Original Research Article

Indian Journal of Anesthesia and Analgesia
January – February 2020; 7(1) (Part -II): 215-222
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.7120.29

Comparison of the Efficacy of Neuraxial Blockade Analgesic Effect between Intrathecal Clonidine and Tramadol as An Adjuvant with 0.5% Bupivacaine

P Sridhar[1], VA Sabapathy[2], R Shankar[3]

[1]Associate Professor, Department of Anesthesiology, Danalakshmi Srinivasan Medical College and Hospitals, Perambalur, Tamil Nadu 621113, India. [2]Professor, Department of Anesthesiology [3]Professor, Department of Preventive Medicine, Vinayaka Missions Kirupananda Variyar Medical College and Hoapital, Salem, Tamil Nadu 636308, India.

Abstract

Background: A number of adjuvants in the form of opioids analgesics were routinely used intrathecally to prolong the analgesia effect both in the intraoperative and postoperative period. Clonidine and tramadol were the common agents used intrathecally along with bupivacaine for increasing the duration of analgesia. *Aim:* To assess and compare the neuraxial blockade analgesic effect between intrathecal clonidine and intrathecal tramadol along with 0.5% hyperbaric bupivacaine for lower limb surgeries. *Methodology:* A prospective double blinded randomized study was conducted for a period of one year at Dhanalakshmi Srinivasan Medical College and Hospital. A total of 100 patients who had been posted for elective lower limb surgery were included in our study and they were randomized into two groups of 50 each. Group A patients received clonidine hydrochloride 37.5 mcg (0.25 ml) and Group B patients received tramadol 25 mg (0.5 ml) and both the groups received 0.5% hyperbaric bupivacaine hydrochloride (3 ml) along with normal saline. Assessment of pain score was done using VAS scale and the motor blockade was assessed using Bromage motor blockade score and the vital parameters were also assessed along with it. *Results:* The onset of sensory analgesia was found to be much faster and the duration of sensory analgesia was found to be more prolonged among the group which received clonidine and the pain score which was measured using VAS was higher among the patients who received tramadol and the difference was found to be statistically significant ($p < .05$). The duration of motor function recovery was almost similar in both the groups and no significant side effects reported between the two groups. *Conclusion:* Both the groups were effective in producing adequate surgical anesthesia with hemodynamic stability without causing serious adverse events but clonidine group was found to have a faster onset of action with prolonged duration of analgesia.

Keywords: Clonidine; Tramadol; Intrathecal; Analgesia.

How to cite this article:
P Sridhar, VA Sabapathy, R Shankar. Comparison of the efficacy of neuraxial blockade analgesic effect between intrathecal clonidine and tramadol as an adjuvant with 0.5% bupivacaine. Indian J Anesth Analg. 2020;7(1 Part -II):215-222.

Introduction

Local anesthetic agents are the common drugs used for spinal anesthesia and because of its early onset and short duration of action additional requirement of analgesia is needed much earlier during the postoperative period. A number of adjuvants in the form of opioids analgesics were routinely used intrathecally to prolong the analgesia effect both in the intraoperative and postoperative period. Use

Corresponding Author: VA Sabapathy, Professor, Department of Anesthesiology, Vinayaka Missions Kirupananda Variyar Medical College and Hoapital, Salem, Tamil Nadu 636308, India.

E-mail: Sabapathyva@yahoo.com

Received on 30.11.2019, **Accepted on** 17.12.2019

of opioids as intrathecal analgesia has a prolong analgesic effect which extends throughout the postoperative period without significant motor or autonomic blockade. However, few side effects such as pruritus, nausea, vomiting, urinary retention, respiratory depression has prompted future research towards nonopioid analgesics which would cause less serious adverse events.[1-3]

Clonidine being a selective alpha (α) 2 agonist agent, commonly used as a premedication agent when the patient is given general anesthesia, as it has the advantage of reducing the additional usage of analgesics and anesthetic drugs intraoperatively. Clonidine when used intrathecally it produces analgesic activity by indirectly inhibiting the activity of Wide Dynamic Range (WDR) neurons.[4] Other than intrathecal route clonidine can also be used orally, epidural, spinal or parenteral route for obtaining analgesic effect in the postoperative period.[5] The dosage of clonidine used in the previous studies ranged between 15–150 mcg without producing any significant side effects.[6]

Tramadol is a synthetic opioid introduced initially in mid -1970s. It has opioid agonist activity for all types of opioid receptors with more selectivity for mu (μ)-receptors. Tramadol, a synthetic 4-phenyl-piperidine analog of codeine, is a racemic mixture of two enantiomers, with synergistic antinociceptive interaction. The (+) enantiomer has moderate affinity for the opioids μ-receptor and inhibits serotonin uptake, and the (−) enantiomer is a potent norepinephrine synaptic release inhibitor and through this receptor it provides an effective analgesic property when given intrathecally. Moreover tramadol is very much cost-effective.[7]

Previous studies done earlier had compared clonidine with other sedatives or hypnotics like fentanyl or midazolam to assess the difference in hemodynamic response as well as the analgesic property, not much studies done previously had compared the analgesic property between clonidine and tramadol and so, the present study was undertaken to assess the effect of these two drugs in providing analgesia postoperatively and hemodynamic response.[8-10]

Aim

To assess and compare the neuraxial blockade analgesic effect between intrathecal clonidine and intrathecal tramadol along with 0.5% hyperbaric bupivacaine for lower limb surgeries.

Materials and Methods

A prospective double blinded randomized study was conducted for a period of one year at Dhanalakshmi Srinivasan Medical College and Hospital in the Department of anesthesiology. The study was started after obtaining clearance from the institutional ethical committee and informed consent was obtained from all the study subjects involved in the study. All patients in the age group of 18 to 60 years with ASA grading of I or II and have been posted for elective lower limb surgeries under spinal anesthesia were included as our study subjects. A total of 100 patients were included in our study and they were randomized into two groups of 50 each. Randomization was done through lot system and double blinding technique was followed where both the patient and the anesthetist is not aware of the which patient belong to which group. Group a patients received clonidine hydrochloride 37.5 mcg (0.25 ml) and Group B patients received tramadol 25 mg (0.5 ml) and both the groups received 0.5% hyperbaric bupivacaine hydrochloride (3 ml) along with normal saline. A complete preanesthetic evaluation was performed on all patients before the start of the procedure. Preanesthetic medication IV midazolam was given to all the patients. Under strict aseptic precautions midline lumbar puncture was performed using a 25 G quincke needle with patient in lateral decubitus position and the anesthetic drugs were given based on the group the patient belong to. Patients was then placed in supine position, the time when the intrathecal injection was given was considered as 0 mins and from then the patients were monitored every 5 mins for the first 15 mins and then onwards they were monitored for every half an hour till 180 mins. During this time the vital parameters such as heart rate, systolic and diastolic BP, respirator rate and SpO_2 were monitored and recorded along with the time duration for sensory blockade, motor blockade, duration of analgesia and sedation. Assessment of pain score was done using VAS scale and the motor blockade was assessed using Bromage motor blockade score and these two parameters were assessed upto 360 mins. Apart from the above mentioned drugs when the patients complained more pain a rescue analgesic injection of diclofenac 75 mg was given. Duration of effective analgesia was defined as the time interval between the onset of subarachnoid block and the time to reach VAS ≥ 4. Patient was kept in the recovery room till complete recovery had occurred from motor blockade and later shifted to the postoperative room. In the postoperative room patient was monitored for the occurrence of any side effects like vomiting, dry mouth or pruritus for 24 hours.

All the data were entered and analyzed using SPSS version 22. Student *t*-test and Chi-square test was used to derive the statistical inference by comparing the parametric and nonparametric variables that were measured among the two groups, considering $p < 0.05$ as statistical significance.

Results

The mean age group between the two groups was between 40 and 42 and in both the groups females outnumbered males. Other demographic variables like height, weight and BMI did not show statistical significant difference between the two groups. Most of the surgeries performed did not extend more than 2 hours in both the groups and the duration of the surgery did not show statistical significant difference between the two groups shows as in Table 1. The mean onset of sensory analgesia was found to be much quicker in the group that received clonidine (151.4 mins *vs* 172.4 mins) and similarly the mean duration of sensory analgesia was prolonged among the patients who received clonidine compared to the patients who received tramadol (319.6 mins *vs* 295.8 mins) and the difference in the time duration between the two groups was found to be statistically significant. The maximum sensory blockade among both the groups was achieved between T6 and T8 levels and there was no difference in the levels of achievement of sensory blockade and similarly the mean duration of full motor recovery was slightly more in the clonidine (286.7 mins) group compared to tramadol group (282.9 mins) but the difference was not statistically significant shows in Table 2.

Pain score was assessed using the visual analog scale and the motor functional activity was assessed using the Bromage scale score in our study subjects. The VAS score for the first 120 mins was zero among both the groups and a statistical significant difference was seen in VAS score from 180 mins to 300 mins, in which the mean VAS score among the tramadol group was higher than the mean VAS score among the clonidine group.

Table 1: Comparison of the demographic variables and the duration of surgery between the two groups

Variables	Group A (clonidine hydrochloride group)	Group B (tramadol group)	*p* - value
Age	40.25 ± 9.76	41.92 ± 10.26	0.891
Gender (M/F)	12/38	10/40	0.585
Height (in cms)	165.26 ± 6.21	163.45 ± 7.59	0.717
Duration of surgery (in mins)	104.6 ± 8.94	99.4 ± 7.48	0.285

Table 2: Comparison of sensory and motor blockade functions between the two groups

Variables		Group A (clonidine hydrochloride group)	Group B (tramadol group)	*p* - value
Mean onset of sensory analgesia (in secs)		151.4 ± 25.5	172.4 ± 32.8	0.0167
Maximum sensory blockade	T6	23	24	0.798
	T8	25	25	
	T10	2	1	
Mean duration of sensory analgesia (mins)		319.6 ± 27.5	295.8 ± 28.8	0.0108
Mean duration of full motor recovery (in mins)		286.7 ± 21.9	282.9 ± 15.8	0.329

Table 3: Comparison of VAS score and Bromage score between the two groups at various time intervals

Time (mins)	VAS score (mean ± SD)			Bromage score (mean ± SD)		
	Group A	Group B	*p* - value	Group A	Group B	*p* - value
0	0	0	1.00	0	0	1.00
15	0	0	1.00	3	3	1.00
30	0	0	1.00	3	3	1.00
60	0	0	1.00	3	3	1.00
120	0	0	1.00	3 ± 0.36	2.65 ± 0.31	0.0031
180	1.12 ± 0.12	1.72 ± 0.18	0.0028	2.45 ± 0.28	2.39 ± 0.29	0.0851
240	2.16 ± 0.35	3.01 ± 0.41	0.0019	2.21 ± 0.45	2.18 ± 0.25	0.761
300	2.85 ± 0.43	3.45 ± 0.56	0.0197	1.08 ± 0.29	0.55 ± 0.13	0.0017
360	5.65 ± 0.76	6.05 ± 0.81	0.0866	0	0	1.00

The Bromage motor functional score for the first 60 mins was similar among both the groups but a statistical significant difference was seen in the bromage score from 120 to 180 mins, where the mean bromage score was high among the clonidine group compared to tramadol group and a similar pattern was observed at 300th min shows in Table 3.

Very few side effects were reported among the study subjects in both the groups such as

Table 4: Incidence of side effects between the two groups

Side effects	Group A (clonidine hydrochloride group)	Group B (tramadol group)	*p* - value
Hypotension	4 (8%)	2 (4%)	0.0816
Bradycardia	2 (4%)	2 (4%)	1.000
Vomiting	1 (2%)	3 (6%)	0.219
Dryness of mouth	1 (2%)	0	0.384

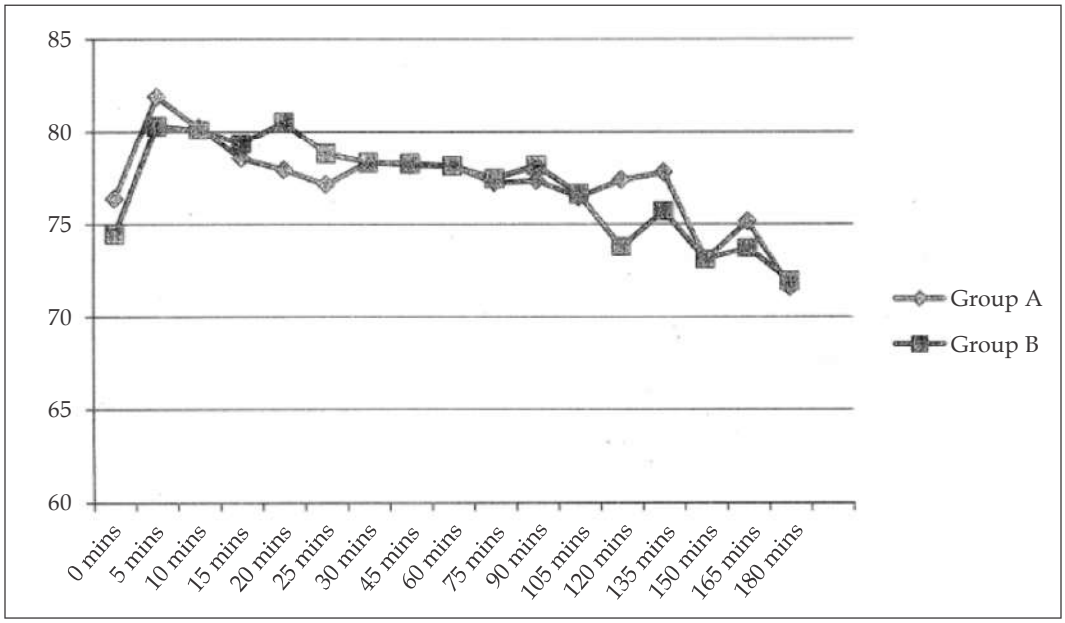

Fig. 1: Heart rate comparison between the two groups over a period of time

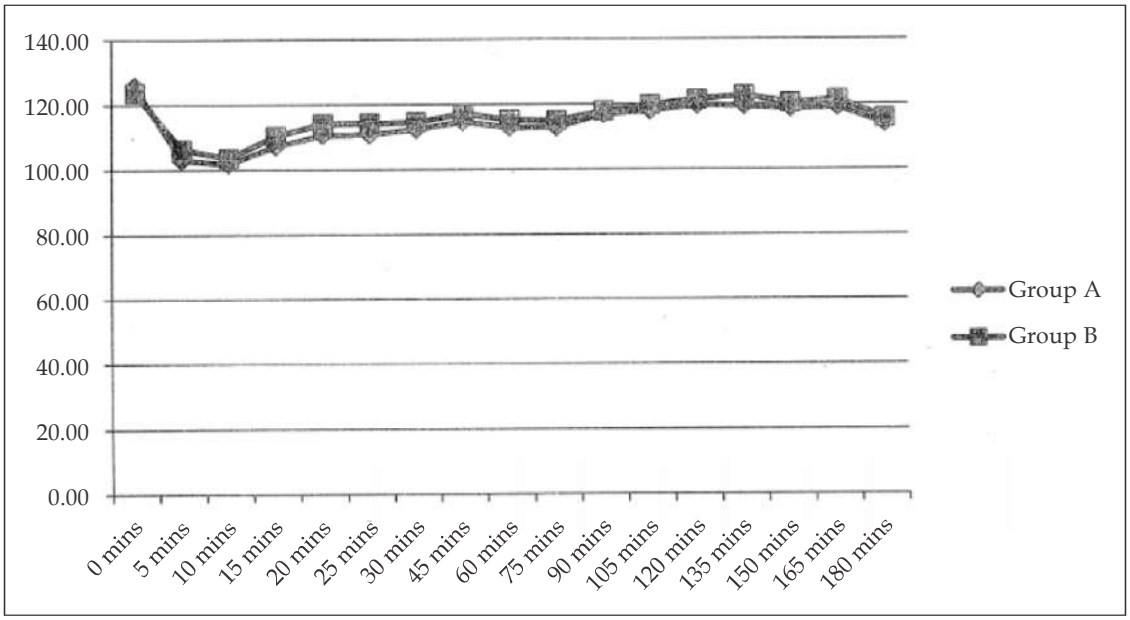

Fig. 2: Systolic blood pressure comparison between the two groups over a period of time

hypotension, bradycardia, vomiting and dryness of mouth and the distribution of these side effects were very minimal among the patients in both the groups and none of the side effect had shown a statistical significant difference between the two groups shows in Table 4. The vital parameters measured in the study subjects were heart rate, systolic and diastolic blood pressure and SpO_2. All these vitals were measured from the time of infusion of the anesthetic drug upto 180 minutes and the readings between the two groups were almost similar no statistical significant difference was observed between them at any point of time. It is represented shows in Figs. 1–4.

Discussion

Clonidne, being an alpha-2 agonist when added to local anesthetics had shown an excellent surgical anesthesia. It increases the sensory and motor block of the local anesthesia. Studies had shown that intrathecal administration of opioid provides effective postoperative analgesia but with a risk of causing respiratory depression.[6] In contrast to the opioid analgesics tramadol is a drug which shows less affinity towards μ-receptors and so, causing a minimal effect on respiratory depression. Added to this tramadol also inhibits the reuptake of serotonin

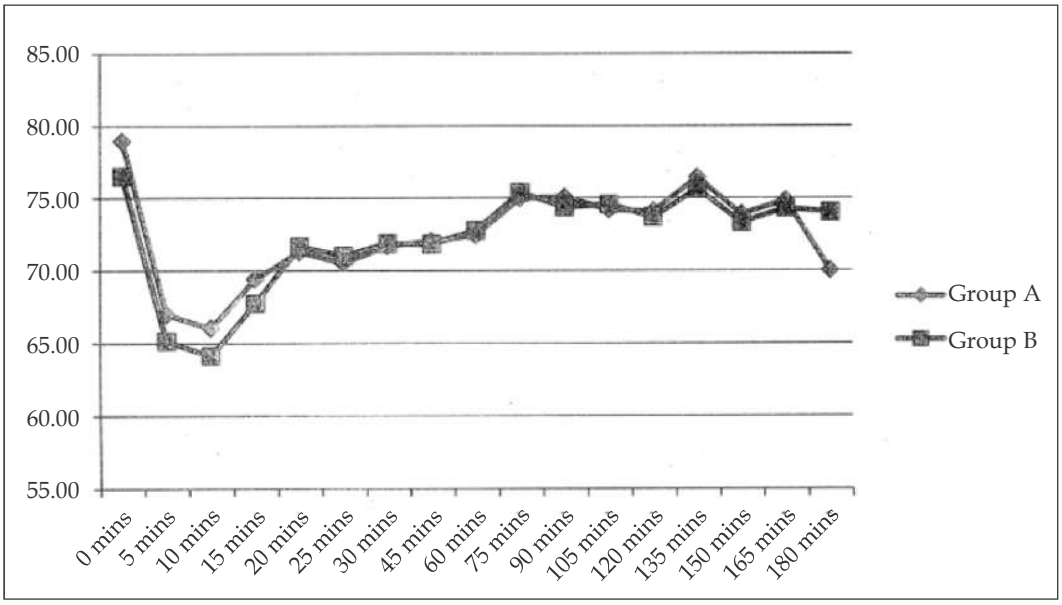

Fig. 3: Diastolic blood pressure comparison between the two groups over a period of time

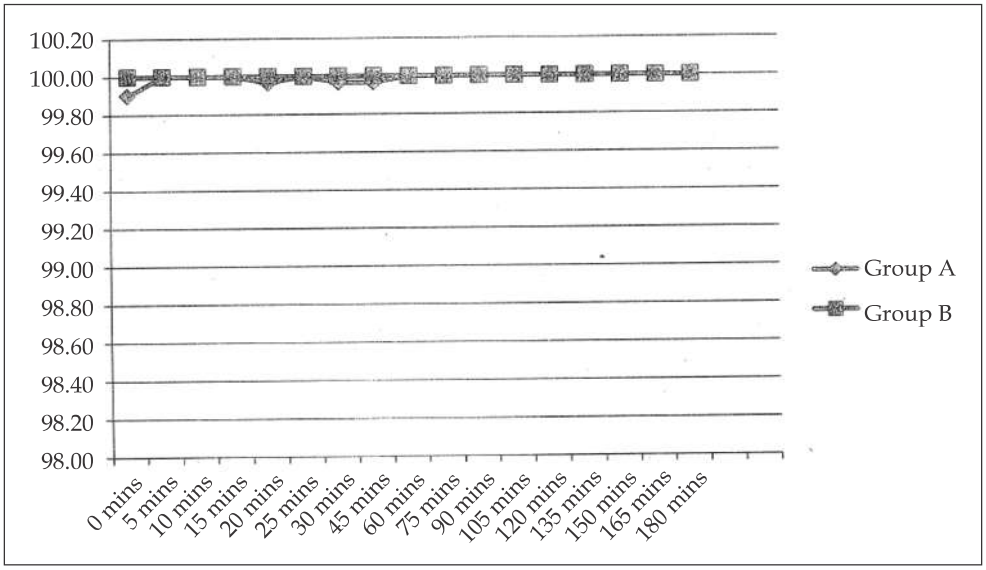

Fig. 4: SpO_2 comparison between the two groups over a period of time

and norepinephrine in the spinal cord and so, no neural toxicity was reported.[11]

In the present study, we compared the analgesic effects of clonidine and tramadol when given intrathecally along with the routine spinal anesthesia for patients undergoing lower limb surgeries. It was done through randomization technique by dividing the entire study subjects into two groups and one group received tramadol and the other group received clonidine by following a double blinded technique. The demographic variables and the types of surgeries along with the duration of surgery were found to be almost similar in both the groups without any significant variations between the two groups.

In our study, we found that the mean time of onset of sensory analgesia among the group that has received clonidine drug was 151.4 mins compared to the group that received tramadol which was 172.4 mins and the difference was found to be statistically significant. It is similar to the previous studies done by Khezri et al. and Bajwa et al. where they had shown that the onset of sensory analgesia was much earlier in the group which received clonidine, these two studies compared clonidine with either bupivacaine or fentanyl and proved clonidine was much superior in achieving the onset of sensory analgesia.[10,12] In the current study, the maximum level of sensory block that was achieved in both the groups was T6 and T8 where no statistical significant difference was observed between them and a similar type of results was also seen in a study done by Nishikawa et al., in his study he compared fentanyl with tramadol and proved that the maximum level of sensory blockade achieved in both the groups was at T6 level and another study done by Singh et al., comparing clonidine and tramadol and shown that the maximum number of patients had achieved the level of blockade at T8 level.[13,14] The duration of sensory analgesia lasted for 320 mins among the patients received clonidine whereas it was 296 mins among the group that received tramadol and the difference was found to be statistically significant. As most of the studies done earlier had compared the analgesic effect between clonidine and fentayl or fentayl with tramadol or clonidine with bupivacaine, not many studies done comparing clonidine with tramadol.[15–17] So, as per the results of the previous studies it was found that clonidine was much superior to fentanyl and fentanyl was superior to tramadol in achieving the maximum duration of sensory block.

In our study, we didn't find a statistically significant difference in full motor recovery between the two groups whereas studies which had compared clonidine with bupivacaine had showed that the group that received clonidine showed more time for complete motor recovery and the studies done comparing fentanyl with tramadol did not show any significant time difference in full motor recovery and similarly studies comparing clonidine with fentanyl showed no difference in motor recovery time.[17–19]

In the present study, the analgesic effect was assessed by using visual analog scale and through that we found a statistical significant difference was seen in VAS score from 180 mins to 300 mins, in which the mean VAS score among the tramadol group was higher than the mean VAS score among the clonidine group and a similar type of result was observed in the study done by Pratapa Reddy et al. in a tertiary hospital at Hyderabad.[20] In a study, done by Benhamou comparing addition of clonidine to bupivacaine *versus* bupivacaine alone among patients undergoing cesarean section had showed that adding a small dose of Intrathecal Clonidine to Bupivacaine had increased the duration of intraoperative analgesia and the patients were free from pain postoperatively for a longer period and the study further proved that adding fentanyl to clonidine further improves analgesia.[21] Filoskriton in their study, intrathecal Clonidine was used as a solo analgesic for pain relief after cesarean section and they found that the pain scores were lower in Clonidine group patients.[22] A study done by Sanjul Dandona et al. in Uttarkand in comparing between tramadol and fentanyl had found that profound analgesia was seen in fentanyl group rather than tramadol group and similar type of results was seen in studies done by Singh et al., Biswas et al. and Dahlgren et al.[14,23–25] Later after 5 hrs the pain score showed no difference between the clonidine and tramadol group in our study.

In the current study, the mean bromage score was high among the clonidine group compared to tramadol group between 120 and 180 mins which can be explained because of the high sedation effect produced by clonidine compared to tramadol. These results were comparable to the study done by Pratappa Reddy et al. and the results of Dobrydnjov et al. who reported excellent or good operating conditions in patients receiving 15 and 30 mcg clonidine with Bupivacaine.[20,26] In another study, done by Klimscha et al. 12 showed that intrathecal Clonidine 150 mcg added to 0.5% bupivacaine significantly increased the intensity of motor block when compared to 0.5% of bupivacaine

given alone.[27] A study done by Sanjul Dandona et al. showed that the motor block was more prolonged among the group that received fentanyl compared to the group received tramadol.[23] There was no significant difference in the intraoperative heart rate between the two groups. A small dose of intrathecal clonidine is not usually associated with side effects such as bradycardia, hypotension or sedation. Accordingly studies using very low-doses of intrathecal clonidine 15 to 30 mcg. found no hemodynamic instability.[6,9] A similar type of results was also observed with systolic and diastolic blood pressure. Most of the studies using 37.5 mcg to 150 mcg[28] reported significant hypotension and bradycardia while with higher doses of 300 and 450 mcg, relative hemodynamic stability is observed, suggesting a pressor effect on peripheral sites as shown by Goudas Leonidas et al. and H Saxena et al. found in their study that 30% of patients who received 37.5 mcg Clonidine had a significant fall in mean arterial pressure and heart rate and 90% patients were sedated.[29,30] Another study done by Alsheshmi JA et al. 17 in 2003 found that intrathecal tramadol did not seem to influence the intraoperative hemodynamic profile as it acts only on the μ-receptors sparing the alpha or beta (β)-receptors which predominate the cardiovascular system.[31] In our study, the dose of clonidine used was 37.5 mcg but the hemodynamic stability was well-maintained as that of the tramadol group.

The incidence of side effects such as hypotension, bradycardia, nausea, vomiting and dryness of mouth was found to occur in very minimal number of patients in both the groups and it is similar to the results derived by Chiari Astrid et al. and Filoskritonetal and in both these studies clonidine was compared with fentanyl and the incidence of the above mentioned side effects was very minimal among these groups. Another study Seah YS et al. which used clonidine dose of 75 mcg and found the incidence of hypotension was slightly higher but well-managed with ephedrine and atropine.[22,32,33]

Conclusion

Bupivacaine when combined with clonidine or tramadol it provides acceptable subarachnoid block for performing lower limb surgeries. Both the groups were effective in producing adequate surgical anesthesia with hemodynamic stability without causing serious adverse events but clonidine group was found to have a faster onset of action with prolonged duration of analgesia without any prolongation in the time for full motor recovery.

References

1. Kaur M. Adjuvants to local anesthetics: A combination wisdom. Anesth Essays Res 2010;4(2):122–23.
2. Kaur J, Bajwa SS. Comparison of epidural butorphanol and fentanyl as adjuvants in the lower abdominal surgery: A randomized clinical study. Saudi J Anesth 2014; 8:167–71.
3. Hunt CO, Naulty JS, Bader AM, et al. Perioperative analgesia with subarachnoid fentanyl-bupivacaine for Cesarean delivery. Anesthesiology 1989 Oct;71(4):535–40.
4. Eisenach JC. Overview: First International Symposium on α2 adrenergic mechanism of spinal anesthesia. Reg Anesth. 1993 Jul-Aug;18(4):207–12.
5. Chiari A, Eisenach JC. Spinal Anesthesia. Mechanisms, agents, methods and safety. Reg Anesth Pain Med. 1998 Jul-Aug;23(4):357–62.
6. Van Tuiji, Van Klei, Van der Werff DB, et al. The effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain and morphine requirement and cesarean section: A randomized controlled trial. Br J Anesth 2006;97:365–70.
7. Chakraborty S, Chakravarti J, Bhattacharya D. Intrathecal tramadol added to bupivacaine as spinal anesthetic increases analgesic effect of the spinal blockade after major gynecological surgeries. Indian J Pharmacol 2008;40(4):180–82.
8. Belzarena SD. Clinical effects of intrathecally administered fentanyl in patients undergoing cesarean section. Anesth Analg 1992 May;74(5):653–57.
9. Bonnet F, Buisson VB, Francois Y, et al. Effects of oral and subarachnoid clonidine on spinal anesthesia with bupivacaine. Reg Anesth. 1990;15(4):211–14.
10. Khezri MB, Rezaei M, Delkhosh Reihany M, et al. Comparison of postoperative analgesic effect of intrathecal clonidine and fentanyl added to bupivacaine in patients undergoing cesarean section: A prospective randomized double-blind study. Pain Res Treat 2014;2014:513628.0–7.
11. Vickers MD, O'Flaherty D, Szekely SM, et al. Tramadol: pain relief by an opioid without depression of respiration. Anaesthesia. 1992;47(4):291–96.
12. Bajwa BS, Singh AP, Rekhi AK. Comparison of intrathecal clonidine and fentanyl in hyperbaric bupivacaine for spinal anesthesia and postoperative analgesia in patients undergoing lower abdominal surgeries. Saudi J Anesth 2017 Jan-Mar;11(1):37–40.

13. Nishikawa K, Kanaya N, Nakayama M, et al. Fentanyl improves analgesia but prolongs the onset of axillary brachial plexus block by peripheral mechanism. Anesthesia and Analgesia 2000;91(2):384–87.
14. Singh R, Gupta D, Jain A. The effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain after lower segment cesarean section: A randomized control trial. Saudi J Anesth 2013 Jul-Sep;7(3):283–90.
15. Shidhaye RV, Shah BB, Joshi SS, et al. Comparison of clonidine and fentanyl as adjuvant to intrathecal bupivacaine for spinal anesthesia and postoperative analgesia in patients undergoing cesarean section. Sri Lankan J Anesthesiol 2013;22:15–20.
16. Bhattacharjee A, Singh NR, Singh SS, et al. A comparative study of Intrathecal clonidine and fentanyl along with bupivacaine in spinal anesthesia for cesarean section. J Med Soc 2015;29(3):145–59.
17. Kaur U, Sidhu J, Aggarwal S. Evaluation of intrathecal bupivacaine-clonidine combination in lower abdominal surgeries: A double blind randomized control study. Sch J Appl Med Sci 2015;3:379–86.
18. Alhashemi JA, Kaki AM. Effect of intrathecal tramadol administration on postoperative pain after transurethral resection of prostate. Br J Anesth 2003;91: 536–40.
19. Baraka A, Jabbour S, Ghabash M, et al. A comparison of epidural tramadol and epidural morphine for postoperative analgesia. Can J Anaesth. 1993;40(4):308–13.
20. Pratapa Reddy G, Sarada G. A Comparative Study of Intrathecal Clonidine and Intrathecal tramadol for Prolongation of Neuraxial blockade analgesia with 0.5% Bupivacaine in lower limb surgeries. MRIMS Journal of Health Sciences 2015;4(1); 70–73.
21. Benhamou. Intrathecal clonidine and fentanyl with hyperbaric bupivacaine improves analgesia during cesarean section.Anesthesia and Analgesia. 1998 Sep;87(3): 609–613.
22. Filos Kriton. Intrathecal clonidine as a sole analgesic for pain relief after cesarean section Anesthesiology 1992;77(l2);267–74.
23. Sanjul Dandona, Neha Batra, Surendra Singh. Comparison of intrathecal tramadol and fentanyl as adjuvant in abdominal and lower limb surgeries: A randomized clinical study. International Journal of Medical and Health Research 2017 Feb;3(2): 46–49.
24. Biswas BN, Rudra A, Bose BK, et al. Intrathecal fentanyl with hyperbaric bupivacaine improves analgesia during cesarean delivery and in early postoperative period. Indian J Anesth 2002;46(6):469–72.
25. Dahlgren G, Hultstrand C, Jakobsson J, Norman M, Eriksson EW, Martin H. Intrathecal sufentanil, fentanyl, or placebo added to bupivacaine for cesarean section. Anesth Analg. 1997;85(6):1288–93.
26. Dobrydnjov I, Axelsson K, Thörn SE, et al. Clonidine combined with small-dose bupivacaine during spinal anesthesia for inguinal herniorrhaphy: a randomized double-blinded study. Anesth Analg. 2003;96(5):1496–503.
27. Klimscha W, Chiari A. Hemodynamic and analgesic effects of clonidine added repetitively to continuous spinal and epidural block. Anesthesia and Analgesia 1995;80(2):322–27.
28. Sethi BS, Samuel M, Sreevastaava D. Efficacy of analgesic effect of low-dose intrathecal clonide as adjuvant to bupivacaine. Indian J Anesth 2007;51:415–19.
29. Filos KS, Goudas LC, Patroni O, et al. Hemodynamic and analgesic profile after intrathecal clonidine in humans. A dose-response study. Anesthesiology. 1994;81(3):591–28.
30. Saxena H, Singh and Ghildiyal S: Low-dose intrathecal clonidine with bupivacaine improves onset and duration of block with hemodynamic stability. The Internet Journal of Anesthesiology 2010;23(1):1–10.
31. Alhashemi JA, Kaki AM. Effect of intrathecal tramadol administration on postoperative pain after trans urethral resection of prostate. British J Anesth 2003 Oct;91(4):536–40.
32. Chiari Astrid, Lorber Christine, James C, et al. Analgesic and hemodynamic effects of intrathecal clonidine as the sole analgesic agent during first stage of labor: A dose-response study. Anesthesiology 1999 Aug 8;91:388–96.
33. Seah YS, Chen C, Chung KD, et al. Prolongation of hyperbaric bupivacaine spinal anesthesia with clonidine. Ma Zui Xue Za Zhi 1991 Mar;29(1):533–37.