

A prospective double blinded study on effect of intrathecal dexmedetomidine as adjuvant to hyperbaric bupivacaine on onset and duration of subarachnoid blockade

Sudhanshu Gupta^{1,*}, Abha Gupta², Brahma Pada Sarkar³

¹DNB Resident, ³HOD, Dept. of Anaesthesia, DSP Main Hospital, Durgapur, West Bengal, ²Associate Professor, Dept. of Physiology, IQ City Medical College, Durgapur, West Bengal

***Corresponding Author:**

Email: drsudhanshugupta@gmail.com

Abstract

Objective: To study the effect of low dose intrathecal dexmedetomidine as adjuvant to hyperbaric Bupivacaine in relation to onset & duration of sensory & motor block

Material and Methods: In the present double blinded prospective, randomized controlled trial study, we have aimed to compare the two groups of ASA –grade I patients divided in two groups i.e., group B - Bupivacaine 2.5ml (12.5 mg) alone (control group) and group BD - Bupivacaine 2.5 ml (12.5 mg) combined with Dexmedetomidine 5 µg undergoing lower abdominal and lower limb surgeries to evaluate whether there is any clinching evidence of augmentation of motor and sensory block by addition of low dose dexmedetomidine (5µg).

Results: Among both the groups, mean time to achieve onset of sensory & motor blockade was found to be not statistically significant ($P>0.05$). The duration of sensory block observed in group BD was 143.6 ± 12.74 in contrast to group B 107 ± 9.74 . The difference in mean duration of analgesia between group B vs. BD, is statistically significant ($P<0.001$). The duration of motor blockade in group B found was 174.2 ± 11.26 in relation of group BD 276.4 ± 13.96 which is statistically significant ($P<0.001$).

Conclusions: It was concluded from the present study that addition of low dose dexmedetomidine to hyperbaric bupivacaine for subarachnoid block definitely prolongs the duration of sensory and motor blockade.

Keywords: Dexmedetomidine, Hyperbaric Bupivacaine, Sub arachnoid block.

Introduction

Sub Arachnoid blockade is the most commonly used anaesthetic technique widely used for lower abdominal and lower limb surgeries. Bupivacaine heavy is the commonest drug used for spinal anaesthesia. Various agents like Magnesium sulphate, fentanyl and clonidine have been tried as adjuvant for prolongation of sensory and motor blockade with varying degree of success. Clonidine, an α_2 agonist has been widely used intrathecally and through intravenous route to prolong bupivacaine induced spinal blockade. Dexmedetomidine shows more specificity towards α_2 receptor (α_2/α_1 1600:1) compared with clonidine (α_2/α_1 200:1). The mechanism of the analgesic action of dexmedetomidine have not been fully elucidated. A number of sites, both supraspinal and spinal, modulate the transmission of nociceptive signals in the CNS. Even peripheral α_2 adrenoceptors may mediate ant nociception. It has been widely used as an adjuvant to general as well as spinal anaesthesia. It has been found to produce earlier onset of motor blockade and prolongation of duration of both motor and sensory blockade with preserved hemodynamic stability and arousable sedation when given intrathecally. On this background we proposed to conduct a prospective randomized double blind study to see whether intrathecal dexmedetomidine as adjuvant to Bupivacaine (Heavy) given for spinal blockade can affect the onset and duration of sensory and motor blockage.

Materials and Methods

After obtaining institutional ethical and scientific committee approval, and written informed consent from all patients, a randomized, prospective, double blinded, analytical study was started. The study was conducted in the department of Anesthesiology of Durgapur Steel Plant Main Hospital, Durgapur. Sample size was calculated using power analysis and considering the effect size of 35 patients has been calculated in each group considering α error at 5% and power at 90%. To be on safer side and to round off the figure we propose to take 50 patients in each group, using computer generated randomization.

In the present study, 100 patients of either sex of age group between 18 to 60 years belonging to American society of Anesthesiology (ASA) physical status Grade I and II scheduled for elective lower abdomen, lower limb and perineal surgeries under sub arachnoid block at Durgapur Steel Plant Hospital, were enrolled in this study.

Exclusion Criteria of the study were:

1. Patients receiving any drugs that could influence hemodynamic and autonomic function.
2. Patients with the history of allergy to local aesthetics or any contraindication to spinal anaesthesia.
3. Patients on oral Alpha blockers and Calcium channel blockers.
4. Chronic Alcoholics and malnourished.
5. Hypovolemia.
6. ECG Abnormalities including A-V block,

- incomplete or partial heart block.
7. Coronary artery, Respiratory, Renal, Cerebral diseases.
 8. Pregnancy.
 9. Age < 17 years and > 60 years.
 10. ASA grade III and above.
 11. Patient who refuse to give consent.
 12. History of Spine surgery, increased intracranial tension and coagulopathy.

The study was done to study the onset and duration of 5 mcg of Inj. Dexmedetomidine as adjuvant to Hyperbaric Bupivacaine intrathecally in lower abdomen and lower limb surgeries. Patients satisfying the inclusion criteria were placed in two groups of 50 each as follows: **Group BD** - 50 Patients receiving Inj Dexmedetomidine 5mcg as adjuvant to intrathecal hyperbaric bupivacaine 12.5 mg. **Group B** - 50 Patients receiving intrathecal hyperbaric bupivacaine 12.5 mg alone. In Pre-operative PAC, a detailed history, systemic examination and laboratory tests were taken, following patient admission. An informed written consent was taken from each patient who satisfies the inclusion criteria. Anthropometric measures - age, height, weight and BMI of all patients were recorded.

All patients were given premedication with tab Alprazolam 0.5mg and Tablet Omeprazole 20mg at bed time previous night. Tab Omeprazole 20mg at 2 hours before surgery in the morning. In the operation theatre, essential monitors like electrocardiogram, pulse oximetry and non-invasive blood pressure were attached to patient. All patients were co-loaded with IV fluids through 18 G IV cannula was administered. Basal parameters like heart rate, NIBP, and SpO₂ was recorded.

Under full aseptic precautions, spinal anaesthesia was performed in sitting position at L3-L4 level through midline approach using 25G Quincke spinal needle (B Braun Medical) with the hole pointing upwards with bupivacaine heavy 2.5ml (12.5 mg) and 5 mcg of Dexmedetomidine in Group BD and bupivacaine heavy 2.5 ml (12.5 mg) alone in group B. Drug given in spinal anaesthesia was loaded and appropriate mixture prepared by third party (another colleague) and a coding done by same third party (another colleague), so that investigator and patient were blinded. 0.9% normal saline used as diluent for dexmedetomidine as per computer generated randomization. Drug was administered slowly over a period of 10 seconds. After successful lumbar puncture, vital parameters as well as sensory and motor blockade level were recorded at 2, 4, 6, 8, 10, 15, 20 minutes since spinal blockade and then again at 120, 130, 140, 150, 160, 170, 180 minutes till three hours. Patients were given 2-3 lit/min of oxygen via simple face mask. Hypotension, defined as SBP <90 mm Hg or >30% fall from the baseline value were treated by injection mephentermine 3 mg intravenous (i.v) and i.v crystalloids. Bradycardia is defined as HR <60

beats/min or >30% decrease from the baseline value and was be treated with i.v atropine 0.3 mg increments. All Patients received as maintenance fluid with isotonic fluids. Sensory blockade was assessed by using pin prick method.

Motor blockade was assessed by Bromage Scale as discussed below:

Table 1: Description of the Bromage score

Grade	Criteria	Degree of block
I	Free movement of legs and feet	Nil (0%)
II	Just able to flex knees with free movement of feet	Partial (33%)
III	Unable to flex knees, but with free movement of feet	Almost complete (66%)
IV	Unable to move legs or feet	Complete (100%)

Observations

Table 2: Demographic Data of Studied patients

	Group -B	Group-BD	P-Value	Significance
Age (In Years)	39.22±9.79	39.64±9.14	0.825	Not Significant
Sex				
Male	58.00	62.00	p>0.05	Not Significant
Female	42.00	38.00	p>0.05	Not Significant
Weight (In Kgs)	55.26±7.73	55.32±7.38	0.968	Not Significant

Table 3: Onset of Sensory Effect Distribution

	Group		P Value	Significance
	Group B	Group BD		
	Mean±Std. Deviation	Mean±Std. Deviation		
Onset of Sensory Block	7.82±0.92	7.72±0.97	0.598	Not Significant

Table 4: Onset of Motor Block Distribution

	Group		P Value	Significance
	Group B	Group BD		
	Mean±Std. Deviation	Mean±Std. Deviation		
Onset of Motor Block	9.2±0.93	9.48±0.99	0.148	Not Significant

Table 5: Duration of Sensory Block Distribution

	Group		P Value	Significance
	Group B	Group BD		
	Mean±Std. Deviation	Mean±Std. Deviation		
Duration of Sensory Block	107±9.74	143.6±12.74	<0.001	Significant

Table 6: Duration of Motor Blockade Distribution

	Group		P Value	Significance
	Group B	Group BD		
	Mean±Std. Deviation	Mean±Std. Deviation		
Duration of Motor Block	174.2±11.26	276.4±13.96	<0.001	Significant

Results

All selected patients under study were clinically hemodynamic stable and devoid of any side effects. None required use of vasopressors for hypotension or Inj. Atropine for bradycardia. None of patient required conversion to general anesthesia due to insufficient block.

In our study we compared the mean time taken to achieve sensory block. In group B it was 7.82 min, which was 1.29% greater than group BD. In group BD the mean time taken to achieve sensory block was 7.72 min, which was 1.28% lesser than group B. It appears that dexmedetomidine causes faster onset of sensory block but the difference between group B and BD were statistically not significant ($P>0.05$). So it implies that addition of low dose dexmedetomidine with bupivacaine in spinal anesthesia did not affect the onset of sensory block.

On comparison of motor block onset the mean time to achieve motor block to achieve modified Bromage scale level among the groups B & BD were 9.2 and 9.48 minutes respectively. In Group B, the mean time taken to achieve motor block was 9.2 ± 0.93 min, which was 2.95% lesser than group BD. Whereas in group BD the mean time taken to achieve motor block was 9.48 ± 0.99 min, which was 3.03% greater than group B. The difference in mean time for motor block onset between group B and BD is statistically not significant ($P>0.05$), means addition of low dose dexmedetomidine with bupivacaine in spinal anaesthesia did not affect the onset of motor block.

In our study, the mean duration of sensory block among the group B and BD was 107 ± 9.74 and 143.6 ± 12.74 minutes respectively. In group B the mean duration of sensory block was 107 ± 9.74 minutes, that was 33.64% lesser than group BD. Contrary to the group B, in the group BD, the mean duration of sensory block was 143.6 ± 12.74 minutes, which was 25.17% greater than Group B. The difference in mean duration of analgesia between group B vs. BD, is statistically significant ($P<0.001$). Thus the present study suggests that, addition of dexmedetomidine to bupivacaine in spinal anaesthesia significantly increases the mean duration of sensory block in comparison to bupivacaine alone (control group).

It was found that, the mean time to achieve motor block from Bromage scale level three to Bromage scale level zero among the group B and BD was 174.2 ± 11.26 and 276.4 ± 13.96 minutes respectively. Among group B

the mean time to achieve motor block from Bromage scale level three to Bromage scale level zero was 181.03 ± 20.83 min that was 56.35% lesser than group BD. In group BD members, the mean time to achieve motor block from Bromage scale level three to Bromage scale level zero was 353.37 min, which was 36.95% greater than group B. The difference in motor block duration between group B vs. BD, is statistically significant ($P<0.001$). Hence, it was observed that addition of dexmedetomidine to bupivacaine in spinal anesthesia significantly increases the mean duration of motor blockade in comparison to bupivacaine alone (control group).

Conclusions

The results of the present study suggest that addition of dexmedetomidine in doses given, to bupivacaine for subarachnoid block prolonged sensory and motor blockade in clinically beneficial manner. However, adverse effects that could be encountered by using dexmedetomidine are shivering, bradycardia, hypotension, insufficient block, sedation, nausea and vomiting were not found in our study. It appears that augmentation of sensory and motor blockade by dexmedetomidine may be due to synergism between these drugs although they have got different mechanism of action. The combination of dexmedetomidine and bupivacaine for neuraxial block, herefore appears to be quite attractive for wider clinical practice.

References

1. Wulf, HFW (1998). "The centennial of spinal anesthesia". *Anesthesiology* 89(2):500–6.
2. Quincke HI (1891). "Verhandlungen des Congresses für Innere Medizin, Zehnter Congress". Wiesbaden 10. pp. 321–331.
3. Rudolf Metas (1899) spinal anesthesia for surgery in United States, 1899.
4. Fournace, Babcock WW. "The technique of spinal anesthesia". *New York Journal of Medicine* 1914;50:637–702.
5. Spiller WG. "The occasional clinical resemblance between caries of the vertebrae and lumbothoracic syringomyelia and the location within the spinal cord of the fibres for the sensations of pain and temperature". *Univ Penn Med Bull* 1905;18:147–54.
6. Huskisson EC (1979). "Huskisson EC. Measurement of pain". *Lancet*. 1974 Nov 9;2(7889):1127–1131.
7. Löfgren N, Lundqvist B (1946). "Studies on local anaesthetics II". *Svensk Kemisk Tidskrift* 58:206–17.
8. Gordh T "Xylocain, a new local analgesic". *Anaesthesia* 1949;4:4–9.
9. Chapman PJ, Macleod AW. "A clinical study of bupivacaine for mandibular anesthesia in oral surgery". *Anesth Prog*. 1985;32:69–72.
10. N. M. Greene, "Distribution of local anesthetic solutions within the subarachnoid space, "Anesthesia and Analgesia, vol. 64, no. 7, pp. 715–730, 1985.
11. J. Bannister and et al. "Effect of Glucose concentration on the Intrathecal spread of 0.5% Bupivacaine". *British Journal of Anaesthesia* (1990);64(2):232-234.
12. U. Bakshi and etal "Adjuvant Drugs in Central Neuraxial Analgesia- a Review" *The Internet journal of*

- Anaesthesia; vol 26(1).
13. Varrassi G; Celleno D; Capogna G et al. "Ventilatory effects of subarachnoid fentanyl in the elderly". *Anaesthesia* 1992;47:558-62.
 14. Singh H; Yang J: "Intrathecal fentanyl prolongs sensory bupivacaine block." *Cand. J. Anaesth*, 1995,42(11):987-91.
 15. Shikha Gupta et al (2013) "The intrathecal sufentanil or fentanyl as adjuvants to low dose bupivacaine in endoscopic urological procedures" *Journal of Anesthesiology and Clinical Pharmacology* 2013;29:509-15.
 16. Liu N et al (1993) "Clonidine comparably decreases the thermoregulatory thresholds for vasoconstriction and shivering in humans." *Anesthesiology*. 1993 Sep;79(3):470-4.
 17. Malinovsky JM et al (1993) "Spinal clonidine fails to provide surgical anesthesia for transurethral resection of prostate. A dose-finding pilot study." *Regional Anesthesia*. 1996 Sep-Oct;21(5):419-23.
 18. Klimscha W et al (1995) "Haemodynamic and analgesic effects of clonidine added repetitively to continuous epidural and spinal block." *Anaesthesia and analgesia*. 80,320-327.
 19. Safiya I. Shaikh "Dexmedetomidine as an adjuvant to hyperbaric spinal bupivacaine for infra-umbilical procedures- A dose related study" *Anaesthesia, Pain and Intensive Care*.
 20. Kip A. Lemke "Perioperative use of selective alpha-2 agonists and antagonists in small animals" *The Canadian Veterinary Journal*. 2004 Jun;45(6):475-480.
 21. K Sudheesh, et al. "Dexmedetomidine in anaesthesia practice: A wonder drug?" *Indian Journal of Anaesthesia*; 2011;55(4):323-324.
 22. Filos KS, Goudas LC, Patroni O, Polyzoou V. "Intrathecal clonidine as a sole analgesic for pain relief after cesarean section." *Anesthesiology*. 1992;77:267-74.
 23. Filos KS, Patroni O, Goudas LC, Bosas O, Kassaras A, Gartaganis S. "A dose-response study of orally administered clonidine as premedication in the elderly: evaluating hemodynamic safety." *Anaesth Analg*. 1993;77(6):1185-92.
 24. De Negri, Salvatore R, Visconti C, De Vivo P, Mastronardi P. "Spinal anaesthesia with clonidine and bupivacaine in young humans, interactions and effects on cardiovascular system." *Minerva Anaesthesiology*. 1997;63:119-25.
 25. Borg PA, Krijen H. "Long-term intrathecal administration of midazolam and clonidine." *Clin Journal Pain*. 1996;12(1):63-68.
 26. Gunnar MD et al. "Intrathecal Sufentanil, Fentanyl, or Placebo Added to Bupivacaine for Cesarean Section." *Anesthesia & Analgesia*: December 1997 - Volume 85 - Issue 6 - pp 1288-1293.
 27. Ben-David B et al. "Intrathecal fentanyl with small-dose dilute bupivacaine: better anesthesia without prolonging recovery." *Anesth Analg*. 1997 Sep; 85(3):560-5.
 28. Benhamou D, Thorin D, Brichtant JF, Dailland P, Milon D, Schneider M. "Intrathecal clonidine and fentanyl with hyperbaric bupivacaine improves analgesia during cesarean section." *Anesth Analg*. 1998;87:609-13.
 29. Armand S, Langlade A, Boutros A, Lobjoit K, Monrigal C, Ramboatianna R, Rauss A, Bonnet F. "Meta-analysis of the efficacy of extradural clonidine to relieve postoperative pain: an impossible task." *Br J Anaesth*. 1998;81:126-128.
 30. Gabriel JS and Gordin V. "Alpha 2 agonist in regional anaesthesia and analgesia." *Curr Opin Anaesthesiol*. 2001;14:751-53.
 31. Kaabachi O, Zarghouni A, Ouezini R, Abdelaziz AB, Chattaoui O, and Kokki H. "Spinal anaesthesia in children: comparative study of hyperbaric bupivacaine with or without clonidine". *Ann Fr Anaesth Reanim*. 2002;21:617-21.
 32. Biswas B N et al. "Intrathecal fentanyl with hyperbaric bupivacaine improves analgesia during caesarean delivery and in early post-operative period". *Indian J. Anaesth*. 2002;46(6):469-472.
 33. Cowan CM, Kendall JB, Barelay PM, Wilkes RG. "Comparison of intrathecal fentanyl and diamorphine in addition to bupivacaine for caesarean section under spinal anaesthesia". *Br J Anaesth*. 2002;89:452-458.
 34. M.S. Khanna, Ikwinder KJP Singh. "Comparative evaluation of Bupivacaine plain versus bupivacaine with fentanyl in spinal anaesthesia in geriatric patients". *Indian J. Anaesth*. 2002;46(3):199-203.
 35. Jain PN, Gehdoo RP, Priya V, Myatra Sheila. "Study of intrathecal clonidine for postoperative pain relief". *Ind pain*. 2003;17(2).
 36. Dobrydnjov I, Axelsson K, Matthesen P, Klockhoff H, Holmstrom B, Gupta. A. "Clonidine combined with small-dose bupivacaine during spinal anaesthesia for inguinal herniorrhaphy: a randomized double-blind study". *Anaesth Analg*. 2003;96:1496-503.
 37. U Srivastava et al. "Hyperbaric or plain bupivacaine combined with fentanyl for spinal anaesthesia during caesarean delivery". *Indian J. Anaesth*. 2004;48(1):44-46.
 38. Strebel S, Gurzeler JA, Schneider MC, Aeschbach A, Kindler CH. "Small-Dose Intrathecal Clonidine and Isobaric Bupivacaine for Orthopedic Surgery: A dose-response study". *Anaesth Analg*. 2004;99:1231-38.
 39. J Bogra et al. "Synergistic effect of intrathecal fentanyl and bupivacaine in spinal anaesthesia for cesarean section". *BMC Anesthesiol*. 2005 May 17;5(1):5.
 40. Paech MJ, Pavy TJ, Orlikowski CE, Yeo ST, Banks SL, Evans SF. "Post cesarean analgesia with spinal morphine, clonidine or their combination". *Anaesth Analg*. 2004;98(5):1460-66.
 41. Van Tuiji, Van Klei WA, Van Der Werff DBM, Kalkman CJ. "The effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain and morphine requirements after caesarean section: a randomized controlled trial". *British Journal of Anaesthesia*; 2006;97(3):365-70.
 42. Kanazi GE, Aouad MT, Jabbour-khoury SI. "Effect of low dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block". *Acta anaesthesiol scand*. 2006;50:222-227.
 43. B S Sethi, Mary Samuel, Deepak Srivastava. "Efficacy of analgesic effects of low dose intrathecal clonidine as adjuvant to bupivacaine". *Indian J Anaesthesia*. 2007;51(5):415-419.
 44. Gradhe RP, Wig J & Yaddanapudi LN. "Evaluation of bupivacaine-clonidine combination for unilateral spinal anaesthesia in lower limb orthopaedic surgery". *J Anaesth Clin Pharmacol*. 2008;24(2):155-158.
 45. Mahmoud M Al-Mustafa, Sami A Abu-Halaweh, AbdelKarim S Aloweidi, Mujalli M Murshidi, Bassam A ammari, Ziad M Awwad, Ghazi M Al-Edwan, Micheal A Ramsay. "Effect of dexmedetomidine added to spinal bupivacaine for urologic procedure". *Saudi Medical Journal*. 2009;30(3):365-70.
 46. Al-Ghanem SM, Massad IM, Al-Mustafa MM, Al-Zaben KR and Qudaisat IY. "Effect of adding dexmedetomidine versus fentanyl to intrathecal bupivacaine on spinal block characteristics in gynecological procedures: A double

- blind controlled study". *Am J Applied Sci.*2009;6:882-887.
47. Gupta R, Bogra J, Verama R. "Dexmedetomidine as an intrathecaladjuvent for post-operative analgesia". *Indian J Anaesthesia.* 2011Jul;55(4):347-51.
 48. Hala EA, Shafie MA, Youssef H. "Dose-related prolongation of hyperbaric bupivacaine spinal anesthesia by dexmedetomidine". *Ain Shams J Anesthesiol* 2011;4:83-95.
 49. Vidhu Mahendru et al. "A comparison of intrathecal dexmedetomidine, clonidine, and fentanyl as adjuvants to hyperbaric bupivacaine for lower limb surgery- A double blind study". *Journal of Anesthesiology Clinical Pharmacology*,2013;29(4).
 50. Charles R Babst et al "Bupivacaine – A review". *Anesth Prog.* 1978 May-Jun;25(3):87–91.
 51. Paul G. Barash "Clinical Anesthesia". Fourth edition, Lippincott Williams and Wilkins, 2001, Page 460-462.
 52. Mariann A. Haselman (2008) "Dexmedetomidine" *AANA Journal*; October 2008: vol 76 (5).
 53. Grewal A. "Dexmedetomidine: New avenues." *J Anaesthesiol Clin Pharmacol* 2011;27:297-302.
 54. Mantz J, Jossierand J, Hamada S. "Dexmedetomidine: New insights". *Eur J Anaesthesiol* 2011;8:3-6.
 55. Kalso E et al (1991) Spinalantinociception by dexmedetomidine, a highly selective α 2-adrenergic agonist". *Pharmacol Toxicol* 1991;68:140—3.
 56. Pertovaara A, Haapalinna A, Sirviö J, Virtanen R (2005). "Pharmacological properties, central nervous system effects, and potential therapeutic applications of atipamezole, a selective α 2-adrenoceptor antagonist". *CNS Drug Reviews* 11(3):273–88.
 57. Palmeri A, et al (1990) "Concomitant depression of locus coeruleus neurons and of flexor reflexes by an α 2-adrenergic agonist in rats:a possible mechanism for an α 2-mediated muscle relaxation" .*Neuroscience.* 1990;34(1):177-87.
 58. Ebert, T. J.; Hall, J. E.; Barney, J. A.; Uhrich, T. D.; Colinco, M. D. "The effects of increasing plasma concentrations of dexmedetomidine in humans". *Anesthesiology* 93(2):382–394.
 59. Elia N, Culebras X, Mazza C, Schiffer E, Tramèr MR(2008). "Clonidine as an adjuvant to intrathecal local anesthetics for surgery: systematic review of randomized trials" *RegAnesth Pain Med.* 2008 Mar-Apr;33(2):159-67.
 60. Shukla D, Verma A, Agarwal A, Pandey HD, Tyagi C.(2011) "Comparative study of intrathecal dexmedetomidine with intrathecal magnesium sulfate used as adjuvants to bupivacaine". *J Anaesthesiol Clin Pharmacol.* 2011 Oct;27(4):495-9.
 61. Shimode N, Fukuoka T, Tanimoto M, Tashiro C, Tokunaga A, Noguchi K. "The effects of dexmedetomidine and halothane on Fos expression in the spinal dorsal horn using a rat postoperative pain model". *Neurosci Lett.* 2003 May 29;343(1):45-8.
 62. Sherif A Abdelhamid et al.(2013) "Intrathecal dexmedetomidine: Useful or not?" *J Anesth Clin Res* 4:351.
 63. Hem Anand Nayagam, N Ratan Singh, H Shanti Singh "A prospective randomised double blind study of intrathecal fentanyl and dexmedetomidine added to low dose bupivacaine for spinal anesthesia for lower abdominal surgeries" *IJA, Year:2014:58(4):430-435.*
 64. Udita Naithani, Mahendra Singh Meena, Sunanda Gupta, Khemraj Meena, Lalatendu Swain, DS Pradeep "Dose-dependent effect of intrathecal dexmedetomidine on isobaric ropivacaine in spinal anesthesia for abdominal hysterectomy: Effect on block characteristics and hemodynamics" *J AnaesthesiolClinPharmacol;2015 Dec 15;31:72-9.*