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Chloroprocaine spinal Aanaesthesia and the effects of added Clonidine

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Abstract
Background and Aim: *2-Chloroprocaine (C13H19ClN2O2) an ultra-short acting, ester derivative of benzoic acid, is being investigated intrathecally in small doses (30 to 60 mg) and it was find reliable for procedures of short duration. Clonidine (C9H9Cl2N3) an imidazoline derivative, centrally-acting alpha2-adrenergic agonist, improves the quality of spinal bupivacaine and ropivacaine. It has not been studied in combination with 2-CP. So we conducted this study to evaluate effect of adding clonidine to spinal Chloroprocaine.*
Methods: *In this prospective randomized controlled study, spinal 2-CP (30 mg) with and without clonidine (30 mcg) in 60 adult patients posted for elective surgery of lower abdomen or lower limb. Patients were randomly divided randomly in 2 groups who received intrathecally either chloroprocaine (30mg+0.2 ml saline) or chloroprocaine (30 mg) with clonidine (30 mcg, 0.2ml). Hemodynamic changes, onset and duration of sensory blockade, onset and duration of motor blockade, 2-segment regression time, Peak height for sensory block, time to attain peak height for sensory block were studied in both the groups.*
Results: *Mean systolic and diastolic blood pressures were significantly more decreased in group of patients who received clonidine with intrathecal chloroprocaine. Duration of sensory block averaged 3.90 ± 1.12 sec and 5.10 ± 1.55 sec without clonidine, time of peak heights of sensory block averaged 7.70 ± 1.56 sec with clonidine and 5.84 ± 1.61 sec without clonidine, duration of sensory blockade averaged 101.00 ± 14.99 min with clonidine and 54.77 ± 7.91 min without clonidine, mean 2-segment regression time was 76.63 ± 15.69 min with clonidine and 40.90 ± 6.99 min without clonidine, onset of motor blockade was averaged 4.40 ± 1.28 sec with clonidine and 6.5 ± 1.20 sec without clonidine, mean duration of motor blockade was 91.80 ± 14.47 min with clonidine and 48.30 ± 8.97 min without clonidine.*
Conclusion: *We found significantly enhancement in duration of motor and sensory blockade, peak height of sensory anaesthesia and 2 segment regression time by adding clonidine to intrathecal chloroprocaine. No significant adverse effects were seen in the patients while conducting the study. We found Chloroprocaine to be an effective and safe alternative for lower limb and lower abdominal surgeries of short duration.*
Keywords: *Chloroprocaine, Clonidine, Spinal Anaesthesia, Motor blockade, Sensory blockade.*

Introduction

Local anaesthetics (LA) are indispensable in context of regional anaesthesia and pain management Local anaesthetics (LA) are a heterogeneous group of compounds which block voltage-gated sodium channels. Sodium channel block is caused by conformational change and the creation of a positive charge in the channel lumen.[1] LA can be divided into short-acting (e.g., chloroprocaine), intermediate-acting (e.g., mepivacaine, lidocaine), and long-acting (e.g., bupivacaine, ropivacaine) compounds. For Spinal anaesthesia, the target binding sites are located within the spinal cord (superficial and deep portions) and on the spinal nerve roots in the subarachnoid and epidural spaces. Chloroprocaine being an ultra–short-acting local anesthetic, came in the 1950s.[2] In 1952, Foldes FF[3] first used Chloroprocaine for spinal anaesthesia in 214 patients without neurologic complications. Chloroprocaine ($C_{13}H_{19}ClN_2O_2$) is an ultra-short acting, ester derivative of benzoic acid and has been used intrathecally in small doses (30 to 60 mg) and it was reliable for procedures of short duration. Many drugs have been used in spinal anaesthesia as adjuvant to LA. It has been shown that use of adjunct to spinal anaesthetics significantly improves quality and duration of sensory and motor blockade. TNS can occur with modern chloroprocaine preparations, albeit at a considerably lesser rate (0.6%) than lidocaine (14%), so newer preparation of Chloroprocaine is much safer to use for Spinal anaesthesia.[4] Clonidine ($C_9H_9Cl_2N_3$) is an imidazoline derivate and centrally-acting alpha2-adrenergic agonist, with antihypertensive activity. Clonidine was first used in 1984 in epidural blocks.[5] Epidural clonidine in doses of 25-50 µg/h has been found to have beneficial effects in various study populations like spine instrumentation and orthopaedic procedures.[5]

After taking clearance from ethical committee, we conducted this study in department of Anaesthesiology, Rohilkhand Medical College, Bareilly. In this study we have evaluated and compared the effect of Chloroprocaine alone and in combination with clonidine in lower limb and lower abdominal surgeries.

Methods

This was a prospective randomized controlled study carried out in patients posted for lower limb and lower abdominal surgeries of different specialities. After taking ethical committee clearance, 60 patients were randomly divided into two groups: Group "A" and "B". In Group A, for spinal anaesthesia chloroprocaine (30mg + 0.2 ml saline) was used, while in Group B, for spinal anaesthesia chloroprocaine (30 mg) with clonidine (30 mcg, 0.2ml) was used and the drugs was prepared by an anaesthetist not involved in observations. Spinal anaesthesia was performed with all aseptic precautions at the L2-3 inter-vertebral space with the patient sitting, using the midline approach and a 25-gauge spinal needle. After completing spinal injection, patients were placed supine, continued evaluation of sensory (with pin-prick method) and motor blocks for every 2 mins for first 20 mins, then every 5 mins for 40 mins, and then every 15 mins until the sensory block regressed to S1 dermatome and complete motor block regression was done. The level of sensory block was assessed using the loss of pinprick sensation (24-gauge hypodermic needle); whereas motor block by modified Bromage scale. After surgical anaesthesia was achieved, readiness for surgery was defined as loss of pin prick sensation ≥ T10 along with motor blockade to modified Bromage ≥2. Sensory and motor functions during the procedure were observed on the non-operative side. If the patient complained of pain during surgery, supplemental analgesia with 0.02 mg/kg inj Butarphanol IV was administered. We Compared hemodynamic changes, onset and duration of sensory blockade, onset and duration of motor blockade, 2-segment regression time, peak height for sensory block, time to attain peak height for sensory block, to find out if any side effects/ complications like

nausea, vomiting, bradycardia, hypotension and Transient neurologic symptoms.

In our study we described Bradycardia, when heart rate was reduced to less than 50 beats / min and Hypotension was described when systolic blood pressure was reduced to more than 30% of base line.

Statistical Analysis: The data from the present study was systematically collected, compiled and statistically analysed. Descriptive & inferential statistical analysis were derived from results on continuous measurements, presented as mean ± SD while results on categorical measurements were presented in numbers (%age). Student t test was used to find the significance of the study parameters on a continuous scale between 2 groups (intergroup analysis).

The *p* value was determined to evaluate the level of significance, $p<0.05$ was considered as significant at 5% significance level, while $p<0.01$, significant at 1% was considered as highly significant. Chi Square/ Fisher's exact test was used to find the significance of the study parameters on the categorical scale where ever applicable between 2 or more groups.

The statistical data analysis was done by Microsoft Excel 2016 and Microsoft Word 2016 it was used to generate graphs, charts and tables.

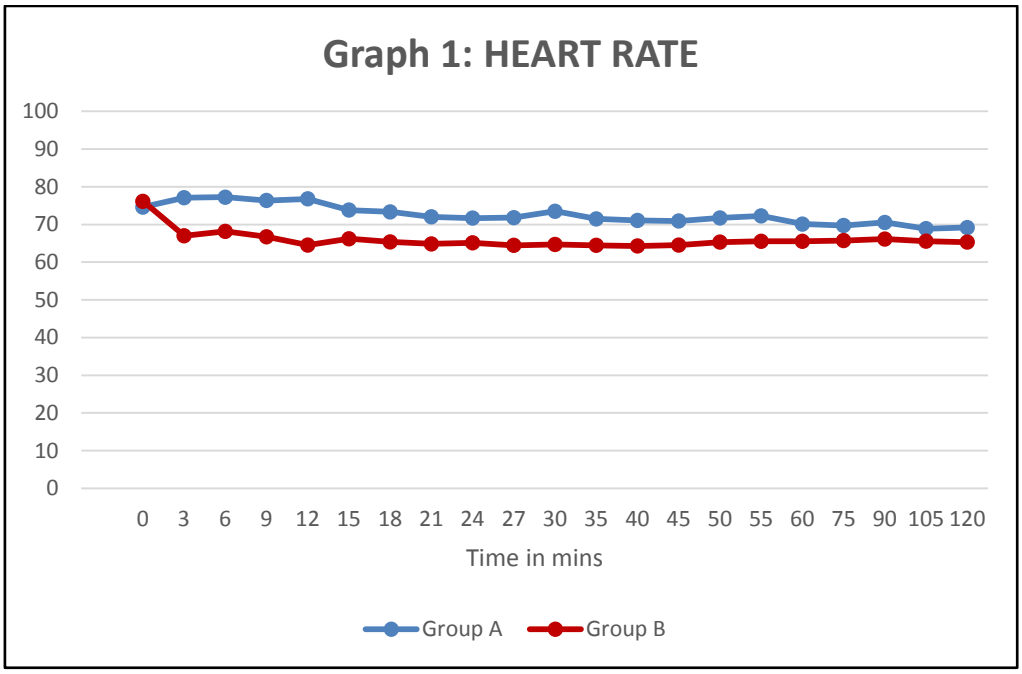
Results

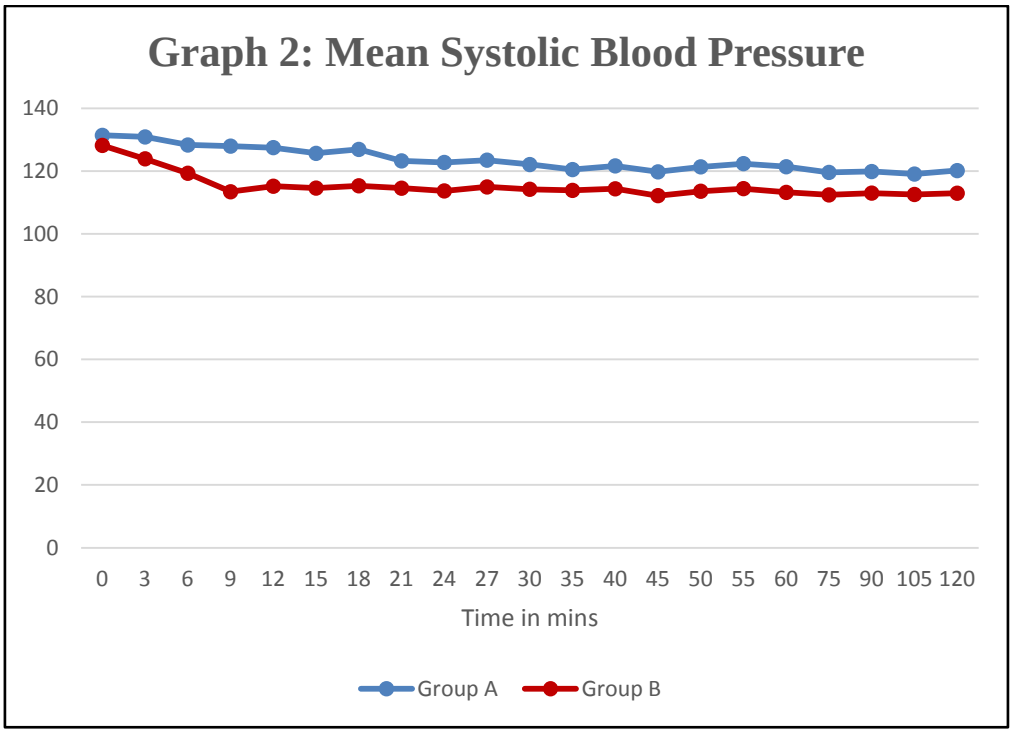
In our study, in comparison between both the groups, mean heart rate was significantly more decreased in group of patients who received clonidine with intrathecal chloroprocaine. In group A there was no incidence of clinically significant bradycardia in any patient while in group B, bradycardia was seen in 2 patients (6.6%), out of which one patient was given 0.5 mg injection Atropine to treat bradycardia. Rest 3 patients recovered without any intervention. In our study mean systolic and diastolic blood pressures were decreased from base line in both the groups after spinal anaesthesia. In comparison between both the groups mean systolic and diastolic blood pressures were significantly more decreased in group of patients who received clonidine with intrathecal chloroprocaine. In patients of group A, there was not clinically significant reduction in blood pressure after spinal anaesthesia while in patients of group B hypotension was seen in 10% of patients in our study. Which was treated with boluses 200ml – 250 ml of iv fluid and only 1 patient required vasoactive agent injection Mephentermin in the dose of 6mg, once. In the present study, we found that mean time of onset of sensory analgesia was less in group of patients who received Chloroprocaine with clonidine. We found that peak height of sensory block attained was higher in group of patients who received Chloroprocaine with clonidine. The mean time taken to achieve highest level of sensory analgesia was significantly more in group of patients who received Chloroprocaine with clonidine. The mean time for two segment sensory regression in was significantly more in group of patients who received Chloroprocaine with clonidine. In the present study mean time taken for sensory regression to L1 was significantly more in group of patients who received Chloroprocaine with clonidine. The mean time of onset of Bromage 3 blockade was significantly less in group of patients who received Chloroprocaine with clonidine. The mean time of total duration of motor block was significantly more in group of patients who received Chloroprocaine with clonidine. We found significantly enhancement in duration of motor and sensory blockade, peak height of sensory anaesthesia and 2 segment regression time by adding clonidine to intrathecal chloroprocaine. No significant adverse effects were seen in the patients while conducting the study.

Table-1 Comparison of Age, Weight and Gender in Between Group A and Group B

	GROUP A	GROUP B		
AGE	42.40 ± 12.29	45.27 ± 13.85	*t*-value 0.848	*p*-value 0.400#
SEX				
MALE	21(70%)	26(86.7%)	X^2 -value 2.455	*p*-value 0.117#
FEMALE	9(30%)	4(13.7%)		
WEIGHT	70.77 ± 6.64	68.50 ± 6.08	*t*-value 1.381	*p*-value 0.1726#

#statistically not significant





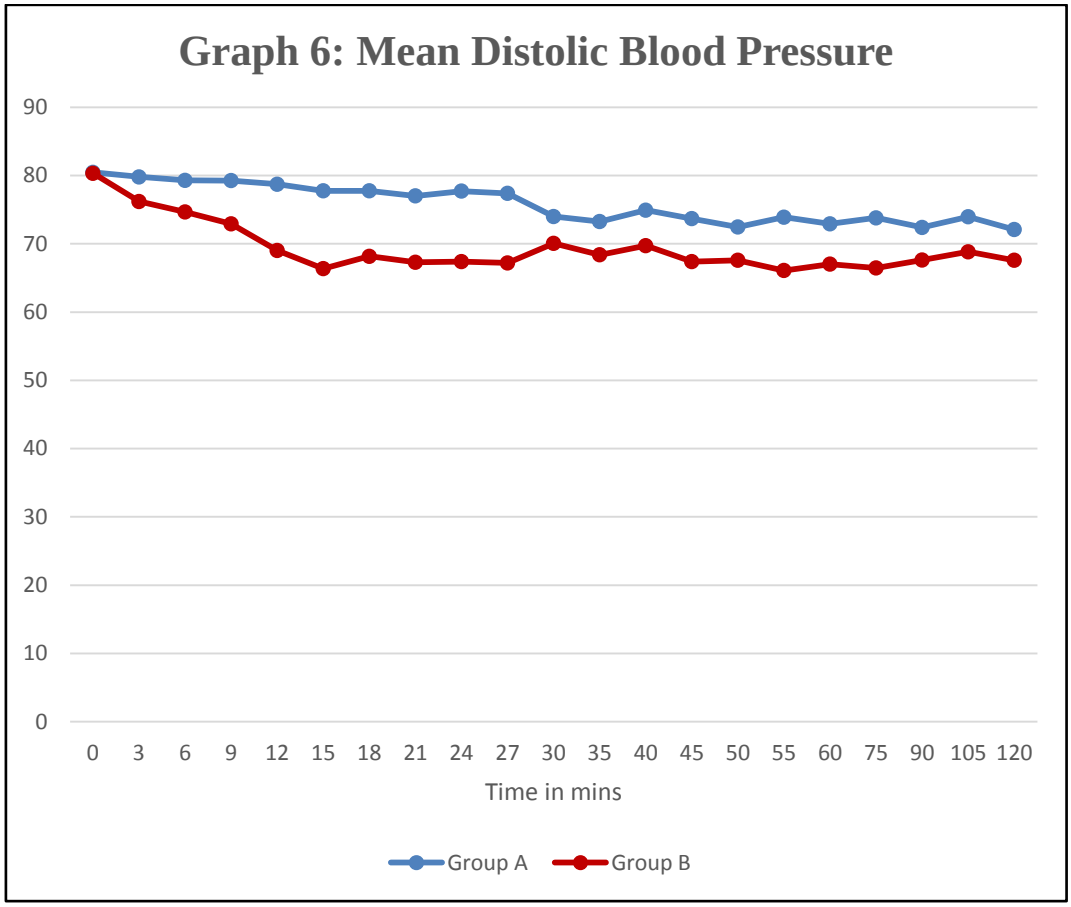


Table-2 Comparison of Mean Onset of Sensory Block, Time of Peak Height For Sensory Block, Duration of Sensory Block and 2-Segment Regression time in between Group A and Group B.

	GROUP A	GROUP B		
	MEAN ± SD	MEAN ± SD	*t*-Value	*p*-Value
Onset of sensory blockade	5.10 ± 1.55	3.90 ± 1.12	**3.437**	<0.001*
Time of Peak height for sensory block	5.84 ± 1.61	7.70 ± 1.56	**4.544**	<0.001*
Duration of sensory	54.77 ± 7.91	101.00 ± 14.99	**14.94**	<0.001*
2-segment regression time	40.90 ± 6.99	76.63 ± 15.69	**11.444**	<0.001*

*statistically significant.

Table-3 Comparison of Mean Onset of Motor Block at Different Time Interval in Between Group A and Group B.

	GROUP A	GROUP B		
	MEAN ± SD	MEAN ± SD	*t*-Value	*p*-Value
Onset of motor blockade	6.5 ± 1.20	4.40 ± 1.28	6.556	<0.001*
Duration of motor block	48.30 ± 8.97	91.80 ± 14.47	13.99	<0.001*

*statistically significant.

Table-4 Comparison of Peak Height for Sensory Block in Between Group A and Group B.

	GROUP A		GROUP B			
Peak height for sensory block	**number**	**%**	**number**	**%**	X^2 -value	P -value
T6	0	0.0	8	26.7	10.58	0.014*
T8	18	60.0	16	53.3		
T9	1	3.3	0	0.0		
T10	11	36.7	6	20.0		
TOTAL	30	100.0	30	100.0		

*statistically significant.

Table-5 Comparison of Mean Onset of Side Effect In Between Group A and Group B.

Side Effect	Group A	Group B
TNS	0	0
Hypotension	0	**3**
Bradycardia	0	**2**
PONV	**1**	**3**
Respiratory Depression	0	0
Pruritus	0	0
Shivering	**0**	**4**

Discussion

Day Care Surgeries are the latest trend in practice to reduce hospital stay and cost burden. The patients do not wish to lose work. They prefer to resume their day today activities at the earliest. A faster recovery for the patients not only benefits the patients but also reduces the burden from the already overburdened health care services in our country.

Our study showed that intrathecal 30 mg preservative free chloroprocaine produces adequate sensory and motor anaesthesia for short duration procedure of lower abdomen and lower limb and that the addition of 30 mcg clonidine to intrathecal chloroprocaine prolongs both quality and duration of sensory and motor blockade. Casati A *et al* [6] evaluated the dose-response relationship of 2-Chloroprocaine for lower limb outpatient procedure and concluded that chloroprocaine provided adequate spinal anaesthesia for outpatient procedures lasting 45–60 min. Förster JG *et al* [7] also found similar results and stated Chloroprocaine as an appealing option for spinal anaesthesia.

In studies adding 15 mcg of clonidine with bupivacaine[8] and ropivacaine[9] showed increased block height compared with each drug alone. Spinal clonidine has been shown to improve the quality of spinal anesthesia, but in doses of 1–2 mcg/kg, significant systemic side effects were seen, including sedation, hypotension, and bradycardia [10,11,12]. Recent studies have evaluated the effects of clonidine in doses as small as 15 mcg and have found it to be effective and without these unwanted side effects [8,9]. Kouri ME *et al*[13]on Chloroprocaine has shown mild hemodynamic changes and none of patient needed vasoactive agents. Casati A *et al*[14], Dobrydnjov I *et al*[15] and Gonter *et al*[15] also found similar results.. In other studies done by Siddaiah *et al*[16], Teunkens A *et al*[17], Lacasse MA *et al*[18], on Chloroprocaine and they did not find significant bradycardia in patients. In our study the mean systolic and diastolic blood pressure was significantly more decreased in patients of group B than group A. In the studies done by Kouri *et al*[13], Casati *et al*[19] and Gonter *et al*[15] on Chloroprocaine have shown mild blood pressure changes with none of patient needed vasoactive agents.

The study conducted by Lacasse MA *et al*[18], Siddaiah *et al*[16]and Camponovo *et al*[21] on Chloroprocaine found incidence of hypotension 8%, 12%, 4.5% respectively. We found significant early onset of sensory blockade in group of patients who received clonidine to spinal chloroprocaine. Similar results to our study were

found by Chetty DK *et al*[22] Dissimilar results with this study were seen by Agarwal *et al*[23] and Davis BR *et al*[2]. There was significant difference in Peak height for sensory block in between group A and Group B(P=0.014). We found that peak height of sensory block attained was higher in group of patients who received Chloroprocaine with clonidine. Our results were similar with the study done by De Kock M *et al*[24], Agarwal *et al* [23] and Dobrydnjov I *et al*[25]. Although in their study Davis BR *et al* [2] didn't find any significant change in peak height of sensory block.

Time taken for highest level of sensory analgesia was statistically significant in both the group and the time needed was more in patients who received clonidine as an adjuvant to Chloroprocaine intrathecally. Our observations were same as found by Agarwal *et al*[23] as time to achieve peak height was statistically more in group of patients who received 15 mcg Clonidine as an adjuvant to spinal block. In spite of this our findings were different than the observations found by Singh G *et al*[26]. In our study, time for 2 segment regression was statistically higher in group of patients who got spinal anaesthesia with Chloroprocaine along with Clonidine. Our observations were concurrent with study done by Agarwal *et al* [23] as time to two segment sensory regression was statistically more in group of patients who received 30mcg Clonidine as an adjuvant to spinal block. Same results were found by Dobrydnjov I *et al*[25] although our observations were dissimilar to the study done by Davis BR *et al*[2] on Intrathecal 30mg Chloroprocaine alone and with 15 mcg Clonidine. In the present study duration of sensory blockade was statistically significant ($p<0.001$) and different among the groups, it was prolonged in the group who received Chloroprocaine with Clonidine intrathecally. Our observations were similar to the studies done by Davis BR *et al*[2], Kanazi GE *et al*[21] and Singh G *et a* [26]. Time for onset of motor block was the mean time of onset of motor blockade with modified Bromage grade 3. In our study we found significant less time required for onset of motor blockade in group of patients who received intrathecally Chloroprocaine with Clonidine. Our result was same with the observations found by Kanazi GE *et al*[27] although our results were different to study done by Singh G *et al* [26]. In our study we found more mean time of total duration of motor block in group of patients who received clonidine as an adjuvant to intrathecal chloroprocaine. Our results were similar with the results observed in study done by Davis BR *et al*[2], Dobrydnjov I *et al*[25] and Singh G *et al* [26] they observed significant increase in duration of motor block by using Clonidine as an adjuvant to intrathecal Bupivacaine.

No adverse effects were seen in the patients while conducting the study.

Side Effects

In our study incidence of post-operative nausea and vomiting was seen in 1 patient (3.3%) in group A and in 3 patients (10%) of group B which may be due to more incidence of hypotension in patients of group B. None of patient from group A had shivering while 4 patients (13.3%) of group B developed shivering. None of our patient gave complaint of pruritis. In our study there was no incidence of transient neurologic symptoms. None of our patients gave complaint of pruritis or Respiratory depression in either group.

Conclusion

We concluded that low-dose clonidine increases the duration and potentiates the quality of both sensory and motor blockade when used as an adjuvant to chloroprocaine spinal anesthesia. Up to low dose of 30 µg, the unwanted side effects seen with the traditional larger doses were not observed. The duration of sensory and motor blockade was shorter in Chloroprocaine and better suited for elective short duration surgery. Peak Sensory Block achieved was higher with CP with Clonidine group and the slower regression of the block, made it a good choice for elective lower limb surgery. This makes it a suitable combination for outpatient anesthesia.

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