JMSCR Vol||05||Issue||11||Page 31085-31093||November 2017

www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 71.58
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i11.219

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Effect of Clonidine and/or Fentanyl in Combination with Intrathecal Bupivacaine for Lower Limb Orthopedic Surgeries in Spinal Anaesthesia

Authors
Abdul Hakim, Arif Amin Bhat*, Masrat Jan
GMC Srinagar, Kashmir University India
Corresponding Author
Dr Arif Amin Bhat
GMC Srinagar, Kashmir University India
Email: *Arifbhat6@gmail.com*

Abstract

Background and Aims: *Fentanyl and clonidine both prolong sensory and motor block of spinal anaesthesia and duration of postoperative analgesia when used as an adjuvant to intrathecal bupivacaine. This prospective observational study was conducted to evaluate the efficacy of adding clonidine and fentanyl in combination to bupivacaine.*

Material and Methods: *A total of 90 patients of (ASA) physical status I-II of both sexes, aged between 18 and 70 years, were randomly allocated to three groups. Each group consists of 30 patients. Group A: 2.5ml of 0.5% hyperbaric bupivacaine and 50ug of clonidine in 0.5ml of normal saline. Group B: 2.5ml of 0.5% hyperbaric bupivacaine and 25ug of fentanyl in 0.5ml of normal saline. Group C: 2.5ml of 0.5% hyperbaric bupivacaine and 12.5ug of fentanyl in 0.25ml of normal saline and 25ug of clonidine in 0.25ml of normal saline. The time of onset and duration of sensory block, highest dermatome level of sensory block, time of onset of motor block, time to complete motor block recovery and duration of spinal anesthesia, intraoperative and postoperative hemodynamics and side effects if any were recorded. VAS, total number of patients who were administered supplemental analgesic in each group and the total amount of supplemental analgesic administered in the next 24 h was quantified and documented in all the groups.*

Results: *The time of onset of sensory block (min) in groups A, B, and C was 9.10 ± 1.40, 12.50 ± 1.30 and 9.0 ± 0.90 respectively, thus onset of sensory block was significantly earlier in groups A and C. Similarly, onset of motor block was also quicker in groups A and C. Time of requirement of supplemental analgesia was 208.80 ± 26.32 min, 198.20 ± 21.92 min, and 210.00 ± 26.58 min in groups A, B and C respectively.*

Conclusion: *We conclude that the addition of clonidine in doses of 50 μg and 12.5 μg to low-dose bupivacaine and bupivacaine fentanyl prolongs the sensory and motor block while increasing the duration of postoperative analgesia without significant side-effects.*

Keywords: *Subarachnoid block, Intrathecal clonidine, spinal adjuvants, subarachnoid fentanyl.*

Introduction

Subarachnoid block (Spinal anaesthesia), is the preferred anaesthetic technique in lower extremity, anorectal, urologic, obstetric, and lower abdominal surgeries.[1] Compared to general anaesthesia. Subarachnoid block (Spinal anaesthesia) has decreased incidence of cardiovascular morbidity, deep venous thrombosis

(DVT) and pulmonary embolism (PE), blood loss, pain, and length of hospital stay. It is also known that Subarachnoid block improves rehabilitation compared to GA.[2,3]

During spinal anesthesia, sympathetic blockade is the first event to occur, and the last to disappear. This blockade causes hemodynamic instability, such as hypotension and delayed bradycardia, which is critical to prevent and recognize early, in order to avoid dramatic consequences such as cardiac arrest. Sympathetic block generally extends 2-6 dermatomes above the sensorial blockade .[4,5]

Various additives have been evaluated in the quest for an ideal adjuvant, which can enhance the quality of analgesia and prolong the duration of spinal anesthesia with minimal adverse effects. However, success with many additives has been variable, especially with regards to side-effects such as hypotension, bradycardia, pruritus, respiratory depression, nausea, vomiting, and urinary retention.[6]

The highly lipid soluble drugs such as fentanyl and sufentanil have a more rapid onset than hydrophilic opioids such as morphine. Fentanyl acts primarily as agonist at μ-opioid receptors to produce analgesia of long duration and reduces the systemic toxicity by allowing dose reduction of local anesthetic. But this combination of local anesthesia with opioids may lead to undesirable effects of pruritus, nausea, vomiting, urinary retention and respiratory depression.[7]

Alpha-2 adrenoceptor agonists are also used as spinal adjuvant. They act on prejunctional and post-junction α-2 adrenoreceptors in the dorsal horn of spinal cord. Clonidine is a centrally acting selective partial α2 adrenergic agonist and prolongs the duration of sensory and motor blockade by virtue of its ability to decrease sympathetic nervous system outflow. It increases the duration of analgesia, intensify the motor block and prolongs the duration of postoperative analgesia but it can cause hypotension and bradycardia.[8]

The present study was underwent to combine two adjuvants to local anaesthetics with the purpose to improve the quality of subarachnoid block.

Material and Methods

This prospective observational study was conducted in the department of anesthesiology Govt; medical collage Srinagar from 2015 to 2017 for ninety patients of (ASA) physical status I-II of both sexes, aged between 18 and 70 years, equally divided in to three groups, Group A (n=30), Group B (n=30) and group C (n=30), scheduled for elective lower limb and hip surgeries.

After getting approval from Institutional Ethical Committee, written informed consent was obtained from all the patients before surgery. Patients with any moderate to severe systemic disorders, patients unwilling to accept regional anesthesia, patients with any contraindication for spinal anesthesia, were excluded from the study. Baseline measurements of systolic, diastolic and mean arterial pressure, using a cuff on the right arm, and heart rate were recorded in the operating room. After preloading with 1000ml of ringer lactate solution patients were randomly assigned into three groups according to computer generated random numbers. Spinal anesthesia was administrated in the sitting position using midline approach.

The procedure began by identifying anatomic landmarks. The patient was placed in the sitting position and the line joining the superior aspect of the iliac crests posteriorly (Tuffier's line) was palpated. When the Tuffier's line crossed an interspinous space, the spinal level was identified as L3–L4 interspace. According to this land-mark, the L2–L3 interspace was identified as one inter-space above. Identification of lumbar interspaces was performed separately by a junior and senior anesthesiologist and if there was any discrepancy in the identification of lumbar interspace, the patient was excluded from the study.

All patients in each group received (Group A, 2.5ml of 0.5% hyperbaric bupivacaine and 50ug of clonidine in 0.5ml of normal saline ,Group B,

2.5ml of 0.5% hyperbaric bupivacaine and 25ug of fentanyl in 0.5ml of normal saline and Group C, 2.5ml of 0.5% hyperbaric bupivacaine and 12.5ug of fentanyl in 0.25ml of normal saline and 25ug of clonidine in 0.25ml of normal saline , via 25 G Quincke's needle and the same junior anesthesiologist gave the spinal injection to every patient to avoid inter operator variability. The dose was injected at a rate of approximately 0.2 mL/s. All patients were then placed supine and administered air/oxygen mixture (60%: 40%) via facemask. During the procedure an electrocar-diogram, the heart rate and pulse oximetry were monitored continuously. Non-invasive blood pressure was taken before the conduct of spinal anesthesia and every 5 minutes after the intrathecal injection until the end of surgery. Hypotension was defined as a decrease in the mean arterial blood pressure, more than 20% from baseline within a 5 min interval. Hypotension was treated with either fluid boluses or aliquots of intravenous mephentermine 6 mg since the efficacy of mephentermine) was recognized in earlier studies. Bradycardia was defined as heart rate less than 50 beats min^{-1} and was treated with i.v. injection of atropine 0.5–1 mg. The quality of anesthesia was assessed by testing severity of intra operative pain using a 10 cm VAS, where VAS 0 meant no pain and VAS 10 worst pain imaginable. VAS was evaluated every 5 min from the time of skin incision until the end of surgery. The use of VAS had previously been explained to each patient before surgery. VAS 1–3 was considered as mild pain, VAS 4–6 as moderate, VAS 7, 8 as severe and VAS 9, 10 as unbearable pain. Five minutes thereafter, the VAS was assessed. The height of sensory block was also noted. The level of sensory block was determined by the loss of pinprick sensation and was performed using a 22 G hypodermic needle. Sensory block level was tested every 5 minutes during the first 30 minutes after the intrathecal injection. The surgeon started all operations 30 minutes after intrathecal injection in every patient. No sensory testing was performed during surgery.

Intraoperative parameters

The following parameters were studied in the intra operative period.

1. Onset and duration of sensory block: The onset at T10 of sensory block was assessed by pinprick test performed at 2, 5, 10, 15, 20, and 30 min and total duration of sensory block was noted.
2. Quality of intraoperative anaesthesia: Using a "four Grade scale". This was graded as:
   - Excellent: No supplementary sedative or analgesia required.
   - Good: Only sedative required.
   - Fair: Both sedative and analgesic required.
   - Poor: General anesthesia and tracheal intubation required.
3. Motor blockade: This was assessed by Modified Bromage Scale as under:
   - Grade 0: No paralysis
   - Grade 1: Unable to raise extended leg.
   - Grade 2: Unable to flex knee.
   - Grade 3: unable to flex ankle (complete block).
4. Alteration in vital parameters like heart rate and blood pressure.
5. Other undesirable sequelae like nausea, vomiting or any other Complication.
6. Sedation was assessed by modified Ramsay sedation score.

Modified Ramsay Sedation score

1) Patient anxious, agitated or restless.
2) Patient cooperative, oriented and tranquil.
3) Patient responds to commands only.
4) Patient exhibits brisk response to light glabellar tap or loud auditory stimulus.
5) Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus.
6) Patient exhibits no response.

Postoperative period

Patients were evaluated for 24 hours regarding total duration of analgesia, postoperative analgesia requirements and other sequelae. Postoperatively, the pain was recorded by using visual analogue scale (VAS) between 0 and 10 (0= no paon,10= most severe pain), initially every 1 hourly for two hours, then every 2 hourly for the next 8 hours and then after every 4 hourly till 24 hours. Injection Diclofenac (75mg) was given intramuscularly as rescue analgesia when visual analogue scale was > 4.

Dada analysis plan

Data was analyzed using spss (version 10)

= Mean and standard deviation was calculated for quantitative variables i.e. Time of onset of blocks, age, weight and height.

= frequency and percentage were presented for qualitative variables i.e. Hypotension, sensory block, motor block.

= Independent sample t-test was used to compare time of onset of block in both groups.

= chi squre test was applied to compare hypotension, sensory block, motor block.

Results:

The treatment groups were comparable with respect to age, weight, height, sex distribution, and duration of surgery [Table 1].

Table 1. Patient demographic characteristics:

Parameters	Group A	Group B	Group C
Number(N)	30	30	30
Age(years)	42.6±14.58	44.73±15.08	44.0±14.10
Weight(kg)	61.50±8.87	62.50±10.99	63.20±9.50
Height(cm)	160.3±6.49	169.2±6.07	166.4±5.44
Gender(M/F)	20/10	18/12	21/09
ASA status I/II	25/5	26/4	27/3
Duration of surgery	97.66±13.70	94.66±14.45	92.73±16.04

Values in the table are mean ± SD or absolute numbers (percentage). SD = Standard deviation, ASA = American Society of Anesthesiologists.

The mean time of onset of sensory block in groups A, B and C were 9.10±1.40 min, 12.50±1.30 min, and 9.00±0.90 min respectively. The time of onset of sensory block in group B was delayed significantly as compared to groups A and C. In addition, it was significantly shorter in group C as compared to group A and B ($P < 0.05$). No, statistically significant differences were observed between group A and C [Table 2].

Table 2. Characteristics of spinal block:

Parameters	Group A	Group B	Group C
Number(N)	30	30	30
Time of onset of sensory block (min)	9.10±1.40	12.50±1.30	9.00±0.90
Time of onset of motor block (min)	13.45±1.40	15.20±1.50	13.00±1.20
Duration of sensory block (min)	126.10±12.80	86.00±10.50	135.50±10.80
Duration of motor block (min)	110.50±8.50	86.20±6.48	111.30±9.50
Highest dermatome level of sensory block	T7	T7	T7
Time of first analgesic request (min)	208.80±26.32	198.20±21.92	210.00±26.58

Values in the table are mean ± SD or absolute numbers (percentage). All times are in calculated from time of intrathecal injection. SD = Standard deviation.

Table:-3: Quality of Intra operative anesthesia:-

Quality of Intra operative anesthesia	Group		
	A	B	C
Excellent	27	28	28
Good	03	02	02
Fair	0	0	0
Poor	0	0	0
Total	30	30	30

The quality of intraoperative anesthesia remains excellent in all the groups and statistical difference between the Groups was not significant (p=0.851).Table 3.

The mean time of onset of motor block in groups A, B and C was 13.45±1.40 min, 15.20±1.50 min, and 13.00±1.20 min respectively. The time of onset of motor block was significantly delayed in group B as compared to groups A and C (P = 0.0001). Intergroup comparison did not reveal any statistically significant difference between the group B and C [Table 2].

The duration of sensory block in groups A, B and C was 126.10±12.80 min, 86.00±10.50 min, and 135.50±10.80 min respectively. Whereas, the duration of motor block in groups A, B and C were 110.50±8.50 min, 86.20±6.48 min, and 111.30±9.50 min respectively. The duration of both sensory and motor block was significantly prolonged in groups A and C as compared to groups B (P = 0.0001). However, there was no statistically significant difference between group A and C with respect to duration of motor and sensory block [Table 2]. Visual analogue scale scores were significantly higher in group B at 3 h and 12 h when compared to groups A and C (P = 0.009). At 4 h and 8 h, groups A and C had significantly lower VAS compared to group B. (P = 0.004 and 0.008)

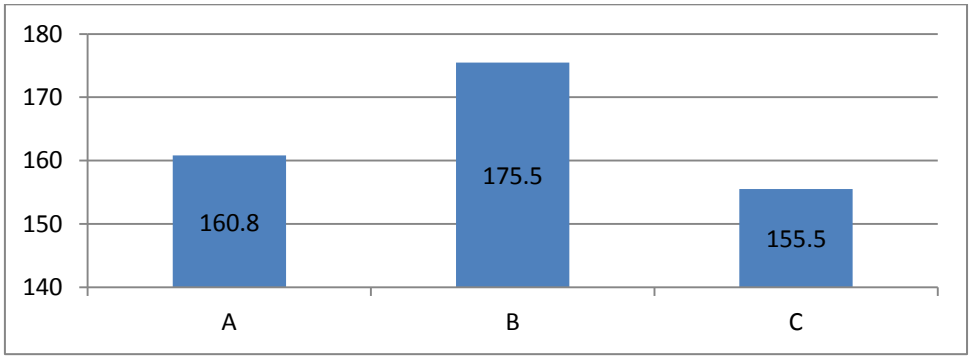

Figure 1: Requirement of rescue analgesic in each group for 24 h.

The requirement of rescue analgesic was significantly higher in group B as compared to other two groups at 2 h and 3 h postoperatively (P = 0.04 and P = 0.007). At 4 h postoperatively, groups B required more analgesic when compared to groups A and C and the difference was statistically significant. [Figure 1] Group B patients required significantly more amount of analgesic consumption as compared to group C at 12 h. Mean 24 h analgesic consumption was significantly more in group B followed by groups A and C (P = 0.005). Group C had the lowest amount of mean dose of analgesic consumption.

Intraoperative and postoperative changes in HR, MAP, SpO2, and RR were statistically insignificant and comparable among all the groups at all-time intervals. The intraoperative adverse effects, Hypotension, Bradycardia, Nausea, Vomiting, Respiratory Depression, Pruritus And Sedation score were statistically insignificant and comparable among all the groups (p=0.48). Mean nausea vomiting scores were comparable among all the groups. None of the patients reported the dryness of mouth.

Discussion

Subarachnoid block is commonly used regional anesthetic technique for patients who require surgical anesthesia for lower extremities, perineum, pelvic girdle or lower abdomen. It may be useful in patients with difficult airway or suffered from co-morbidities of severe respiratory disease. Spinal anesthesia covering the mid-thoracic level yields a contracted small intestine to provide superior surgical conditions in combination with profound muscle relaxation of abdominal muscles.[9]

Many previous studies have used intrathecal clonidine combined with opioids and local anesthetics for labour analgesia and orthopedic surgery.[10,11,12] Gautier and colleagues recommend 15 to 45 µg of clonidine as optimal for supplementing spinal anesthesia;[13] in keeping within this range, we chose 25 µg as optimal. Clonidine (15-30 µg) significantly prolongs sensory blockade and improves postoperative analgesia for gynecological operations,[14] knee arthroscopy and ambulatory inguinal herniorrhaphy.[15] The data match with our results concerning the duration of sensory block-postoperative analgesia. Our results showed that the addition of a small dose (25 µg) of clonidine increased the spread (onset-T9) and duration of sensory block, thereby prolonging postoperative analgesia. According to some previous studies, intrathecal clonidine alone, even at doses above 450 µg, does not cause muscular weakness and motor blockade, [16] but combined with local anesthetics it significantly enhances the intensity and duration of motor blockade.[17,18] In our study, however, we found a significant difference in the TAMB between the two groups, in favour of the clonidine group, but we failed to achieve statistical significance in the duration of the motor block. The higher doses of clonidine have been reported to cause important decreases in arterial pressure and marked sedation.[19,20,21] However, as our results demonstrate, a small dose of intrathecal clonidine is not usually associated with systemic side effects, such as bradycardia, hypotension or sedation.[13]

Clonidine has been used intrathecally in different doses. The dose of clonidine used in the present study corresponds to that of van Tuijl et al. who administered intrathecal clonidine in a dose of 25 mcg/kg.[22] The results of our study demonstrates that that the addition of clonidine in doses of 25 µg to Bupivacaine (7.5 mg) and 25 µg to bupivacaine (7.5 mg) plus fentanyl (12.5 µg) truncates the time of onset of sensory and motor block. Similar results were observed by Strebel et al.[23] and Gecaj-Gashi et al.[24] who reported shorter onset of sensory and motor block in patients receiving intrathecal clonidine. Grace et al., however observed prolonged time to onset of motor block in pethidine-clonidine group which is in contrast to the results of our study.[25] The difference in the result could be due to the fact that higher doses of pethidine 0.75 mg/kg was used in this study. It is possible that the higher dose of intrathecal pethidine could mask the effect of intrathecal clonidine.

We also observed significant prolongation of the duration of motor block in the groups A and C. Singh et al.[26] and Benhamou et al. [27] also reported significant prolongation of motor block when clonidine was used as an adjuvant for intrathecal use. The time of duration of motor block was similar in the group A and C. Similar results were reported by Nazareth et al. [28] who obtained corresponding duration of motor block in the intrathecal clonidine group and in a group where combination of intrathecal clonidine and fentanyl were administered.

Postoperatively, lower VAS scores were observed for 12h and significantly reduced cumulative 24h supplemental analgesic consumption was noted in groups receiving intrathecal clonidine, indicating good postoperative analgesic effect. The results of our study are comparable to those of Strebel et al.,[23] Merivirta et al.,[29] and Benhamou et al.[27] where addition of clonidine intrathecally resulted in significantly reduced VAS scores and significant reduction in postoperative analgesic consumption.

Intrathecal clonidine has been reported to result in intraoperative hypotension.[30,31] However, we observed stable hemodynamics among all the groups without any incidence of respiratory depression. This could be explained by adequate preloading which was performed in all the patients prior to subarachnoid block. In addition, the dose used in our study was small, and the mean level of anesthesia achieved was T8-9. Our results are similar to those of Singh et al. who observed no significant difference in HR and blood pressure in patients receiving 50 µg and 75 mcg of clonidine

intrathecally Undergoing cesarean section.[26] Similarly, Nazareth et al. also reported stable hemodynamic parameters in the groups receiving intrathecal clonidine and fentanyl combination.[28] However, Dobrydnjov et al. reported significant decreases in patients receiving clonidine and fentanyl intrathecally. The difference could be explained by the fact that they used 3.5 ml of hyperbaric bupivacaine and clonidine as compared to the present study, accounting for higher level of sensory blockade achieved and thus explaining hypotension.[32]

Patients in groups A and C were sedated as evidenced by higher sedation scores. However, sedation never exceeded grade 2 and did not cause any problems in any of the patients. Singh et al.[26] and Nazareth et al.[28] also reported mild to moderate degree of sedation in the clonidine groups. Clonidine is known to cause sedation, and this hypnotic response is believed to be mediated via locus coeruleus where alpha-2- adrenergic receptors are abundant.[31]

A potential limitation of our study design relates to small sample size. Secondly, we did not attempt dose-response effect by using various doses of clonidine. Recently, there are few studies which report beneficial effects of using 30 or even 15 mcg of intrathecal clonidine with minimal adverse effects.[33,44] possibly; further reducing the dose of clonidine could have elucidated dose-response relationship.

Conclusion

To conclude, our study demonstrated that the use of intrathecal fentanyl and clonidine in combination as adjuvant to hyperbaric bupivacaine in very low dose in surgical procedures provides good quality of intraoperative analgesia, hemodynamic stability, minimal side effects and excellent quality and duration of postoperative analgesia.

References

1. Wheatley RG, Schug SA, Watson D. Safety and efficacy of postoperative epidural analgesia. Br J Anaesth. 2001 Jul;87(1):47–61.
2. Rodgers A, Walker N, Schug S, McKee A, Kehlet H, van Zundert A, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ. 2000 Dec 16;321(7275):1493.
3. Macfarlane AJR, Prasad GA, Chan VWS, Brull R. Does regional anesthesia improve outcome after total knee arthroplasty? Clin Orthop. 2009 Sep;467(9):2379–402.
4. Comparison of outcomes of using spinal versus generalanesthesia in total hip arthroplasty. Am J Orthop (Belle Mead NJ) 2007;36:E101-6
5. Rawal N, Schollin J, Wesstrom G. Epidural versus combined spinal epidural block for cesarean section. Acta Anaesthesiol Scand 1988; 32: 61-6.
6. Leo S, Sng BL, Lim Y, Sia AT. A randomized comparison of low doses of hyperbaric bupivacaine in combined spinal-epidural anesthesia for cesarean delivery. Anesth Analg 2009; 109: 1600-5.
7. Ngan Kee WD, Khaw KS, Lee BB, Lau TK, Gin T. A doseresponse study of prophylactic intravenous ephedrine for the prevention of hypotension during spinal anesthesia for cesarean delivery. Anesth Analg 2000; 90: 1390-5.
8. Tercanli S, Schneider M, Visca E, Hösli I, Troeger C, Peukert R et al. Infl uence of volume preloading on uteroplacental and fetal circulation during spinal anaesthesia for caesarean section in uncomplicated singleton pregnancies. Fetal Diagn Th er 2002; 17: 142-6.
9. Hindle A (2008) Intrathecal opioids in the management of acute postoperative pain. Continuing Education in Anaesthesia, Critical Care and Pain. Br J Anaesth 8(3): 81-85.
10. Maze M, Tranquilli W (1991) Alpha-2 adrenoceptor agonists: defining the role in

clinical anaesthesia. Anaesthesiology 74 (4): 581 605.

11. Roussel JR, Heindel L (1999) Effect of intrathecal fentanyl on duration of bupivacaine spinal blockade for outpatient knee arthroscopy. AANA J 67(4) 337-343.
12. Mercier FJ, Dounas M, Bouaziz H, et al. The effect of adding a minidose of clonidine to intrathecal sufentanil for labour analgesia. Anesthesiology 1998;89: 594-601. http://dx.doi.org/10.1097/00000542-199809000-00007
13. Sites BD, Christopher R, Biggs R, et al. Intrathecal clonidine added to a bupivacaine-morphine spinal improves postoperative analgesia following total knee arthroplasty. Anesthesiology 2002;96:A918.
14. De Kock M. Gauthier P. Fanord L. Intrathecal ropivacaine and clonidine for ambulantory knee arthroscopy. A dose response study. Anesthesiology 2001;94:574-8. http://dx.doi.org/10.1097/00000542-200104000-00008.
15. Gautier PE, De Kock M, Luc F, et al. Intrathecal clonidine combined with sufentanil for labour analgesia. Anesthesiology 1998;88:651-6. http://dx.doi.org/10.1097/00000542-199803000-00015
16. Juliao MC, Lauretti GR. Low-dose intrathecal clonidine combined with sufentanil as analgesic drugs in abdominal gynecological surgery. J Clin Anesth 2000;12:357-62. http://dx.doi.org/10.1016/S0952-8180(00)00171-9
17. Dobrydnjov I, Axelsson K, Thorn SE, et al. Clonidine combined with small-dose bupivacaine during spinal anesthesia for inguinal herniorrhaphy: a randomized double-blinded study. Anesth Analg2003;96:1496-503. http://dx.doi.org/10.1213/01.ANE.0000061110.62841.E9
18. Filos KS, Goudas LC, Patroni O, et al. Hemodynamic and analgesic profile after intrathecal clonidine in humans: a dose-response study. Anesthesiology 1994;81:591-601. http://dx.doi.org/10.1097/00000542-199409000-00011
19. Racle JP, Benkhadra A, Poy JY, et al. Prolongation of isobaric bupivacaine spinal anesthesia with epinephrine and clonidine for hip surgery in the elderly. Anesth Analg 1987;66:442-6. http://dx.doi. org/10.1213/00000539-198705000-00013.
20. Bonnet F, Buisson VB, Francois Y, et al. Effects of oral and subarachnoid clonidine on spinal anesthesia with bupivacaine. Reg Anesth 1990;15:211-4.
21. Filos KS, Goudas LC, Patroni O, et al. Hemodynamic and analgesic profile after intrathecal clonidine in humans: a dose-response study. Anesthesiology 1994;81:591-601. http://dx.doi.org/10.1097/00000542-199409000-00011
22. Pan PM, Huang CT, Wei TT, et al. Enhancement of analgesic effect of intrathecal neostigmine and clonidine on bupivacaine spinal anaesthesia. Reg Anesth Pain Med 1998;23:49-56.
23. Fogarty DJ, Carabine UA, Milligan KR. Comparison of the analgesic effects of intrathecal clonidine and intrathecal morphine after spinal anaesthesia in patients undergoing total hip replacement. Br J Anaesth 1993;71:661-4. http://dx.doi.org/10.1093/bja/71.5.661 Anesthesiology 1998;88:651-6. http://dx.doi.org/10.1097/00000542-199803000-00015
24. van Tuijl I, van Klei WA, van der Werff DB, 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. Br J Anaesth 2006;97:365-70.
25. Strebel S, Gurzeler JA, Schneider MC, Aeschbach A, Kindler CH. Small-dose intrathecal clonidine and isobaric bupivacfor orthopedic surgery: A dose-response study. Anesth Analg 2004;99:1231-8.aine
26. Gecaj-Gashi A, Terziqi H, Pervorfi T, Kryeziu A. Intrathecal clonidine added to small-dose bupivacaine prolongs postope-rative analgesia in patients undergoing transurethral surgery. Can Urol Assoc J 2012;6:25-9.
27. Grace D, Milligan KR, Morrow BJ, Fee JP. Co-administration of pethidine and clonidine: A spinal anaesthetic technique for total hip replacement. Br J Anaesth 1994;73:628-33.
28. Singh R, Gupta D, Jain A. The effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain after lower segment caesarean section: A randomized control trial. Saudi J Anaesth 2013;7:283-90.
29. Merivirta R, Kuusniemi K, Jaakkola P, Pihlajamäki K, Pitkänen M. Unilateral spinal anaesthesia for outpatient surgery: A comparison between hyperbaric bupivacaine and bupivacaine-clonidine combination. Acta Anaesthesiol Scand 2009;53:788-93.
30. Staikou C, Paraskeva A. The effects of intrathecal and systemic adjuvants on subarachnoid block. Minerva Anestesiol 2014;80:96-112.
31. Gabriel JS, Gordin V. Alpha 2 agonists in regional anesthesia and analgesia. Curr Opin Anaesthesiol 2001;14:751-3.
32. Dobrydnjov I, Axelsson K, Gupta A, Lundin A, Holmström B, Granath B. Improved analgesia with clonidine when added to local anesthetic during combined spinal-epidural anesthesia for hip arthroplasty: A double-blind, randomized and placebo-controlled study. Acta Anaesthesiol Scand 2005;49:538-45.
33. Engelman E, Marsala C. Efficacy of adding clonidine to intrathecal morphine in acute postoperative pain: Meta-analysis. Br J Anaesth 2013;110:21-7.
34. Thakur A, Bhardwaj M, Kaur K, Dureja J, Hooda S, Taxak S. Intrathecal clonidine as an adjuvant to hyperbaric bupivacaine in patients undergoing inguinal hernior-rhaphy: A randomized double-blinded study. J Anaesthesiol Clin Pharmacol 2013;29:66-70.