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ORIGINAL ARTICLE

A COMPARATIVE EVALUATION OF LORNOXICAM AND CLONIDINE AS POTENTIAL ADJUNCTS TO LIDOCAINE IN INTRAVENOUS REGIONAL ANAESTHESIA

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ABSTRACT: BACKGROUND: The aim of the study was to evaluate the effect of lornoxicam and clonidine on sensory and motor block onset time, tourniquet pain, sensory and motor block recovery time and postoperative analgesia, when added to lidocaine in intravenous regional anaesthesia (IVRA). **METHODS:** Ninety patients undergoing surgeries on hand and forearm were randomly and blindly divided into three groups as to receive either i.v. saline and IVRA with lidocaine 0.5% (Group I, n=30), i.v. saline and IVRA lidocaine 0.5% with lornoxicam 8mg (Group II, n=30) and i.v. saline and IVRA lidocaine 0.5% with clonidine 1μg/kg (Group III, n=30). Sensory and motor block onset time, time of onset of tourniquet pain was measured after tourniquet application, intraoperative analgesia, sensory and motor block recovery times were recorded. After the tourniquet deflation the time to first analgesic requirement, total analgesic consumption in first 24h, and side effects were noted.[3] **RESULTS:** Sensory and motor block onset times were shorter and the recovery time prolonged in the lornoxicam group compared with the control group and clonidine group (P<0.001). The time to first analgesic requirement was prolonged more in clonidine group compared to lornoxicam group which in turn was prolonged compared to lidocaine group [416(21.73) minutes vs 229(84) minutes vs 21.43(20) minutes, respectively P< 0.001]. However the mean time to onset of tourniquet pain was increased in clonidine group compared with control group 21.13(2.84) minutes vs 18.93(3.43) minutes p< 0.001 and lornoxicam group 18.6(2.22) minutes, p<0.001. **CONCLUSION:** The addition of lornoxicam to lidocaine for intravenous regional anaesthesia shortens the onset of sensory and motor block, prolongs sensory and motor block recovery times and improves postoperative analgesia without causing any side effect. The addition of clonidine to lidocaine for intravenous regional anaesthesia improves tourniquet pain, improves postoperative analgesia, caused negligible side effects without any effect on sensory and motor block onset and recovery times.

KEYWORDS: Anaesthetic techniques, Regional, i.v.; Anaesthetics local, Lidocaine; Analgesia, Postoperative; Analgesics, NSAIDs, Clonidine, Lornoxicam; Pain, Postoperative; Pain, Tourniquet pain.

INTRODUCTION: Intravenous regional anaesthesia (IVRA) was first described in 1908 for anaesthesia of the hand and forearm by August Karl Gustav Bier.[1] It is easy to administer, reliable and cost-effective for short operative procedures of extremities performed on an ambulatory basis.[2] Different additives have been combined with local anaesthetics (LAs) to improve block quality, prolong post-deflation analgesia, and decrease tourniquet pain.[3,4]

Lornoxicam is a new NSAID of the oxicam class with analgesic, anti-inflammatory and antipyretic properties which is available in oral and parenteral form.[5] It is rapidly eliminated, having a short plasma elimination half-life of 3–5 h,[5-6] which suggests its suitability for acute use in the

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postoperative period.[6-7] Lornoxicam provides an alternative to morphine and tramadol for the treatment of postoperative pain with fewer adverse events after hysterectomy.[8] Furthermore, wound infiltration with a combination of LA plus lornoxicam improved postoperative pain control and patient comfort, and decreased the need for opioid as compared with the use of either drug alone suggesting a local effect.[9]

Clonidine, an alpha-2 adrenoceptor agonist enhances peripheral nerve blocks by blocking conduction of A-delta and C fibres. (bbb). It also inhibits the release of noradrenaline from prejunctional alpha-2 receptors in the periphery, thereby potentially inhibiting neural activity in nociceptive pathways. (hulthen). It prolongs anaesthesia and analgesia in a dose dependant manner, when administered as a part of regional anaesthetic technique. (eisen).

However, very few studies have been conducted to establish these drugs as adjuncts to lidocaine in intravenous regional anaesthesia. It is in this context that the present study is being carried out, i.e to establish the facts regarding the role of these drugs as adjuncts to lidocaine in intravenous regional anaesthesia.

PATIENTS AND METHODS: This prospective, randomized and double-blinded study was performed in 90 ASA I–II patients aged between 20-50 years scheduled for hand or forearm surgery (i.e. carpal tunnel, trigger finger, and tendon release). Informed consent and ethical committee approval was obtained. Patients with sickle cell anaemia, or history of drug allergy, bleeding and coagulation disorders, myasthenia gravis, Raynaud disease, liver or renal insufficiency were excluded from the study. Patients were premedicated with 50mg tramadol i/m and 0.2mg glycopyrrolate i/m administered 45 minutes before the surgical procedure. The patients were randomly allocated into three groups of 30 each. Group I-Patients in this group received 10ml of lidocaine 2% diluted with normal saline to a total volume of 40ml. Group II- Patients in this group received 10ml of lidocaine 2% mixed with lornoxicam 8mg diluted with normal saline to a total volume of 40ml. Group III-Patients in this group received 10ml of lidocaine 2% mixed with clonidine 1µg/kg diluted with normal saline to a total volume of 40ml. After the patients had been taken to the operating room, mean arterial blood pressure (MAP), peripheral oxygen saturation (SpO2), and heart rate (HR) monitoring was started and baseline parameters were noted. Two cannula were placed; one in a dorsal vein of the operative hand and the other in the opposite hand for crystalloid infusion.

The operative arm was elevated for 2 min then exsanguinated with an Esmarch bandage; a pneumatic tourniquet was then placed around upper arm, and proximal cuff was inflated to 100mm Hg above systolic pressure. Circulatory isolation of the arm was verified by inspection, absence of radial pulse, and loss of pulse oximetry tracing in the ipsilateral index finger. Identical syringes containing each drug were prepared according to the study design and randomization of patients according to a computer generated list; drugs were prepared and concealed by a resident not involved in any other part of the study. An anaesthesiology resident blinded to the group and drug allocation applied the concealed syringes and recorded all data. All solutions administered were given before i.v over a period of 90 seconds. When patient felt discomfort at the proximal tourniquet site, the distal tourniquet was inflated to same pressure and proximal one was deflated.

The sensory block was assessed by a pinprick performed with a 22-gauge short-bevelled needle at 1 minute interval. Patient response was evaluated in the dermatomal sensory distribution of the medial and lateral antebrachial cutaneous, ulnar, mean, and radial nerves using palecha score scale of 0-2; 0-sharp pain, 1-touch only, 2-cannot feel touch. Score 2 was taken as onset of complete

sensory block. Motor function was assessed on palecha score scale of 0-3. 0-Able to move arm against resistance, 1-inability to move wrist against resistance, 2-inability to move wrist and elbow against resistance. Score 3 was taken as onset of complete motor block. The surgery was started 10 min after the distal tourniquet inflation in all patients. MAP, HR, SpO2 and visual analogue scale (VAS) scores (0=no pain and 10=worst pain imaginable) were monitored before and after tourniquet application every 10 minutes. Time to onset of tourniquet pain was recorded. Sensory block recovery time was noted as the time elapsed from release of tourniquet to perception of pain in all dermatomes determined by pin prick. Motor block recovery time was noted as time elapsed from release of tourniquet to ability to move arm against resistance. Postoperatively, duration of analgesia was assessed by the time elapsed from release of tourniquet to first demand of analgesics.

The tourniqet was not deflated before 30 min and was not inflated for more than 1h. At the end of surgery, the tourniquet deflation was performed by the cyclic deflation technique. Sensory recovery time was noted (Time elapsed after tourniquet deflation up to recovery of pain in all dermatomes determined by pinprick test). Motor block recovery time was noted (The time elapsed after tourniquet deflation up to movement of fingers). Patients were questioned about side effects during the first 2h in the postanaesthesia care unit and later in the ward every 2h by an anaesthesia resident who was blinded to the study. Skin rash, gastric discomfort, tinnitus, nausea and other side effects were noted if encountered during the first 24 postoperative hours in the ward.

The data was analysed using computer software Microsoft Excel and SPSS version 10.0 for windows. The data was presented as mean and standard deviation and statistical significance was analyzed using one-way analysis of variance (ANOVA). Post-hoc intergroup significance was assessed using Bonferroni's t test. A p value of < 0.05 was considered statistically significant. All analyses was conducted in accordance to intention to treat principle.

RESULTS: The demographic data was comparable in three groups and statistically there was insignificant difference among them ($p>0.05$). The mean time of onset of sensory block was earliest in group II [(lornoxicam) 2.36±0.65 minutes] versus group III [(clonidine) 4.8±0.72 minutes] and group I [(lidocaine) 5.18±1.05 minutes], $p<0.001$. The mean time of onset of motor block was earliest in group II [(lornoxicam) 2.22±0.74minutes] versus group III [(clonidine) 8.63±0.78 minutes] and group I [(lidocaine) 9.01±0.93 minutes], $p< 0.001$. Mean time of tourniquet pain in group I, II, III was 18.93±3.43 min, 18.6±2.22 min and 21.13±2.84 min ($p<0.001$). While comparing VAS scores for tourniquet pain at 10 minute interval, scores were lower in both lornoxicam and clonidine group compared to control group ($p<0.001$). The mean time of recovery from sensory and motor block was earliest in group II [(lornoxicam) 7.5±1.33 min, 6.53±1.38min] versus group III [(clonidine) 2.9±0.92 min, 4.1±1.49min] and group I [(lidocaine) 3.2±1.24 min, 4.36±1.32 min], $p< 0.001$. The mean duration of postoperative analgesia was highest in clonidine [group III(416±21.73 min)] compared to lornoxicam [group II(220±84 min)] which in turn was more than in lidocaine [group I (21.43±3.95 min).The difference in systolic, diastolic blood pressures and heart rate at various time intervals in all the groups was insignificant ($p>.0.05$).

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	Age	Weight
Group I	32.36±5.76	64.66±7.05
Group II	34.53±6.19	64.93±9.23
Group III	34.9±6.85	69.2±8.21
F-value	1.419	2.876
P-value	0.247	0.061

Table 1: Demographic Data of the groups were similar for mean age, weight

	Onset of sensory block (minutes)		
	Mean	± SD	Range
Group I	5.18	1.05	4-7
Group II	2.36	0.65	1.5-4
Group III	4.8	0.72	3.5-6

Table 2: Onset of sensory block (minutes)

F= 102, P Value= 0.0001 (HS)

	Onset of motor block (minutes)		
	Mean	± SD	Range
Group I	9.01	0.93	7.5-11
Group II	2.22	0.74	1-4
Group III	8.63	0.78	7-10

Table 3: Onset of motor block (minutes)

F= 641.3. P Value= 0.0001 (HS)

	Time of onset of tourniquet pain (minutes)		
	Mean	± SD	Range
Group I	18.93	3.43	14-24
Group II	18.6	2.22	15-22
Group III	21.13	2.84	15-25

Table 4: Time of onset of tourniquet pain (minutes)

F= 6.863, p value = 0.001 (HS)

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Intra-operative analgesia by visual analogue scale (0-10cm) at different time period:

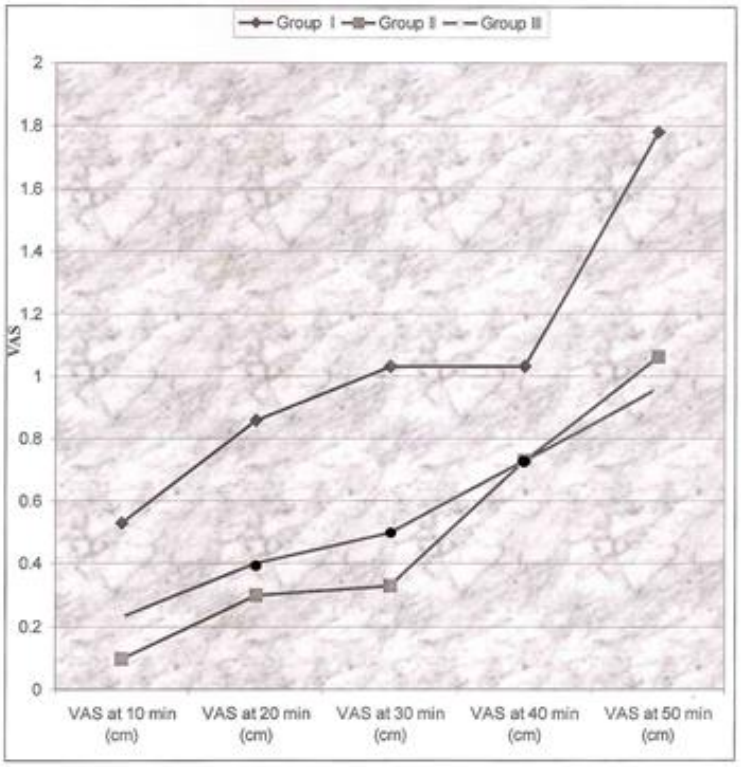

Fig. 1: VAS in different groups at different time period

	Sensory block recovery time (minutes)		
	Mean	**± SD**	**Range**
Group I	3.2	1.24	2-7
Group II	7.5	1.33	5-10
Group III	2.9	0.92	2-5

Table 5: Sensory block recovery time (minutes)

F= 142.866. p value = 0.0001 (HS)

	Motor block recovery time (minutes)		
	Mean	**± SD**	**Range**
Group I	4.36	1.32	3-8
Group II	6.53	1.38	5-9
Group III	4.1	1.49	3-8

Table 6: Motor block recovery time (minutes)

F= 27.164. p value = 0.0001 (HS)

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	Duration of post-operative analgesia (minutes)		
	Mean	± SD	Range
Group I	21.43	3.95	17-30
Group II	220	84	60-320
Group III	416	21.73	360-460

Table 7: Duration of post-operative analgesia (minutes)

F= 458.266. p value = 0.0001 (HS)

DISCUSSION: Intravenous regional anesthesia is a technically simple and reliable, with success rates between 94% and 98%.[10]

IVRA has been limited by tourniquet pain & inability to provide postoperative analgesia. Numerous attempts to reduce the severity of tourniquet discomfort, improve the quality of block & prolong postoperative analgesia have been made by adding a number of agents to local anesthetic.

The mechanism of action of lornoxicam as an adjunct to IVRA is multifactorial. Local anesthetics exists in two forms; the nonionized, lipid soluble free base and the water soluble ionized form. The relative proportions of the each depend upon the pka of drug and pH of the environment. The pka of lidocaine is fixed (7.8) but, by increasing the pH of solution, it is possible to increase the percentage of free base and thus improve the nerve penetration and rate of onset of blockade. The pH value of lornoxicam, intravenous form, is 8.7. Thus alkalinization of local anaesthetic with lornoxicam contributes to faster sensory & motor block onset times by increasing the proportion of free base.[11] It has inhibitory effects on cyclooxygenase-1 & cyclooxygenase-2 enzymes in peripheral receptors, it also increases endogenous dinorphin and beta-endorphin levels promoting central analgesic and antiinflammatory effects. Lornoxicam inhibits both isoforms in same concentration range ($IC_{50}/_{COX-1}/IC_{50/COX-2}=1$).[12] The role of A-delta fibres and unmyelinated C-fibres is considered to be involved in tourniquet pain because of the circumferential compression of peripheral nerves enhanced by ischemia.[3] It also prevents conduction of C-fibres. Lornoxicam also produces a peripheral analgesic effect via nitric oxide c-GMP pathway and the opening of K^+ channels.

Clonidine, an alpha-2 adrenoreceptor agonist enhances peripheral nerve blocks of local anaesthetics by selectively blocking conduction of A-delta and C-fibres.[13] It also causes local vasoconstriction, thereby reducing the vascular uptake of local anaesthetic.[14] It also releases enkephalin like substances.[15] It also inhibits release of noradrenaline from prejunctional alpha-2 adrenoceptors in periphery and inhibits neural activity in nociceptive pathways.[16]

In our study, the mean onset of sensory and motor block was early in lornoxicam group. The mean time of recovery from sensory and motor block was prolonged in lornoxicam group compared with the other groups. However the mean time of onset of tourniquet pain was prolonged only in clonidine group. The mean duration of postoperative analgesia was highest in clonidine group (416±21.73) compared to lornoxicam group (220±84 minutes) which in turn was more than in control group (21.43±3.95).

In conclusion, the present study showed that addition of lornoxicam to lidocaine in IVRA shortens sensory and motor block onset times, prolongs sensory and motor block recovery times, improves postoperative analgesia, whereas addition of clonidine provides better postoperative analgesia without any effect on sensory and motor block onset and recovery times.

REFERENCES:

1. Brill S, Middleton W, Brill G, Fisher A. Bier's block; 100 years old and still going strong!. Acta Anaesthesiol Scand 2004; 48: 117–22.
2. Choyce A and Peng P. A systematic review of adjuncts for intravenous regional anaesthesia for surgical procedure. Can J Anesth 2002; 49: 32–45.
3. Estebe JP, Gentili ME, Langlois G, Mouilleron P, Bernard F, Ecoffey C. Lidocaine priming reduces tourniquet pain during intravenous regional anaesthesia: a preliminary study. Reg Anesth Pain Med 2003; 28: 120–3.
4. Memis D, Turan A, Karamanlioglu B, Pamukcu Z, Kurt I. Adding dexmedetomidine to lidocaine for intravenous regional anaesthesia. Anesth Analg 2004; 98: 835–40.
5. Corpataux J-B, Van Gessel EF, Donald FA, Forster A, Gamulin Z. Effect on postoperative analgesia of smalldose lysine acetylsalicylate added to prilocaine during intravenous regional anaesthesia. Anesth Analg 1997; 84: 1081–5.
6. Rosenow DE, Albrechtsen M, Stolke D. A comparison of patient-controlled analgesia with lornoxicarn versus morphine in patients undergoing lumber disk surgery. Anesth Analg 1998; 86: 1045–50.
7. Bias W and Jansen M. Pain control after hysterectomy: an observerblind, randomised trial of lornoxicam versus tramadol. Br J Clin Pract 1996; 50: 197–202.
8. Rosenow DE, Albrechtsen M, Stolke D. A comparison of patient-controlled analgesia with lornoxicam versus morphine in patients undergoing lumbar disk surgery. Anesth Analg 1998; 86: 1045–50.
9. Deciga-Campos M, Lopez Munoz FJ. Participation of the L-arginine-nitric oxide cyclic GMP-ATP-sensitive K+ channel cascade in the antinociceptive effect of rofecoxib. Eur J Pharmacol 2004; 484: 193–9.
10. Brown EM, McGriff JT, Malinowski RW. Intravenous regional anesthesia (Bier's Block): Review of 20 years' experience. Can J Anaesth 1989; 36: 307-10.
11. Sen S, Ogur B, O. N Aydin, Ogurlu M, Gezer E, Savk O. The analgesic effect of lornoxicam when added to clonidine for intravenous regional anesthesia. Br J Anaesth 2006; 97(3): 408-13.
12. Futaki N, Takahashi S, Kitagawa T. Anti -inflammatory, analgesic, antipyretic and cyclooxygenase inhibitory effects of a non-steroidal anti-inflammatory agent lornoxicam. Jpn Pharmacol Ther 1997; 25: 55-71.
13. Butterworth JF, Strichartz GR. The alpha-2 adrenergic agonist clonidine and guanfacine produce tonic and phasic block of conduction in rat sciatic nerve fibres. Anesth Analg 1993; 76: 295-301.
14. Langer SZ. Pharmacologic and therapeutic significance of alpha- adrenoceptor subtypes. J Cardiovasc Pharmacol 1985; 7: 1-8.
15. Nakamura M, Ferreira SH. Peripheral analgesic action of clonidine: mediation by release of endogenous enkephalin like substances. Eur J Pharmacol 1988; 146: 223-8.
16. Hulthen UI, Kiowski W. Prejunctional alpha-2 adrenoceptors and noradrenaline release in the forearm of normal humans. J Cardiovasc Pharmacol 1985; 7: S144-8.

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