

A Comparative Study on the Effects of Clonidine Plus Lignocaine, Tramadol Plus Lignocaine and Plain Lignocaine for Intravenous Regional Anesthesia

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ABSTRACT

Introduction: Intravenous Regional Anaesthesia (IVRA), though safe and effective, the search continues for an ideal analgesic devoid of side effects, which can be added to IVRA local anaesthetics to improve perioperative analgesia. This study was undertaken to assess the analgesic effectiveness of adding Clonidine to Lignocaine in IVRA in patients of hand and forearm surgeries. This was, further, compared with the addition of Tramadol and plain Lignocaine

Material and Methods: This study was carried out on patients aged 18 to 60 years belonging to ASA grade I and II, undergoing upper limb surgeries lasting for less than 90 minutes. They were divided in three groups: Clonidine Group, Tramadol Group and the plain Lignocaine Group. Intraoperative and postoperative (up to 4 hours) analgesic parameters were observed.

Results: It was found that the Clonidine was much better than Tramadol, which was in turn better than plain Lignocaine in terms of prolongation of sensory and motor action, tourniquet tolerance and duration of analgesia, without any complications.

Conclusion: Addition of Clonidine to IVRA significantly improves perioperative analgesia.

Keywords: Intravenous Regional Anaesthesia, Clonidine, Tramadol, Lignocaine, Bier's Block, Tourniquet Pain, Intraoperative Analgesia, Postoperative Analgesia

INTRODUCTION

Pain is a sense of damage, hurt, fear and punishment. It is also associated with various systemic adverse responses all contributing to increased morbidity and mortality. Hence, an effective pain relief is essential for optimal care of surgical patients. Any method of analgesia must meet the three basic criteria: it must be effective, safe and feasible.

The term regional anaesthesia may be described as anaesthesia of an anatomical part produced by the application of a chemical capable of producing reversible conduction in the nerve. The necessity of regional anaesthesia for surgery of the limb has been recognized for long specially in cases where general anaesthesia is a risky procedure.

In 1908, Bier introduced the new method of venous anaesthesia for upper limb surgeries, known as Intravenous regional Anaesthesia because of him called as 'Bier Block'. Intravenous regional Anaesthesia "IVRA" is a safe and effective way to provide anaesthesia for hand and forearm surgeries expected to last less than 90 minutes. Though it is simple and reliable but it also lacks postoperative analgesia, has tourniquet pain and limits the time to surgical procedure.

Thus, the search continues for an ideal analgesic devoid of side effects, which can be added to IVRA local anaesthetics. In an attempt to improve peri-operative analgesia, this study was undertaken to assess the analgesic effectiveness of adding Clonidine to Lignocaine in IVRA in patients of hand and forearm surgeries. In addition, it was compared with the addition of Tramadol and plain Lignocaine. The rationale for this study is that Clonidine is a α_2 adrenergic agonist first developed as an antihypertensive agent but later found to have analgesic, anxiolytic and sedative properties. Recent studies show that Clonidine appears to mediate analgesic effects peripherally than central. Clonidine enhances peripheral nerve blocks of local Anaesthetics.

For the analgesic effectiveness, the parameters assessed were the onset and duration of sensory and motor blockade, analgesic effect on tourniquet pain, postoperative pain and sedation, duration of postoperative analgesia and complications (if any).

This study was undertaken to assess the analgesic effectiveness of adding Clonidine to Lignocaine in IVRA in patients of hand and forearm surgeries. This was, further, compared with the addition of Tramadol and plain Lignocaine

MATERIAL AND METHODS

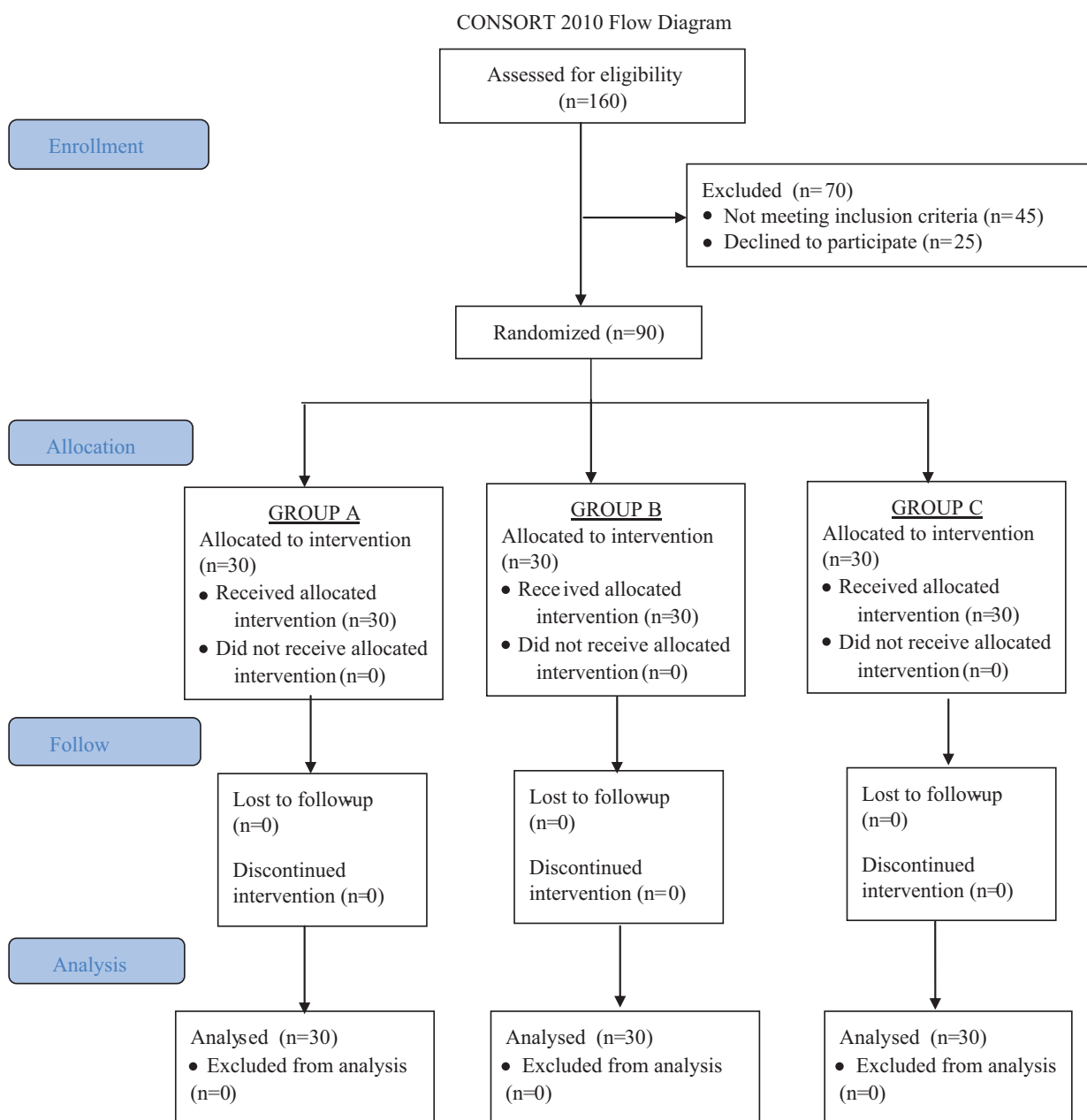
This was a randomized, prospective, single blind (patients), non-crossover type study, which was done after obtaining clearance from the Institutional Ethics Committee. It was carried out on patients aged 18 to 60 years of either sex, belonging to ASA grade I and II, undergoing upper limb surgeries lasting for less than 90 minutes. Patients having Ischemic Heart disease, Valvular Heart disease, Diabetes Mellitus, COPD, Morbid obesity, Coagulation abnormalities, Pregnancy, Peripheral vascular diseases and Hepatic and renal insufficiencies were excluded from the study. A written

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informed consent was obtained. A total of 90 patients were included in the study which were randomly divided into three Groups of 30 each. Pre-anaesthetic checkup (including Lignocaine sensitivity test) was done. Premedications (Inj. Glycopyrrolate: 5 µg / kg i.m., Inj. Ondansetron: 0.08 mg/kg i.v. and Inj. Midazolam: 0.02 mg / kg i.v.) were administered and standard operative guidelines were followed. Bier's block was given using medications as: Group A: 0.5% Lignocaine (preservative free) 40 cc and 1µg/kg of Clonidine, Group B: 0.5% Lignocaine (preservative free) 40 cc and 1mg/kg of Tramadol and Group C: 0.5% Lignocaine (preservative free) 40 cc and Saline 1cc. The time of tourniquet inflation and drug administration were recorded. After administration of drug, the following parameters were assessed:

Sensory block: After blinding the subject, the sensation of pinprick or touch was tested randomly in areas supplied by ulnar, radial and median. The time of onset of block (time

from injecting IVRA to total absence of sensation) and the duration (time interval between onset to recovery, i.e., offset of paresthesia) were noted.

Motor block: The subject was asked to flex and extend his wrist and fingers. The time of onset of block (time from injecting IVRA to total absence of movements of distal limb) and the duration (time interval between onset to recovery, i.e., return of ability to move fingers and wrist) were noted.

Monitoring

- Intraoperative: Pulse rate, Blood pressure, Oxygen Saturation SpO₂, Onset of Sensory block, Onset of motor block, Assessment of Tourniquet pain (VAS score).
- Postoperative: The minimum and maximum duration of inflation of tourniquet was 30 minutes and 90 minutes respectively. The following parameters were noted post operatively:
 - Post deflation pulse rate and blood pressure

- Duration of Sensory block
- Duration of motor block
- Post-operative analgesia: By V.A.S Score at immediate post-operative period, 30min, 60 min, 90min, 120 min, 3rd hour and 4th hour.
Grade 0 (0-1): good analgesia
Grade 1 (1-4): moderate analgesia
Grade 2 (4-7): mild analgesia
Grade 3 (7-10): No analgesia
- Time to first dose of analgesia was noted i.e. If VAS Score>4.
- Post-operative sedation: By a Numeric Scale in the immediate post-op, 30min, 60 min, 90min, 120 min, 3rd hour and 4th hour.
 1. Completely awake.
 2. Asleep but responsive to tactile stimulus.
 3. Asleep but responsive to verbal commands.
 4. Asleep but responsive to painful stimulus.
 5. Asleep and not responsive to any stimulus.

The patients were observed for any complications like allergic reactions, nausea, vomiting, perioral numbness, arrhythmias etc.

STATISTICAL ANALYSIS

Analysis was done using ANOVA (for numeric data) and

Kruscal Wallis test (for ordinal data) considering statistically significant if *P value* < 0.05. Further where *P value* was found to be significant, intergroup comparison was done using Tukey’s test.

RESULTS

There was no significant difference between the mean age, gender and weight of all the three Groups. There was also no significant difference in the duration of surgery and tourniquet time, pulse and systolic blood pressure recorded in the preoperative pulse, post-inflation pulse, post-deflation pulse and postoperative phases and the onset of sensory and motor blockade. However, a statistically significant difference was seen in the duration of sensory action (Tables 1a and 1b), duration of motor action (Table 2), tourniquet pain (Tables 3a and 3b), post-operative analgesia by Visual Analog Score (Table 4), duration of analgesia (Tables 5a and 5b) and sedation score (Table 6: By Kruscal Wallis test for ordinal data).

DISCUSSION

Intravenous regional Anaesthesia (IVRA) is a safe and effective way to provide anaesthesia for hand and forearm surgeries expected to last for less than 90 minutes. In an attempt to improve peri-operative analgesia various methods exist for treating post-operative pain which include systemic

	Number of patients	Duration of sensory action (Mean ± SD)	P-value	Significance (P-value<0.05)
Group A	30	85.50 ± 4.97	0.004	Significant
Group B	30	80.33 ± 6.90		
Group C	30	80.33 ± 7.98		

Table-1a: Comparison of duration of sensory action (minutes) in Group A, Group B and Group C.

	Group A	Group B	Group C	Inference
Group A	-	0.011	0.011	By Tukey’s test P-value < 0.05, so the difference between the Groups is statistically significant.
Group B	-	-	0.99	
Group C	-	-	-	

Table-1b: P-value table for pair wise comparison of duration of sensory action (minutes).

	Number of patients	Duration of motor action (Mean ± SD)	P-value	Significance (P-value<0.05)
Group A	30	71.83 ± 8.46	0.004	Significant
Group B	30	67.17 ± 8.78		
Group C	30	66.83 ± 7.82		

The difference between the Groups was not statistically significant (by Tukey’s test)

Table-2: Comparison of Onset of motor action (minutes) in Group A, Group B and Group C.

	Number of patients	Tourniquet pain (Mean ± SD)	P-value	Significance (P-value<0.05)
Group A	30	0.63 ± 0.96	<0.001	Significant
Group B	30	1.83 ± 1.46		
Group C	30	4.57 ± 1.33		

Table-3a: Comparison of Tourniquet pain in Group A, Group B and Group C.

	Group A	Group B	Group C	Inference
Group A	-	0.001	< 0.001	By Tukey’s test P-value < 0.05, so the difference between the Groups is statistically significant.
Group B	-	-	< 0.001	
Group C	-	-	-	

Table-3b: P-value table for pair wise comparison of the duration of tourniquet pain

	VAS (Mean \pm SD)			P-value	Significance (P-value<0.05)
	Group A	Group B	Group C		
Immediate post operative	0.70 \pm 0.92	1.13 \pm 1.46	4.87 \pm 1.43	< 0.001	Significant
30 min	1.07 \pm 1.17	1.27 \pm 1.44	3.30 \pm 1.06	< 0.001	Significant
60 min	1.17 \pm 1.32	1.40 \pm 1.45	3.30 \pm 0.95	< 0.001	Significant
90 min	1.37 \pm 1.50	1.87 \pm 1.68	3.20 \pm 0.92	< 0.001	Significant
120 min	1.67 \pm 1.56	2.70 \pm 2.10	3.23 \pm 1.28	0.002	Significant
180 min	2.13 \pm 1.83	3.20 \pm 1.92	3.63 \pm 1.03	0.002	Significant
240 min	3.07 \pm 1.74	3.70 \pm 1.60	4.37 \pm 1.03	0.005	Significant

Table-4: Comparison of Postoperative analgesia by Visual Analog Score (VAS) in Group A, Group B and Group C

	Number of patients	Duration of analgesia (Mean \pm SD)	P-value	Significance (P-value<0.05)
Group A	30	235.33 \pm 100.23	<0.001	Significant
Group B	30	100.00 \pm 81.65		
Group C	30	99.31 \pm 81.02		

Table-5a: Comparison of duration of analgesia (minutes) in Group A, Group B and Group C.

	Group A	Group B	Group C	Inference
Group A	-	0.002	< 0.001	By Tukey's test P-value < 0.05, so the difference between the Groups is statistically significant.
Group B	-	-	0.041	
Group C	-	-	-	

Table-5b: P-value table for pair wise comparison of the duration of analgesia

	Numeric Scale (mean \pm SD)			P-value	Significance (P-value<0.05)
	Group A	Group B	Group C		
Immediate post operative	2	2	1	0.002	Significant
30 min	1	1	1	0.728	Not Significant
60 min	1	1	1	0.947	Not Significant
90 min	1	1	1	0.99	Not Significant
120 min	1	1	1	0.99	Not Significant
180 min	1	1	1	0.368	Not Significant
240 min	1	1	1	0.342	Not Significant

Table-6: Comparison of Sedation Score (minutes) in Group A, Group B and Group C in the postoperative period.

narcotics, NSAIDs, etc., but the search continues for an ideal analgesic, devoid of side effects, that can be added to IVRA local anaesthetics.

Clonidine is a selective partial α_2 -adrenergic agonist with a selectivity ratio of about 200:1 in favor of receptors. Clonidine has been added to local anaesthetics for various peripheral nerve blocks, resulting in improved anaesthesia and analgesia.¹ The analgesic effect of Clonidine appears to be mediated peripherally and not the result of central redistribution. Studies have found that the patients receiving intravenous Clonidine failed to demonstrate any additional analgesia compared with lidocaine alone.^{2,3}

The precise mechanism by which Clonidine exerts its analgesic effect remains unknown. Clonidine enhances peripheral nerve blocks of local anaesthetics by selectively blocking conduction of A- δ and C fibers.⁴ Clonidine may produce a peripheral analgesic effect by releasing enkephalin-like substances.⁵ Clonidine also inhibits the release of norepinephrine from prejunctional α_2 -adrenoceptors in the periphery,⁶ it may potentially inhibit neural activity in nociceptive pathways.

This study is in comparison with study done by Scott S. Reuben et al⁷ in 1999 which showed no differences among

the groups in demographic variables like age, sex and weight of the patient. The hemodynamic changes were comparable between groups using Clonidine in IVRA and plain Lignocaine in IVRA. There were no differences among the groups with respect to tourniquet duration and duration of surgery, which were also comparable with the present study. There was also no significant postoperative sedation from Clonidine at dose of 1 μ /kg used in IVRA.

Hemodynamic changes: There was also no difference in the pulse and systolic BP in the preoperative, post-inflation, post-deflation and postoperative phases, though there was an overall increase in pulse rate and Systolic BP from baseline to post deflation value which was similar in all three groups. The increase in pulse rate and decrease in systolic blood pressure in the immediate post deflation period could be due to the release of vasoactive mediators from the ischemic areas of the operative limb due to tourniquet.

This was similar to studies by Siddiqui AK et al⁸ in 2008 (Tramadol + Lignocaine vs plain Lignocaine) and Goel Sunita N et al⁹ (Tramadol vs plain Lignocaine).

Tourniquet time: In this study, the tourniquet was inflated

for a minimum duration of 30 minutes and a maximum duration of 90 minutes, as per recommendations by Bier¹⁰ and Henderson.¹¹ There was no statistically significant difference between the three groups.

Sensory and Motor Blockade: The onset of sensory and motor blockade were comparable between the groups and did not show any statistical significance, but the difference in duration was significant. This can be due to Clonidine causing local vasoconstriction, thereby reducing the vascular uptake of local anaesthetic and causing prolongation of sensory and motor action.¹²

As such there were no previous studies on, duration of sensory and motor blockade involving Clonidine but there is a study by Memis et al¹³ who compared dexmedetomidine which is an α_2 adrenergic agonist similar to Clonidine along with Lignocaine in IVRA. They showed that duration of sensory blockade was statistically prolonged (7 ± 3 minutes post deflation of tourniquet) compared to plain Lignocaine (4 ± 1 minutes) in IVRA. Also that duration of motor blockade was statistically prolonged (8 ± 3 minutes post deflation of tourniquet) compared to plain Lignocaine (5 ± 1 minutes) in IVRA.

Tourniquet pain: There was a statistically significant difference in the Visual Analog Score (VAS) for tourniquet pain among the three groups. Further, Tukey's test showed the tourniquet tolerance was significantly better in Clonidine group (Group A) compared to Tramadol group (Group B), which was further better than the Control group (Group C).

This was similar to the conclusion of the studies by Lurie SD et al¹⁴ in 2000 (Clonidine: 55 ± 6 minutes vs Plain Lignocaine: 45 ± 5 minutes), Marc Gentili et al¹⁵ in 1999, Gorgias NK et al,¹⁶ in 2001, Siddiqui AK et al,⁸ (Tramadol added in the dosage of 100 mg in IVRA).

Postoperative analgesia: It was found that the postoperative analgesia was significantly better in Clonidine group (Group A) compared to Tramadol group (Group B), which was further better than the Control group (Group C).

It is comparable to the study of Choyce A, Peng P¹⁷ in 2002.

Duration of analgesia: Depending on the mean time for analgesic supplementation, a significantly prolonged duration of analgesia was seen in the Clonidine group (Group A) as compared to Tramadol group (Group B) and Control group (Group C).

This result is comparable to the studies of Hoffmann V et al,¹⁸ in 1997 (Clonidine with Prilocaine for IVRA) and Siddiqui AK et al⁸ in 2008 (used Tramadol 100 mg as an additive to Lignocaine for IVRA).

Reuben SS, Sklar J¹⁹ in 2002, showed that IVRA-Clonidine is a useful treatment modality in the management of Chronic Regional Pain Syndrome of the knee by IVRA for lower limb. Clonidine doses of $1 \mu\text{g}/\text{kg}$ appear to be well tolerated without significant side effects.

Reuben SS et al²⁰ in 1999 concluded that addition of $1 \mu\text{g}/\text{kg}$ Clonidine to lidocaine, 0.5%, for IVRA improves

postoperative analgesia with duration of analgesia (median value) of 360 minutes as compared to 115 minutes for control group, without causing significant side effects. They also showed that analgesic effect of Clonidine appears to be mediated peripherally and not the result of central redistribution. Patients receiving IVRA lidocaine and intravenous Clonidine failed to demonstrate any additional analgesia compared with lidocaine alone in their study.

Sedation: Though there was a significant difference between sedation score in the immediate postoperative period, no significant difference was seen in the sedation score after 30 to 240 minutes. This could be due to enhanced analgesia and subjective comfort patients get from either of Clonidine or Tramadol as compared to control group.

This was comparable to the study by Lurie SD et al.¹⁴ in 2000.

Though Marc Gentili et al¹⁵ in 1999, which shows a higher degree of sedation in Clonidine group as compared to plain Lignocaine group, but the dose of Clonidine used for IVRA was much higher $150 \mu\text{g}$.

Complications: In this study, 2 patients in Group B complained of nausea and vomiting after tourniquet release. Patients were given injection Ondansetron 4 mg i.v. and became comfortable within 10 minutes. No other complications were observed in Groups A and C.

Brown EM et al⁵ in 1989, revealed incidence of adverse effects in 1.6% of patients only and adverse effects consists of minor events like temporary dizziness, tinnitus and mild bradycardia. There was no mortality or major morbidity associated with IVRA.

Limitations: This study is limited by the number of OPD attendance. Therefore, the results might not be generalized.

CONCLUSION

In this study 90 patients were divided into 3 groups and received either 0.5% Lignocaine 40 ml with $1 \mu\text{g}/\text{kg}$ Clonidine or 0.5% Lignocaine 40 ml with $1 \text{mg}/\text{kg}$ Tramadol or 0.5% Lignocaine 40 ml for IVRA in upper limb procedures. It can be concluded that the addition of Clonidine to IVRA showed a much better response than the addition of Tramadol which was in turn better than plain Lignocaine in terms of prolongation of sensory and motor action, tourniquet tolerance and duration of analgesia, without any complications.

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