Comparison Between Lignocaine Intravenous Lignocaine Infusion and Ketorolac in Reducing Postoperative Opioid Requirement in Upper Limb Surgeries

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ABSTRACT

Objective: To compare the frequency of opioid requirement, after intravenous lignocaine infusion and ketorolac tromethamine in the upper limb surgeries.

Study Design: Quasi-experimental study.

Place and Duration of Study: Combined Military Hospital, Lahore Pakistan, from Oct 2017 to Apr 2018.

Methodology: ASA I/II patients of either gender undergoing upper limb surgery were included. Patients were randomly divided into two equal groups, "L" (Lignocaine) and "K" (Ketorolac). In L-group, patients were given intravenous 1.5 mg/kg lignocaine bolus, followed by 2.0 mg/kg/hr infusion during entire procedure; while in K-group, patients were given intravenous 0.5 mg/kg (maximum 30 mg) ketorolac, at induction. The patients were monitored for 12 hours postoperatively and in case of severe postoperative pain (Visual Analogue Scale score >5), rescue analgesia (intravenous Nalbuphine 0.1 mg/kg) was provided.

Results: Total eighty patients were included in the study. There was no statistical difference between the two groups with age (*p*-value 0.823), gender (*p*-value 0.808) and ASA status (*p*-value 0.184). There was statistically significant difference between the two groups in terms of opioid requirement at 1-hour (*p*-value 0.035), 6-hours (*p*-value 0.032) and 12-hours (*p*-value 0.035), with K-group showing more requirement as compared to the L-group.

Conclusion: Intraoperative administration of intravenous lignocaine infusion is superior to ketorolac in effective postoperative pain management in patients undergoing upper limb surgeries.

Keywords: Frequency, Ketorolac tromethamine, Lignocaine, Opioid analgesics, Postoperative pain.

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INTRODUCTION

The word 'pain' is derived from a Latin word "poena", meaning penalty or punishment and is a complex medical problem and the most prevailing and universal form of human distress.[1] The typical problems in the surgical recovery are acute postoperative pain, hyper-coagulation, ileus and cognitive dysfunction.[2] As much as 80% of the surgical patients experience acute postoperative pain and approximately 75% of them report pain severity as moderate, severe or extreme.[3] Evidence suggests that less than half of the patients, after any type of surgical procedure, reported adequate postoperative pain relief.[4]

Inadequately controlled pain has a negative impact on quality of life, functional status, recovery, risk of post-surgical complications and the risk of persistent pain.[1] Fast-track protocols aim to prevent or decrease these postoperative complications, facilitating early recovery. Parenteral opioids have traditionally been used for severe postoperative pain management.[4] Their perioperative use can improve hemodynamic stability and reduce anaesthetic requirements, postoperative pain and discomfort; however the undesirable effects of narcotic analgesics, such as addictive potential, respiratory depression, constipation and sedation, have prompted the search for non-narcotic alternatives; having little or no effect on activity and behavior.

One medication that has shown potential in perioperative pain management is lignocaine.[5] Lignocaine has been typically used as a local or regional anaesthetic and an anti-arrhythmic agent, and is known to have analgesic, anti-inflammatory and anti-hyperalgesic properties.[5,6] It exerts its analgesic effect by suppressing neuronal action potentials arising from injured nerve fibers and posterior root ganglion cells. The analgesic and anti-inflammatory effects are induced by reduction of cytokines production, through inhibition of neutrophil activation, leucocyte priming, and inhibition of N-methyl-D-aspartate receptor (NMDA) receptors. Continuous intravenous (IV) lignocaine infusion has been shown to be effective in treating pain secondary

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to terminal illness, post-amputation pain, severe neuropathic pain and postoperative pain, particularly after major abdominal surgery.[6] Perioperative IV lignocaine administration, given as a single dose or as a continuous infusion, has been shown to decrease the hospital stay, and to improve the quality of life, without affecting the time to discharge from Post Anaesthesia Care Unit (PACU).[7] The opioid-sparing properties of IV lignocaine infusion also make it a viable option for pain control in chronic opioid users.

Ketorolac tromethamine, a non-steroidal anti-inflammatory drug (NSAID), is also a potent non-narcotic analgesic, with confirmed anti-inflammatory and antipyretic properties.[8] Its anti-prostaglandin action is responsible for its analgesic efficacy, especially in postoperative settings, where prostaglandins are believed to be a pain modulating factor.[8] Perioperative ketorolac administration promotes early ambulation, improves patient participation in respiratory physical activity and reduces the opioid consumption by 25-45%.[9] In a study from Thailand, the efficacy of ketorolac was comparable to that of meperidine and with lesser sedative effects.[10]

Purpose of this study was to compare the frequency of opioid requirement with perioperative IV lignocaine versus ketorolac in patients undergoing upper limb surgeries under general anaesthesia. Literature states that perioperative IV infusion of lignocaine is beneficial for patients undergoing any kind of surgery, but there is also controversy in results. Through this study, we want to observe whether rescue analgesia in the form of opioids is required more in patients given IV lignocaine infusion or in patients given IV ketorolac in our population.

METHODOLOGY

This quasi-experimental study was carried out at the department of Anesthesia, Combined Military Hospital (CMH) Lahore, after permission from Ethics Committee. A total of 88 study participants were selected, by adopting non-probability consecutive sampling technique.

Inclusion Criteria: Patients of either gender with American society of anesthesiologists (ASA) status I/II, undergoing plastic/orthopedic upper limb surgical procedures of duration not more than 120 minutes under general anesthesia, were included in the study.

Exclusion Criteria: Smokers, patients with history of diabetes or hypertension and with massive blood loss (bleeding >1,500 ml during surgery) were excluded from the study.

Informed consent was taken from each patient and confidentiality was ensured. Baseline demographic information was recorded and patients were educated how to use Visual Analogue Scale (VAS) score (0–10) to express the intensity of pain. The patients were randomly assigned by blind balloting into one of the two groups, n1=44 for "L" (lignocaine) group, while n2 =44 for "K" (ketorolac) group.

For all the patients, anaesthetic management was standardized and based on the standards of care adopted in our institution. Premedication was done by IV midazolam 2 mg and dexamethasone 8 mg. General anaesthesia was provided using intravenous propofol 2mg/kg for induction, and tracheal intubation was achieved with IV atracurium 0.5 mg/kg. Intraoperative muscle relaxation was monitored using a nerve stimulator. Arterial blood pressure and heart rate were maintained within 20% of baseline values. Anaesthesia was maintained with isoflurane, in a mixture of air (40%) and oxygen (60%), and end-tidal carbon dioxide concentration was monitored. In L-group, an IV bolus of lignocaine 1.5 mg/kg was given (maximum 100 mg) just before the induction of anaesthesia, followed by an IV infusion at 2.0 mg/kg/hr during the entire surgical procedure. In K-group, ketorolac 0.5 mg/kg (maximum 30 mg) was administered IV at induction.

At the end of the procedure, patients were transferred to PACU, where vital signs were monitored and recorded by nurses who were blinded to the randomization sequence. According to the study protocol, the nursing staff administered IV nalbuphine 0.1 mg/kg bolus as rescue analgesic, only if the VAS score was >5. The time of assessment of pain was 1, 6 and 12 hours postoperatively. VAS score and all the procedures were carried out by a consultant anaesthesiologist or a postgraduate resident and the data collected and recorded from both groups regarding opioid requirement.

Data were entered and analyzed through Statistical Package for Social Sciences (SPSS) version 23. Analysis was carried out to compare the proportion of both groups. Mean ± SD was calculated for quantitative variables, like age. Frequency and percentages were computed for qualitative variables, like gender and ASA status. Chi-square test was applied to compare both groups in terms of opioid requirement and the *p*-value of ≤0.05 was considered as significant.

RESULTS

Total eighty patients were included in the study. There was no statistical difference between the two groups with age (*p*-value 0.823), gender (*p*-value 0.808) and ASA status (*p*-value 0.184). There was statistically significant difference between the two groups in terms of opioid requirement at 1-hour (*p*-value 0.035), 6-hours (*p*-value 0.032) and 12-hours (*p*-value 0.035), with K-group showing more requirement as compared to the L-group (Table-I).

Table-I: Descriptive statistics of opioid requirements at different follow-up times in two groups.

Parameters		L-Group (n1=44)	K-Group (n2=44)	*p*-value
Age (years)	Mean ± SD	34.39 ± 9.17	34.68 ± 8.78	0.823
Gender	Male	32 (73%)	33 (75%)	0.808
	Female	12 (27%)	11 (25%)	
American Society of Anesthesiologists (ASA) Status	I	25 (57%)	31 (70%)	0.184
	II	19 (43%)	13 (30%)	
Patients requiring rescue opioids	Hour 1	3 (7%)	10 (23%)	0.035
	Hour 6	15 (34%)	25 (57%)	0.032
	Hour 12	34 (77%)	41 (93%)	0.035

Association of gender and ASA status revealed a significant difference in opioid requirement in males at 6-hours (*p*-value 0.018), but not at the 1-hour and 12-hours. There was significant difference in opioid requirement in ASA-I patients at 6-hours (*p*-value 0.020) and 12-hours (*p*-value 0.007), with reduced requirement in L-group. ASA-II patients showed no significant difference (Table-II & III).

Table-II: Association of gender with opioid requirements at different follow-up times.

Follow-Up Time	Gender	Groups	n (%)	*p*-value
1-Hour	Male	L	2 (6%)	0.082
		K	8 (24%)	
	Female	L	1 (8%)	0.590
		K	2 (18%)	
6-Hous	Male	L	10 (31%)	0.018
		K	20 (61%)	
	Female	L	5 (42%)	1.000
		K	5 (45%)	
12-Hours	Male	L	25 (78%)	0.082
		K	31 (94%)	
	Female	L	9 (75%)	0.590
		K	10 (91%)	

DISCUSSION

Appropriate pain management in the postoperative period is critical, as it maintains patient functional status, enhances quality of life, improves emotional wellbeing, decreases length of hospital stay, reduces postoperative morbidity and prevents readmission. Additionally, the evidence demonstrates that acute postoperative pain predicts chronic pain.[11] Lignocaine and ketorolac are approved medications that have been used safely in clinical practice. While ketorolac is a common opioid-sparing analgesic, lignocaine is more investigational.

We conducted this quasi-experimental study in patients undergoing upper limb surgeries under general anaesthesia and found a decrease in postoperative opioid requirement in both the groups. In addition, there was a significant difference in opioid requirement in lignocaine group as compared to ketorolac group. The patients in lignocaine group had better pain relief and required less rescue (opioid) analgesia, at follow up 1-hour (*p*-0.035), 6-hours (*p*-0.032) and 12-hours (*p*-0.035).

Table-III: Association of american society of anesthesiologists status with opioid requirements at different follow-up times.

Follow-Up Time	ASA Status	Groups	n (%)	*p*-value
1-Hour	I	L	1 (4%)	0.063
		K	7 (23%)	
	II	L	2 (11%)	0.374
		K	3 (23%)	
6-Hours	I	L	6 (24%)	0.020
		K	17 (55%)	
	II	L	9 (47%)	0.430
		K	8 (62%)	
12-Hours	I	L	17 (68%)	0.007
		K	30 (97%)	
	II	L	17 (89%)	1.000
		K	11 (85%)	

The literature showed many previous studies comparing different drugs, with control groups or other drugs, aiming at decreasing postoperative pain and opioid requirements, but has mainly focused abdominal surgeries. The data on non-abdominal surgeries is limited. The results of our study showed superiority of Lignocaine over Ketorolac and were in coordination with the results of study by Soliman *et al*.[12] They compared the efficacy of systemic lignocaine infusion with systemic Ketorolac in 60 patients undergoing laparoscopic bariatric surgery, where intravenous Lignocaine infusion was found to be an effective and safe adjuvant for rapid recovery in obese patients. Similarly, Ketorolac led to better outcome than that in the control group, but was less effective than lignocaine. Lignocaine group had a better postoperative pain score at all the

time points studied (p-value <0.001). In addition, they did not find any association of patient characteristics with opioid requirement.

In accordance with the results of our study, Kim *et al*, and Ibrahim *et al*, used intraoperative systemic Lignocaine infusion during spinal surgery and found it effective in reducing the pain perception, decreased 24-hours opioid consumption and positive impact on long term postoperative pain intensity; in turn contributing to a reduced length of hospital stay.[13,14] Lignocaine infusion also significantly prolonged the time to first request for rescue analgesia.

In a meta-analysis of five trials from 2008 to 2017, Zhao *et al*, assessed the efficiency and safety of intravenous lignocaine in 274 patients undergoing laparoscopic cholecystectomy and found significantly reduced pain scores and opioid consumption in the lignocaine group.[15] Baral *et al*, assessed the effectiveness of perioperative systemic lignocaine infusion on postoperative pain intensity and analgesic requirement in patients undergoing upper abdominal surgery.[16] The patients in lignocaine group received lignocaine 2.0% (IV bolus 1.5 mg/kg, followed by an infusion of 1.5 mg/kg/hr), with the infusion starting 30 minutes before skin incision and stopped 1 hour after the end of procedure. They found it effective in decreasing the postoperative pain intensity and reducing analgesic consumption, without significant adverse effects. In contrast to this study, we stopped the lignocaine infusion at the end of the procedure and still found significant results.

Contrary to these promising results in our study, Weibel *et al*, performed a review of 68 trials, including 4525 patients, and assessed the effects of systemic lignocaine infusion compared to placebo/no treatment or epidural analgesia in various surgical procedures and did not find many encouraging results.[17] Dale *et al*, tested the efficacy of systemic lignocaine (infusion dose of 2.0 mg/kg/hr for 24 hours) in patients undergoing laparoscopic fundoplication surgery and did not support its use.[18]

The effect of intraoperative systemic lignocaine administration is sustained beyond the infusion period and continues into the postoperative period.[19,20] It has been postulated that the intraoperative administration is sufficient, because modulatory action on the initiation of inflammatory responses primarily takes place during the surgery.[21] The prolonged analgesic effects of lignocaine, which extends well beyond the infusion period, could potentially also be explained by sustained concentrations of lignocaine in CSF and lignocaine metabolites having analgesic action by inhibiting the glycine transporter 1.[22]

Theoretically, lignocaine has the potential to cause neurological and cardiac toxicity. Metallic taste, perioral paresthesia, dizziness, diplopia, tinnitus, confusion, arrhythmias, hypotension and even convulsions can occur with higher serum levels, but studies have shown that systemic lignocaine with a 1.5 mg/kg bolus and a 2.0 mg/kg/hr infusion dose were safe and without potential side effects.[16,23] In the present study, we observed the patients postoperatively for 12 hours (the elimination half-life of lignocaine was 90-120 minutes) and did not observe any notable complications, confirming the safety of the dose used in the present study.

The need for adequate postoperative pain relief with an eye on early ambulation has supported the use of NSAIDs (i.e. ketorolac, ketoprofen) either alone, or in addition to intravenous bolus or PCA delivered opioids. Their use has been reported to be effective in the management of mild to moderate pain, including pain after maxillofacial, orthopedic and outpatient surgical procedures. IV administration of ketorolac (30 or 60 mg), has decreased the postoperative pain severity and subsequent need for opioid analgesics in the recovery period.[24,25]

It is beyond doubt that IV lignocaine infusion is an appealing option for perioperative pain management as suggested by our and other studies. Lignocaine infusion is easy to administer and is inexpensive. Furthermore, its use has not been associated with tolerance, can be repeated as needed, does not require advanced monitoring modalities and has not been associated with significant adverse effects.

It is recommended that a comparative study should be conducted on diverse population from different hospitals and in patients undergoing variety of procedures, so that the results can be generalized on larger population.

LIMITATIONS OF STUDY

Our study had certain limitations. First, we studied the effects of both the drugs for 12 hours only. This should be studied for a postoperative period of at least 24 hours, as it is the time period in which maximum pain occurs. Secondly, we evaluated the effect of these drugs on pain relief; the effects of these drugs on intraoperative hemodynamic effects, postoperative nausea and vomiting (PONV) and length of hospital stay were not evaluated.

CONCLUSION

Intraoperative administration of IV lignocaine infusion (after initial bolus dose) is superior to ketorolac in effective postoperative pain management in patients undergoing upper limb surgeries.

Conflict of Interest: None.

Authors' Contribution

UK: Concept of article, SPB: Final Approval, AH: Data collection, MA: Data collection, MSA: Literature review, JZ: Statistical analysis.

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