

Perioperative intravenous lidocaine infusion on postoperative pain relief in patients undergoing upper abdominal surgery

BK Baral,¹ BK Bhattarai,² TR Rahman,² SN Singh² and R Regmi³

¹Department of Anaesthesiology, Nepal Orthopaedic Hospital, Jorpati, Kathmandu, Nepal,

²Department of Anesthesiology and Critical Care, ³Department of Surgery, BP Koirala Institute of Health Sciences, Dharan, Nepal

Corresponding author: Dr. Bidur K Baral MD, Consultant Anaesthesiologist, Nepal Orthopaedic Hospital, Jorpati, Kathmandu, Nepal; e-mail: bidur_baral@yahoo.com

ABSTRACT

Due to unpleasant nature and physiological consequences of postoperative pain, search of safe and effective modalities for its management has remained a subject of interest to clinical researchers. Analgesic action of lidocaine infusion in patients with chronic neuropathic pain is well known but its place in relieving postoperative pain is yet to be established. The study aimed to assess the effectiveness of perioperative intravenous lidocaine infusion on postoperative pain intensity and analgesic requirement. Sixty patients undergoing major upper abdominal surgery were recruited in this randomized double blinded study. Thirty patients received lidocaine 2.0% (intravenous bolus 1.5 mg/kg followed by an infusion of 1.5mg/kg/h), and 30 patients received normal saline according to randomization. The infusion started 30 min before skin incision and stopped 1 h after the end of surgery. Postoperative pain intensity and analgesic (diclofenac) requirement were assessed at the interval 15 minutes for 1 hour then 4 hourly up to 24 hours. The pain intensity at rest and movement as well as the total postoperative analgesic (diclofenac) requirement were significantly lower (142.50 ± 37.80 mg vs. 185.00 ± 41.31 mg, $P < 0.001$) in lidocaine group. The extubation time was significantly longer in lidocaine group (14.43 ± 3.50 minutes vs. 6.73 ± 1.76 minutes, $P < 0.001$). The time for the first dose of analgesic requirement was longer in lidocaine group (60.97 ± 18.05 minutes vs. 15.73 ± 7.46 minutes, $P < 0.001$). It can be concluded that perioperative infusion of low dose of lidocaine decreases the intensity of postoperative pain, reduces the postoperative analgesic consumption, without causing significant adverse effects in patients undergoing upper abdominal surgery.

Keywords: analgesic sparing effect, lidocaine, lidocaine infusion, postoperative analgesia.

INTRODUCTION

Study of effective modality for postoperative pain management has remained a subject of ongoing clinical researches due to its uniqueness and associated complex physiological consequences with somatic, autonomic and behavioral manifestations.¹ Optimal postoperative pain relief is not only needed for patients' comfort and satisfaction but also to facilitate their early mobilization and rehabilitation. Moreover, optimal postoperative pain relief has been found to be associated with less postoperative cognitive impairment, enhanced quality of life, reduced risk of chronic/persistent post surgical pain with better overall outcome and reduced clinical expenses.²⁻⁷

Although lidocaine infusion is considered to be effective modality for treating stubborn chronic, neuropathic pain,^{6,8,9} its place in acute postoperative pain management is yet to be established and standardized. Further, ease of availability, inexpensiveness, simplicity of administration and safety make lidocaine infusion an attractive subject of clinical investigation.

The present study intended to assess the effectiveness of perioperative intravenous lidocaine infusion on postoperative pain intensity and analgesic requirement in a setting of community based hospital.

MATERIALS AND METHODS

In this prospective, randomized, double blinded, placebo controlled study, 60 patients of ASA (American Society of Anesthesiologists) physical status I or II with the age between 18-60 years, undergoing upper abdominal surgery under general anaesthesia were enrolled. Ethical approval for this study was obtained from the BPKIHS ethical committee and written and informed consent was obtained from each patient.

Exclusion criteria included emergency surgery, known hepatic or renal dysfunction, any cardiac dysrhythmias /atrioventricular block, anticipated duration of surgery more than 3 hours, and known hypersensitivity/allergy to the study medication.

During the pre-anaesthetic check up visit, all patients were explained and familiarized about the study

Table-1: Comparison of patient and surgical characteristics between the two groups. Values are expressed as mean (standard deviation) unless otherwise noted

Variables	Lidocaine group (N=30)	Saline group (N=30)	p-value
Age (years)	36.80 (10.24)	35.63 (9.29)	0.646
Sex (F/M)	27/3	25/5	0.642
Weight (Kg)	50.17 (9.37)	50.40 (8.55)	0.920
ASA PS (I/II)	23/7	25/5	0.522
Duration of Anaesthesia (min)	63.13 (19.86)	70.17 (24.57)	0.228
Duration of infusion (min)	157.80 (25.50)	163.53 (26.99)	0.403
Pethidine used (mg)	49.60 (9.13)	50.00 (8.41)	0.861
Propofol used (mg)	103.0 (20.19)	104.0 (24.29)	0.863
Time of extubation (min)	14.43 (3.5)	6.73 (1.76)	0.001
Type of surgery (No.)			
Open cholecystectomy	26	26	
Open Cholecystectomy + CBD exploration	4	3	
Partial gastrectomy	0	1	

including the use of visual analogue scale for pain assessment (0 as "no pain" to 10 as "worst imaginable pain"). All the patients were pre-medicated with oral diazepam 0.2mg/kg given the night before and 2 hrs prior to surgery. On arrival in the operation theatre, on the day of surgery, peripheral venous access was secured in all the patients with 16G intravenous cannula on the dorsum of left hand. Patients were connected to the patient monitor for monitoring ECG, pulse rate, non-invasive blood pressure (NIBP), and pulse oximetry.

Using the computer generated codes maintained in sequentially numbered opaque envelopes patients were randomly allocated to either lidocaine infusion (L) or saline group (S) with 30 patients in each. Patients in the lidocaine infusion group received IV bolus injection of lidocaine (1.5 mg/kg slowly over 10 min) 30 minutes before the skin incisions followed by a continuous IV infusion at the rate of 1.5 mg/kg/h via infusion pump (B-BRAUN) whereas the patients in the saline group received 0.9% normal saline in equal volume and in the same manner. The infusion was continued throughout the surgery and terminated 60 min after the skin closure. In all the patients, anesthesia was induced with inj. propofol 2.0 mg/kg, pethidine 1.0 mg/ kg, followed by vecuronium 0.1 mg/kg intravenously to facilitate the laryngoscopy and orotracheal intubation. After tracheal intubation, anaesthesia was maintained with isoflurane in oxygen with intermittent intravenous boluses of vecuronium 1 mg as needed. Local anesthetic in any form was not given throughout the surgery.

After completion of surgery, the residual neuromuscular blockade was antagonized with the mixture of inj.

neostigmine 0.05mg/kg and atropine 0.02mg/kg IV. The trachea was extubated once the patient regained consciousness and the patients were transferred to the post-anesthesia care unit (PACU) where the infusion was continued for further 1 hour. During the whole perioperative period heart rates, systolic blood pressure, diastolic blood pressure, mean arterial pressure, ECG were monitored and documented as the base line (0 min) and then at the interval of 10 minutes. When the patient started to respond to verbal command (i.e. open eyes and protrude the tongue on verbal command) he/she was considered to have become conscious. The time required for regaining of conscious after stoppage of inhalational agent was noted.

The patient was evaluated in the post anesthesia care unit and in the surgical ward by the investigator who was unaware about the study medication given. The anesthesiologist, the surgeon, and the nursing staff all were kept unaware about the group allocation.

Intensity of pain and feature of possible systemic toxicity of lidocaine was monitored at the interval of 15 minutes for one hour in the immediate post operative period. The intensity of pain was assessed by asking the patient to indicate on the 10 cm line at the point that corresponded to the level of pain intensity they felt. The distance in centimeter from no pain end of VAS to the patient's mark was used as a numerical index of the severity of pain. The pain intensity was measured both at rest and during movement.

Any patient complaining of pain immediately after extubation was considered to have a pain VAS more than

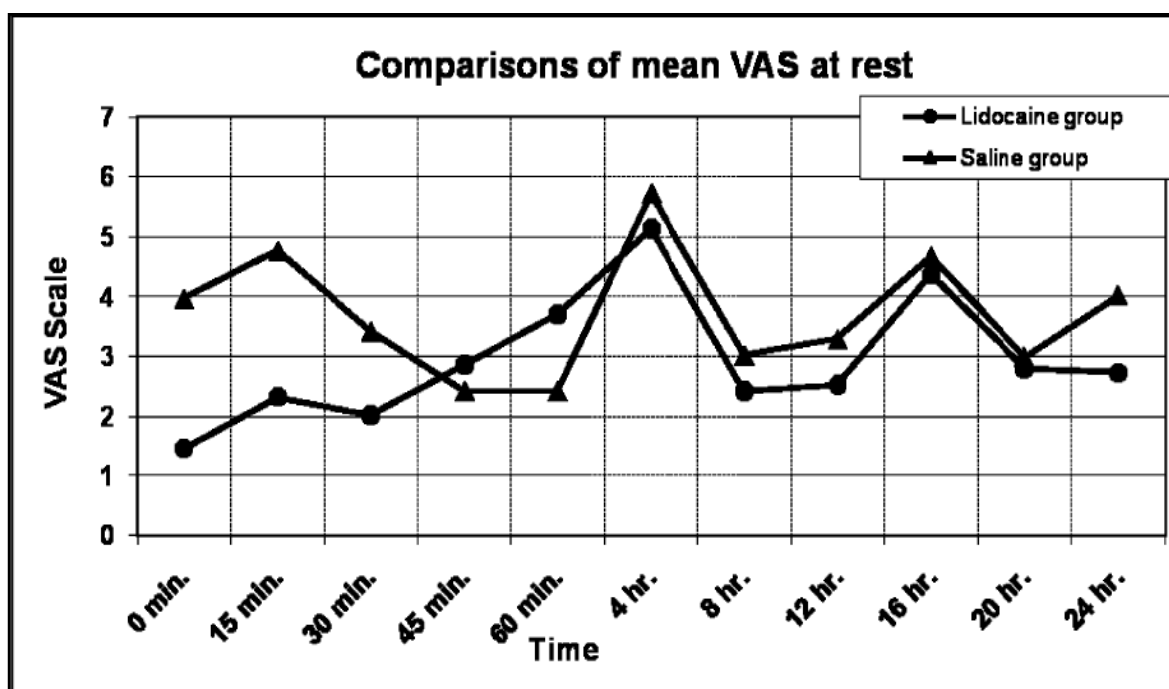


Fig. 1. Comparison of mean VAS at rest

4 and was managed accordingly. A patient with VAS score of more than four was treated with inj. diclofenac sodium 75 mg i.m. If the patient's VAS remained more than four even after 30 minutes of inj. diclofenac sodium then inj. tramadol 100mg IV was given as rescue analgesic. Further and subsequent doses of diclofenac were allowed after an interval of 6 hours without exceeding a total dose of 225mg in 24 hours.

The time between skin closure and first injection of diclofenac was noted. Possible adverse effects of lidocaine i.e. light headedness, perioral numbness, nausea and vomiting, sedation, arrhythmias, hypotension were monitored and documented if present.

Patients were monitored for sedation using the four-point categorical scale (0- alert; 1- sleepy but arousable; 2- stuporous; 3- comatose) and the observation was documented. When the sedation score was 0 or 1, the patient was not treated. If the sedation score was 2 or 3; the patient was treated with supplemental oxygen and air way management according to the requirement of the patient.

After one hour of observation, the patient was shifted to the ward from the PACU. In the ward also the intensity of pain was measured, adverse effects of lidocaine if any were noted every 4 hourly for 24 hours and managed accordingly. The number of cumulative doses of injection diclofenac and tramadol given during study period was recorded. If any sign of systemic toxicity or hypersensitivity reaction of the drug were encountered, they were treated accordingly and patient was excluded from the study.

After completion of the study; decoding of the study medication was done. Data was entered in the Excel 5.0 soft ware and analysis was done on an SPSS 11.0. Parametric and non-parametric tests were applied to identify the significance of difference of the variables. A p-value of <0.05 was considered significant.

RESULTS

Out of the 60 patients enrolled 52 (86.7%) were females and 8 (13.3%) males. In all, 52 (86.7%) patients underwent open cholecystectomy while 7 (11.7%) underwent open cholecystectomy with CBD exploration and 1 (1.7%) exploratory laparotomy. Comparison of general characteristics of the study population of both the groups is given in Table-1. No statistical difference was observed in their age, weight, ASA physical status, sex ratio, duration of anaesthesia, duration of infusion, propofol used, pethidine used and type of surgery between the groups ($p > 0.05$). However, the time for extubation (i.e. regaining consciousness after completion of surgery) was longer in lidocaine group than in normal saline group (14.43 ± 3.50 minutes vs. 6.73 ± 1.76 , $p < 0.001$).

Intensity of pain: In PACU, the mean pain VAS scores in lidocaine group remained significantly less than that in normal saline group ($p < 0.001$) until 30 mins, but it was higher thereafter becoming significant at 60 minutes ($p < 0.001$). Its subsequent values in the ward remained comparable but less than that in the normal saline group. The mean pain VAS score at rest are shown in Fig. 1. Similar values were observed on movement also as shown in Fig. 2.

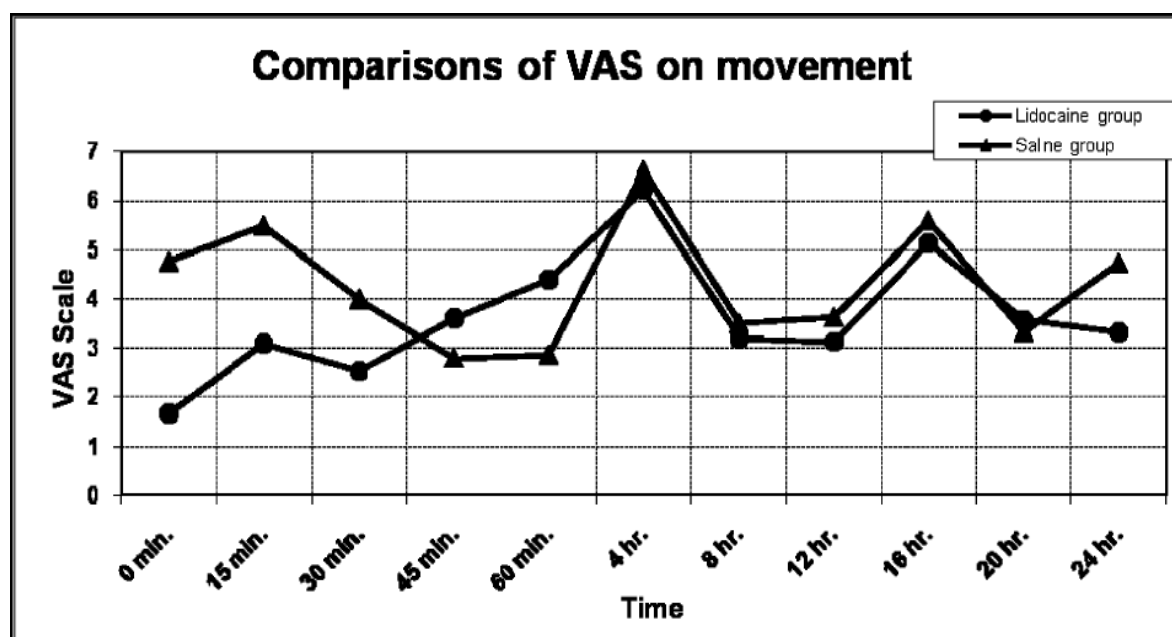


Fig. 2. Comparison of Mean VAS on movement

Analgesic requirements: The mean time for the request of the first dose of analgesic was significantly longer in lidocaine group than in normal saline group (60.97 ± 18.05 minutes vs. 15.73 ± 7.46 minutes, $p < 0.001$). The total mean analgesic (diclofenac) requirement in lidocaine group was significantly less than that in normal saline group (142.50 ± 37.80 mg vs. 185.00 ± 41.31 mg, $p < 0.001$).

None of the patient in lidocaine group required any amount of tramadol as a rescue medicine where as 18 patient (60.0%) of normal saline group patient received tramadol as rescue medicine ($P < 0.001$) of whom 14 (77.8%) required within 30 minutes and the remaining 4 (22.2%) within 4 hours after surgery.

Attenuation of the sympathetic response during laryngoscopy and endotracheal intubation was observed in the lidocaine group. Overall, the mean heart rate, SBP, DBP and MAP in normal saline group remained significantly higher statistically during the entire infusion period than that in the lidocaine group ($p < 0.001$) but within clinically acceptable range. Nausea and vomiting was observed in 11 (36.7%) patients in lidocaine group and 8 (26.7%) patients in saline group with no statistical difference.

Light headache was reported by 3 (10.0%) patients during post operative period in the lidocaine group. Other side effects like cardiac arrhythmias, peri-oral numbness and hypotension were not observed in any patient in any group.

DISCUSSION

The present study demonstrated that perioperative intravenous infusion of nontoxic doses of lidocaine

reduces postoperative pain intensity and analgesic requirement without causing any significant adverse effects in patients undergoing upper abdominal surgery.

The overall mean VAS scores in our study both at rest and on movement were less in lidocaine group than in normal saline group with the exception at 45 minutes and one hour after surgery. This finding may be attributed to the fact that most of the patients of normal saline group (i.e. 60.0%) had already received rescue analgesic by then and the time corresponds to the peak effect of the rescue analgesic. Our study supports the findings of the studies by Groudine *et al*¹⁰ and Kaba *et al*¹ which showed impressive effect on postoperative pain with reduction in total pain scores compared with control groups. Koppert *et al*⁵ also demonstrated the preventive effects of perioperative intravenous lidocaine infusion on postoperative pain and reduced analgesic consumption after major abdominal surgery. But unlike in our study they observed lower postoperative pain ratings in lidocaine infusion group compared to control only during movement (such as deep inspiration and coughing) and not at rest. They found the effect to be most pronounced on the second and third postoperative day. This difference with our findings might be due to the difference in the study designs, type of surgical patients they studied (i.e. without extended tissue trauma) and the type of analgesic used.

Our study showed significantly less total postoperative analgesic (diclofenac) requirement in lidocaine group than in normal saline group. Further, none of the patient in lidocaine group required additional tramadol for pain relief. These findings clearly show and confirm postoperative analgesic effects of perioperative infusion

of nontoxic dose of lidocaine. Various mechanisms have been described to account for the analgesic effect of intravenous lidocaine including suppression of neuronal excitability (in both myelinated A- δ and unmyelinated C fibers), suppression of central sensitization, inhibition of spinal visceromotor neurons, anti-inflammatory effects, decreased neural response by blockade or inhibition of nerve conduction and decreased NMDA receptor activity.¹⁰⁻¹⁶

In our study, all the procedures were major upper abdominal surgeries and we did not use any additional regional anesthesia for pain relief. In upper abdominal surgery with extended tissue damage, there is major input from chemoreceptors to the central nervous system and in humans especially, the mechanoinensitive nociceptors are reported to be tonically activated by chemicals.¹⁸ This class of nociceptors has also been shown to be linked to the induction of central sensitization in experimental, and clinical settings.¹⁷⁻¹⁹ In line with these results, mechanoinensitive nociceptors have been reported to be particularly sensitive to small-dose lidocaine, thus preventing the induction of central hyperalgesia and improving the postoperative pain therapy.²⁰ This probably explains longer time duration for the first request of analgesia in lidocaine group in our study. Similar observation has been reported by Koppert *et al*⁵ also.

The persistence of analgesic effect of lidocaine even after the infusion was discontinued in our study indicates prevention of spinal or peripheral hypersensitivity or both to painful stimuli reflecting its effects on inhibition of spontaneous impulse generation arising from injured nerve fibers and from dorsal root ganglion neurons proximal to the injured nerve segments and suppression of primary afferent evoked polysynaptic reflexes in the spinal dorsal horn.^{21,22} These effects have been postulated to be mediated by a variety of mechanisms, including sodium channel blockade, as well as inhibition of G protein-coupled receptors and *N*-methyl-D-aspartate receptors.²²⁻²⁷

The intravenous lidocaine in most of the previous studies has been administered perioperatively (i.e. during the presence of significant nociceptive input) and the infusion maintained for varying durations postoperatively. Kaba *et al*¹ and Cassuto *et al*²⁶ administered lidocaine in small-dose regimen starting 30 minutes before surgery and continuing for 24 hours after surgery. While Koppert *et al*⁵ and Groudine *et al*¹⁰ administered lidocaine starting prior to anaesthesia and surgery and continuing until 1h postoperatively. We also started the lidocaine infusion 30 minutes prior to anaesthesia and continued until one hour after completion of surgery. In view of feasibility and patient

safety, continuing the infusion would have required a prolonged PACU stay or transfer to a hospital bed with electrocardiogram monitoring facility that would have made the use of IV lidocaine impractical and more expensive.

Since we continued lidocaine infusion up to only one hour post operatively we cannot ascertain whether prolonging the lidocaine infusion could have improved analgesia further.

In our study, we administered lidocaine 1.5 mg/kg as slow i.v. bolus injection followed by a continuous infusion of 1.5 mg /kg/hr. We did not measure the serum level of lidocaine, based on the evidences from previous studies which have shown that plasma level of lidocaine remaining well below toxic level (i.e. 5 μ g/ml) even when it is used at a dose higher than that we used.^{10,22,30}

Expectedly, extubation time (i.e. regaining consciousness after completion of surgery) in our study was significantly longer in lidocaine group than in normal saline group which can be attributed to the increased depth of anaesthesia and prevention of the induction of central hyperalgesia by intravenous lidocaine.^{1,5} This may be considered as a drawback and ignored in view of its desirable analgesic effects of lidocaine infusion.

We did not observe any significant haemodynamic changes in any group in our study except at the time corresponding to laryngoscopy and endotracheal intubation. At this time, the heart rate, SBP, DBP and MAP were significantly attenuated in lidocaine group as compared to normal saline group. The haemodynamic response to direct laryngoscopy and endotracheal intubation is well known and the use of lidocaine for its attenuation is well described.³¹⁻³³ Thus our study further confirms that intravenous lidocaine blunts the direct laryngoscopy and endotracheal intubation reflexes.

The higher incidence of sedation in the lidocaine group in our study until one hour after surgery is quite expected and is obviously explained by central nervous system depressant effect of the drug.³³ Light headedness experienced by 3 patients in lidocaine group in our study has not been reported by other investigators.^{1, 5} We speculate this findings to be due to difference in the demographic and other patient characteristics. As reported in other studies, our study also did not show any difference in the incidence of nausea and vomiting.^{5,9}

Use of diclofenac intramuscularly for analgesia may seem to be inappropriate and a major limitation in our study in view of contemporary literature. However, we wanted to conduct this study in a setting of resource constrained community based hospital of Nepal using its own prevailing practices for post operative analgesia.

It can be concluded that perioperative infusion of non-toxic dose of lidocaine decreases the intensity of postoperative pain, reduces the postoperative analgesics requirement and blunts the haemodynamic responses during laryngoscopy and endotracheal intubation without causing significant adverse effects. Therefore it can be considered as an inexpensive, easy, relatively safe and effective modality as a part of multimodal approach for post operative analgesia in patients undergoing upper abdominal surgery.

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