in HR below 55 bpm was considered significant and was treated with inj. Atropine 0.6mg I/V bolus.
- Headache, pruritus, nausea, vomiting and shivering if occurred were noted.

The data was entered in MS Excel sheet and analyzed by SPSS software. The results were expressed in number, percentage,

mean and standard deviation as appropriate. Quantitative data was presented by mean ± SD (Standard Deviation). Difference between the means of age distribution, hemodynamics (HR, SBP), VAS Score and time to first dose of rescue analgesic (TTRA)were analyzed using the unpaired t-test. Oxygen saturation was analyzed using Mann-Whitney U Test. Non-parametric data such as side effects was analyzed using the Chi Square test/Fischer's Exact test, as appropriate.

RESULTS

We studied 90 patients belonging to ASA Grade I and II posted for lower abdominal or lower limb surgeries under spinal anesthesia. Patients were randomly divided into 3 groups of 30 patients each by computer generated random tables. The entire data was entered in Microsoft excel spreadsheet and was analyzed using SPSS (originally, Statistical Package for the Social Sciences, later modified to Statistical Product and Service Solutions). A *p*-value of < 0.05 is considered statistically significant.

The analysis done is as below

Age Distribution: The highest age in the study groups was 69 years and the lowest age was 15 years. The majority of patients were in the age group of 17-40 years. The mean age in Group B (Bupivacaine) was 30.93 years, in Group F (Fentanyl) was 36.5 years whereas in Group D (Dexmedetomidine) was 32.43 years. The difference in the mean age of the patients between the groups was not statistically significant (p=0.12) i.e. the age-wise distribution in the groups was comparable.

Height and weight distribution: The p value is 0.340 and 0.260 for weight and height respectively, therefore there is no significant difference in weight and height distribution between groups.

Duration of Complete Analgesia: The mean duration of complete analgesia for group 1 was 150± 26 minutes, 215.3 ± 30.9 for group 2 and 252.2 ± 33.4 for group 3. This was found to be stastically significant (p Value<0.05).

Time for 1st analgesic medication: The mean duration of 1st analgesic medication requirement for group 1 was 182.03± 31.99 minutes, 255.1 ± 36.15 minutes for group 2 and 310.5± 38.6 minutes for group 3. This was found to be stastically significant (p Value<0.05). The incidence of Hypotension and bradycardia was significantly higher in Group 3 as compared to group 1 and group 2 (P<0.05). The incidence of Pruritus was significantly higher in group 2 as compared to group 1 and Group 3 (P<0.05)

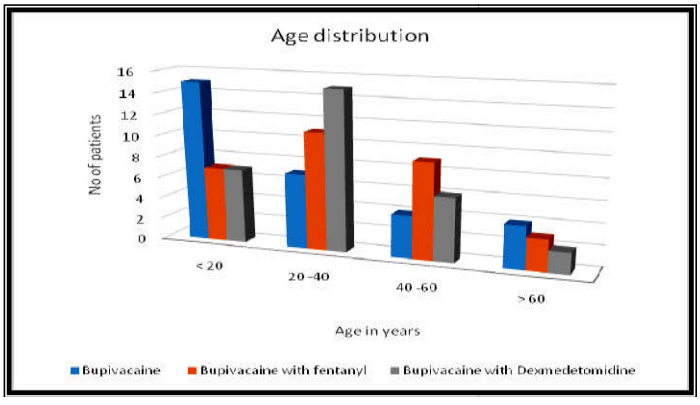

Figure 1. Age Distribution

Table 2. Height and weight distribution

Group	Group B	Group F	Group D	P value
	Mean± SD	Mean± SD	Mean± SD	
Weight	60.93 ± 11.36	62.3 ± 13.12	65.36 ± 11.33	0.340
Height	164.3 ± 9.97	163.26 ± 7.44	162.63 ± 9.75	0.260

Table 7. Duration of Complete Analgesia

Group	Group B	Group F	Group D	
Duration of complete analgesia (in minutes)	Mean ± SD 150.5 ± 26.0$	Mean ± SD 215.3 ± 30.9#	Mean ± SD 252.2 ± 33.4 @	P value 0.00

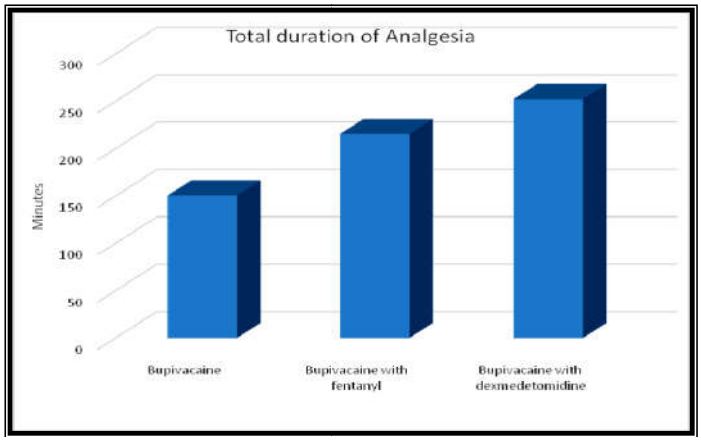

Figure 7. Duration of Complete Analgesia

Table 8. Time for 1st analgesic medication-

Group	Group B	Group F	Group D	P value
Time for 1st Analgesic	Mean ± SD	Mean ± SD	Mean ± SD	
medication	182.03 ± 31.99	255.1 ± 36.15	310.5 ± 38.6	0.000

Table 9. Side effects

Side effects	Group B	Group F	Group D	P Value
Hypotension	3	4	14	0.002
Bradycardia	0	1	8	0.002
Nausea and Vomiting	2	3	8	0.06
Shivering	12	13	3	0.006
Pruritus	0	7	1	0.005

DISCUSSION

Spinal anaesthesia is the most commonly employed anaesthetic technique for performing lower abdominal and lower limb surgeries. It offers many advantages like safety, inexpensive, easy to administer technique and post-operative satisfaction for patients. Bupivacaine is the most commonly used local anaesthetic used for spinal anaesthesia. The aim of this study was to evaluate and compare the effects to commonly used adjuvants, Fentanyl and Dexmedetomidine when added to Bupivacaine for spinal anaesthesia for lower abdominal and lower limb surgeries.

Demographic Profile: The demographic profiles of the two groups were comparable. This helped to eliminate any variability due to demographic differences which could lead to

error in interpretation of data. The mean age in group B using Bupivacaine is 30.93 years, in group F with Bupivacaine with Fentanyl is 36.5 years, and in group D with Bupivacaine with Dexmedetomidine is 32.43 years. Therefore patients in all the three groups had comparable age distribution (p value=0.12).
The mean weight in group B using Bupivacaine is 60.93 Kg, in group F with Bupivacaine with Fentanyl is 62.3 Kg, and in group D with Bupivacaine with Dexmedetomidine is 65.36 Kg. Therefore patients in all the three groups had comparable weight distribution (p value=0.34). The mean height in group B using Bupivacaine is 160.33cm, in group F with Bupivacaine with Fentanyl is 164.3cm, and in group D with Bupivacaine with Dexmedetomidine is 163.26cm. Therefore patients in all the three groups had comparable height distribution (p value=0.26).

Duration of Complete Analgesia & time for 1st analgesic medication: In our study the mean duration of complete analgesia for Group B was 150.5 ± 26.0minutes, Group F was 215.3 ± 30.9and Group D was 252.2 ± 33.4. The difference was found to be statistically significant among the three groups (p value<0.05). The difference was also found statistically significant between group B and group F, group B and group D and group F and group D. (Bonferoni multiple comparison).
The mean time for 1st analgesic medication in our study was 182.03 minutes for Group B, 255.1 minutes for Group F and 310.5 minutes for Group D. The difference was found to be statistically significant among the three groups. The difference was also found statistically significant between group B and group F, group B and group D and group F and group D. (Bonferoni multiple comparison).

T**hese results are *supported* by various studies like: *Chu et al***. (1995) studied intrathecal Fentanyl as adjuvant to Bupivacaine in spinal anesthesia, and found that 10ug improved intra-operative analgesia and 12.5ug lengthened post-operative analgesia. Ceiling effect was seen with further increasing doses.

Hamber and Visconi et al. **(1999)** studied intrathecal Fentanyl as adjuvant to Bupivacaine in Caesarean section and found that 20-30ug causes faster onset of block, improved intra-operative and post-operative analgesia that lasted 2-5 hours and decreased nausea/vomiting during the procedure. ***Idowuetal*** **(**2011) studied the effects of intrathecally administered fentanyl on duration of analgesia in patients undergoing spinal anesthesia for elective caesarean section and found that addition of 25 ug of fentanyl to bupivacaine intrathecally for elective Caesarean section increases the duration of complete and effective analgesia thereby reducing the need for early postoperative use of analgesics. Al Mustafa *et al.,* (2009; Al Mustafa, 2009) studied the effect of Dexmedetomidine and found that Intravenous Dexmedetomidine administration prolonged the sensory and motor blocks of bupivacaine spinal analgesia with good sedation effect and hemodynamic stability. *Deepika et al.* (2011) studied intrathecal Dexmedetomidine with intrathecal magnesium sulfate used as adjuvants to bupivacaine and found that the onset of anesthesia was rapid and of prolonged duration in the Dexmedetomidine group (D). However, in the magnesium sulfate group (M), although onset of block was delayed, the duration was significantly prolonged as compared with the control group (C), but to a lesser degree than in the Dexmedetomidine group (D). The groups were similar with respect to hemodynamic variables and there were no significant side-effects in either of the groups.

Ashraf Amin Mohamed et al. (2012) studied Efficacy of Intrathecally Administered Dexmedetomidine Versus Dexmedetomidine with Fentanyl in Patients Undergoing Major Abdominal Cancer Surgery and found that Dexmedetomidine 5 µg given intrathecally improves the quality and the duration of postoperative analgesia and also provides an analgesic sparing effect in patients undergoing major abdominal cancer surgery. Furthermore, the addition of intrathecal fentanyl 25 µg has no valuable clinical effect. *Kanazi et al.* (2006) found that Dexmedetomidine (3 µg) or clonidine (30 µg), when added to intrathecal bupivacaine, produces a similar prolongation in the duration of the motor and sensory block with preserved hemodynamic stability and lack of sedation. *Li et al.* (2014) found that addition of Dexmedetomidine and clonidine as adjuvants to hyperbaric bupivacaine in caesarean section provided adequate anesthesia and postoperative analgesia compared to fentanyl adjuvant without causing any significant side effects. *Sun et al.* found that use of Dexmedetomidine as an adjuvant to bupivacaine in caesarean surgeries provides better intra-operative and post-operative analgesia without having significant impact on Apgar scores or incidence of side effects.

Nayagam [Nayagam *et al.,* 2014) found that both groups of fentanyl and Dexmedetomidine added to bupivacaine for lower abdominal surgeries provided adequate anaesthesia for all lower abdominal surgeries with hemodynamic stability. Dexmedetomidine is superior to fentanyl since it facilitates the spread of the block and offers longer post-operative analgesic duration. *Gupta et al.,* (2014) found that Intrathecal Dexmedetomidine when compared to intrathecal buprenorphine causes prolonged anaesthesia and analgesia with reduced need for sedation and rescue analgesics. *Yektaş* (2014) found that two different doses of Dexmedetomidine, an α2-adrenoceptor agonist with analgesic effects, resulted in an increased duration of analgesia and efficacy, decreased postoperative analgesic use and was associated with no notable adverse effects. Mahendru *et al.,* (2013) found that IntrathecalDexmedetomidine is associated with prolonged motor and sensory block, hemodynamic stability, and reduced demand of rescue analgesics in 24 h as compared to clonidine, fentanyl, or lone bupivacaine. Kim *et al.* (2013) found that Dexmedetomidine 3 µg when added to intrathecal bupivacaine 6 mg produced fast onset and a prolonged duration of sensory block and postoperative analgesia in elderly patients for transurethral surgery. However, recovery of motor block could be delayed in Dexmedetomidine-added patients. *Esmaoğlu et al.* [2013) found that intrathecal Dexmedetomidine addition to levobupivacaine for spinal anaesthesia shortens sensory and motor block onset time and prolongs block duration without any significant adverse effects. *Eid et al.* (2011) found that Intrathecal Dexmedetomidine in doses of 10 µg and 15 µg significantly prolong the anaesthetic and analgesic effects of spinal bupivacaine in a dose dependent manner.

Side Effects: In our study, Nausea and Vomiting was seen in 2 patients of Group B, 3 patients in Group F and 8 patients in Group D. The P value is 0.06 which was found stastically significant. Bradycardia was seen in 0 patients of Group B, 1 patient in Group F and 8 patients in Group D. The P value is 0.002 which was statistically significant. Hypotension was seen in 3 patients of Group B, 4 patients in Group F and 14 patients in Group D. The P value is 0.002 which was significant. Shivering was seen in 12 patients in group B, 12 patients in Group F and 3 patients in group D. The P value was

0.006 which is statistically significant. Pruritus was seen in 0 patients in group B, 7 patients in group F and 0 patients in group D. The P value was 0.005 which is statistically significant. The strengths of this study include absence of any drop-outs, conduct of postoperative examination by a single blinded investigator and absence of any major side effects.

Conclusion

The following conclusions could be drawn

- Quality of surgical anaesthesia was better with addition of both intrathecal Fentanyl or Dexmedetomidine than with Bupivacaine alone.
- Duration of Complete analgesia was most prolonged with addition of Dexmedetomidine followed by fentanyl than with Bupivacaine alone.
- Requirement for rescue analgesia was delayed most with addition of Dexmedetomidine followed by Fentanyl than with Bupivacaine alone.
- Incidence of Hypotension and Bradycardia were higher with Dexmedetomidine as compared to Fentanyl or Bupivacaine alone

Recommendations

We recommend the use of 25ug fentanyl or 5ug Dexmedetomidine to potentiate the effect of Bupivacaine induced spinal an aesthesia as they prolong the duration of analgesia and delays the need for rescue analgesia. Dexmedetomidine increases the duration of analgesia and delays need for rescue analgesia more than that by Fentanyl.

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