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COMPARISON OF LIGNOCAINE AND LOW-DOSE KETAMINE INFUSION FOR ANALGESIC EFFICACY IN MODIFIED RADICAL MASTECTOMY SURGERY: A PROSPECTIVE RANDOMIZED STUDY

Anaesthesiology

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ABSTRACT

Background & Aims: Effective postoperative pain control is important to reduce morbidity, hospital stay and chronic pain syndrome. This study was designed to evaluate the effect of intravenous lignocaine and ketamine infusion on perioperative analgesic consumptions and analgesia. **Methods:** A total of 80 adult female patients, scheduled for modified radical mastectomy, were randomly assigned into the lignocaine (GroupL, n=40) or ketamine (Group K, n=40) group. Lignocaine(loading dose 1.5 mg/kg, followed by maintenance infusion of 1mg/kg/h) or Ketamine (loading dose of 0.15 mg/kg, followed by maintenance infusion of 0.1 mg/kg/h) were administrated just before induction. Perioperative analgesic consumptions, pain scores and adverse effects were recorded for up to 24 hours after surgery. **Results:** The intraoperative opioid consumption (fentanyl) was comparable between two groups. Total post-operative analgesic consumption (Diclofenac) in24hours was lower ingroup L (75.00±0.00mg)compared to group K (93.75±32.9 mg)(P=0.001) with none of patient requiring fentanyl as second rescue analgesic. The mean verbal numerical rating scale (VNRS) during rest at 7hr, 8hr, 9hr, 12hr, 16hr and 20hr (P<0.001)and24hr(P<0.05) was significantly lower in Group L compared to Group K. Total number of doses of rescue analgesics was less in group L (1.00 ± 0.00) compared to group K (1.25 ± 0.44) (P=0.001), in 24-hour post-operative period. Nausea and vomiting were seen in two patients of Group K whileGroup L experienced no side effects(P=0.152). **Conclusion:** Lignocaine has superior analgesic effect with persistently lower pain scores, less need for postoperative rescue analgesic and lesser incidence of adverse effect in comparison to low-dose ketamine during first 24h after surgery and comparable effect to low-dose ketamine for intraoperative opioids consumption in patients undergoing modified radical mastectomy under general anaesthesia.

KEYWORDS

Analgesia, Postoperative, Intravenous, Infusion, Adjuvant, N-methyl-D-aspartate, Surgery

INTRODUCTION

Concept of preemptive analgesia was given by Wall in 1988. [1]It is defined as a treatment that is started before surgery to prevent the central sensitization which is elicited by the incisional and inflammatory injuries occurring during surgery and in the early postoperative period. [2]Adequate pain management after surgery is important for earlier mobilization and prevention of chronic surgical pain. [3]

Breast cancer is most frequent cancer in India accounting 25-32%ofallcancers.[4]The modified radicalmastectomy surgery plays a principal role in its management. Patients undergoing such surgery often witness excruciating agony. Pain is one of the most common complaints in women after mastectomy. Surgical trauma and postoperative pain can stimulate the inflammatory system and promote hyperalgesia and intensity of pain.

Various approaches have been adopted like regional anesthesia, opioid and non-opioid analgesics to decrease post-surgical pain. Opioids, however, are associated with negative side effects like addiction, sedation, nausea, and vomiting. A regional block may experience technical issues. A multimodal analgesia regimen, which is appropriate, would be based on the idea that there are numerous mechanisms involved in the pathophysiology of pain.[5-7]

Among the medications, there is growing interest in the use of analgesic like, pregabalin, gabapentin, dexmedetomidine, and clonidine. Even though they lessen chronic post-surgical pain, they have no effect on acute post-surgical pain.[8]

Recently, promising analgesic adjuncts like ketamine and lignocaine have emerged. Lignocaine administered intravenously has analgesic, anti-inflammatory, and antihyperalgesic properties.[9,10] Ketamine lessens tissue-damageinduced central sensitization. Additionally, it slows the emergence of opioid tolerance.[11-14] Ketamine reduces organismal stress and release of inflammatory factors. Hence, this study aimed to compare the analgesic effects of lignocaine and ketamine infusion in terms of analgesic consumption as the primary outcomein patients undergoing modified radical mastectomy.

Methods

After receiving Institutional Ethical Committee clearance (no. ECR/836/Inst/PB/2016/RR-20) approval dated 21/02/19 and written informed consents from the subjects, 80adultsfemalepatients of American Society of Anesthesiologists (ASA) Grade I & II, aged 18-65years, scheduled for modified radicalmastectomy under general anaesthesia were enrolled in this study.

The study was a prospective, randomized, double blind, clinical trial registered at Clinical Trials Registry India (no. CTRI/2019/04/018745) and conducted over 18 months in accordance with the principles of the Declaration of Helsinki (2013).

Exclusion Criteria

Patients having a history ofmedication allergies, American Society of Anesthesiologists physical status III or IV, renal, hepatic, or cardiovascular failure(ejection fraction < 30%), or a history of chronic pain were excluded from thetrial.

Randomization and Intervention

A total of 80patients were enrolled, and a computer-generated randomization table was used todividetheminto twostudy groupsof40patients each. Eighty sealed envelopes were prepared by a designated consultant (not included in study protocol), who opened it just before the start of the study and prepared all the drugs in identical syringes as per the code on the envelops. The attending anesthesiologist kept a record of the patients which were divulged on completion of the study.

All patients in lignocaine group(group L) receiveda1. 5mg/kg intravenous lignocainebol us over 5 minutes after anaesthetic induction before skin incision, followedby a continuous infusion of 1 mg/kg/h intraoperatively until operation was completed and those in ketamine group (group K) received a 0.15 mg/kg intravenous ketamine bolus given 5minutes after induction of anesthesia before skin incision, followed by 0.1mg/kg/h, intra-operative infusion until the completion of surgery. The rate of infusion was similar in both the study groups.

Study Design

At the pre-anesthetic visit, patients were informed about the objectives of the study, and instructed to request postoperative analgesia if needed. The verbal numerical rating scale (VNRS) was discussed with the patients and explained to them.

Standard monitors such as an ECG, a pulse oximeter, and a noninvasive blood pressure monitor were attached in the operating room and baseline parameters were collected. Infusion of crystalloid solution began after establishing an18-gauge intravenous cannula. Propofol (2-3mg/kg), fentanyl(1µg/kg), and vecuronium (0.1mg/kg) were used to induce general anaesthesia. One minimum alveolar concentration of isoflurane with oxygen and nitrous oxide mixture (40:60), andvecuronium 0.03 mg/kg were used for maintenance. A forced-aircover was used to keep normothermia in place. The end-tidal carbon dioxide level was keptat 35–45mmHg by adjusting the ventilation.

Intraoperative hemodynamic parameters such as systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial bloodpressure(MAP), arterial saturation(SpO2), temperature(°F), end-tidalcarbondioxide (etCO2), and heart rate (HR) were monitored every 5 minutes for the first thirty minutes of surgery, and every 10 minutes after that until the surgery was completed. If there is a 20% increase in mean arterial blood pressure or if the heart rate is more than 100 beats per minute (after ruling out other causes of tachycardia), intravenous fentanyl (1µg/kg) is given. Thirty minutes before the conclusion of the surgical operation,allpatients received1 g of intravenous paracetamol.

At the end of surgery, residual neuromuscular block was effectively reversed using intravenous glycopyrrolate (0.02mg/kg body weight) and neostigmine (0.05 mg/kg body weight) at the end of the surgical operation, and the patient was then extubated. Fentanyl consumption during surgery was also measured.

Following Surgery, VNRS was measured hourly until 9 hours, then at 12 hours,16hours, 20hours, and 24hours.Analgesia in the form of intravenous diclofenac(75mg)was provided as first rescue analgesic to any patient with a VNRS of greater than 3, while intravenous fentanyl (1µg/kg) was used as second rescue analgesic. During the first 24 hours after surgery, the total analgesic provided, and the total number of rescue doses given were documented. Post operative vitals and perioperative complications, were also noted.

Statistical Analysis

Prior to the study, a power analysis was performed to calculate the necessary number of patients in each group based on analgesic consumption (primary outcome) where 15 pilot cases were conducted in each group. The sample size of 80 patients was determined using a power of 80%, beta error of 0.2, alpha error of 0.05, and to detect a mean difference of 4.2 in analgesic use between the lignocaine and ketamine groups.

After completion of study, data were compiled and analyzed using Statistical Package of Social Sciences (version 21.0, SPSS Inc., USA). Continuous variables were expressed interms of mean and standard deviation (SD), whereas categorical variables were expressed in terms of percent. To compare two groups' means, an unpaired student t test was used. The Chi-square test was used to determine there relationship between category variables. Statistical significance was set at $P<0.05$.

RESULTS

All the 80 participants completed the study protocol (Figure 1). Regarding demographic parameters, including age, gender, weight, height, BMI, American Society of Anesthesiologists physical status and duration of surgery, both the groups were comparable without any statistically significant difference. [Table 1]

Table1: Comparison Of Demographic Variables Between Both The Groups

Variables	GroupL (N=40)	GroupK (N=40)	Pvalue
Age(yrs.)	48.93 ±10.27	47.45±8.33	0.609
Weight(kg)	68.53±5.13	67.70±5.59	0.494
Duration of surgery (min)	98.25±13.94	100.0±13.96	0.576
Height(cm)	164.03±5.51	162.43±6.23	0.227
BMI(kg/m2)	25.50±2.05	25.68±2.02	0.702
ASAGrade (I/II)	19/21	18/22	0.823

Values are presented as mean ± SD or number only. BMI= Body Mass Index, ASA= AmericanSocietyof Anesthesiologists physical status, $P>0.05$, not significant

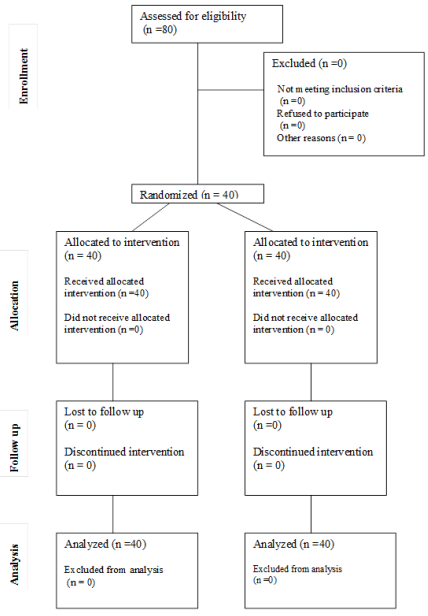

Figure no 1: Consort Diagram

Regarding intraoperative opioid consumption, consumption of fentanyl was 67.4± 5.76 mcg in group L and67.06 ±5.39mcg in group K, this difference did not reach statistical significance ($P=0.881$) (Table 2). During first 24 hours after surgery, patients in group L received significantly less diclofenac (75.00 ± 0.00 mg) as compared to group K (93.75± 32.9mg) ($P=0.001$), although no patient required fentanyl as second rescue analgesic. (Table 2).

Table 2: Comparison Of Perioperative Analgesic Consumptions Between Both The Groups

Variables	Group L (N=40)	GroupK (N=40)	P value
Intraoperative opioidconsumption (µg) (Fentanyl)	67.4±5.76	67.06±5.39	0.881
Post-operative rescue analgesicconsumption (mg) (Diclofenac)	75.0 ± 0.00	93.75 ±32.9	0.001*
Totalnumberof rescueanalgesics	1.00±0.00	1.25±0.44	0.001*

Values are expressed as the mean±SD, SD= Standard deviation, $P<0.05$, significant

Also, diclofenac doses were lower in group L (1.00 ± 0.00) as compared to group K (1.25 ± 0.44), in 24-hour post-operative period which was statistically significant ($P=0.001$)(Figure 2)

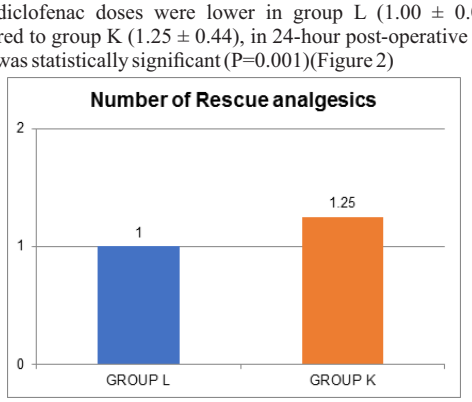

Figure 2- Total Number Of Rescue Analgesics Given In Each Study Group

The mean verbal numerical rating scale (VNRS) scores at rest, in group L were lower than those in group K at almost all-time intervals postoperatively. These differences were statistically significant at

7hr,8hr,9hr,12hr,16hrand20hr(P<0.001) and 24hr(P<0.05)(Figure3).

The incidence of nausea and vomiting reported more frequently in group K (two patients) than patients in group L (no patients experienced PONV), but it was statistically non-significant (P=0.152) (Table 3). Perioperative hemodynamic parameters were comparable in both the groups.

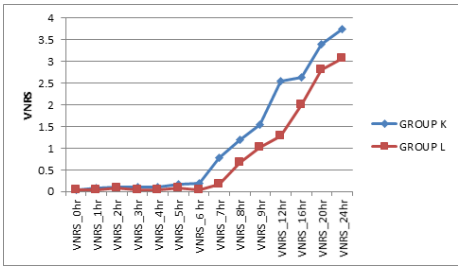

Figure 3- Verbal Numerical Ratingscale In Each Study Group

Table 3: Incidence Of Adverse Events

Side effects	Group L (N=40)	Group K (N=40)	P value
Perioral numbness	0	0	NA
Nausea & vomiting	0	2	0.152
Sedation	0	1	0.166
Hallucination	0	0	NA
Dizziness	0	0	NA

Values are expressed as number. NA-Not applicable, P<0.05, significant

DISCUSSION

The US Food and Drug Administration approved use of lignocaine for humans in 1948. Clinical practice of using intravenous lignocaine as postoperative analgesic began in 1958.In this study we found that, the lignocaine infusion group used less diclofenac as a postoperative rescue analgesic than the ketamine infusion group after a modified radical mastectomy. Secondly, verbal numerical ratingscale (VNRS) scores were also markedly decreased in the lignocaine infusion group compared to the ketamine infusion group during postoperative phase. We were unable to identify any appreciable impact of either study medication on the intraoperative fentanyl needs. There is no statistically significant difference between both the study groups regarding intraoperative fentanyl consumption.

Kang et al. discovered lower opioid intake in the lignocaine infusion group than in the saline infusion group following open gastrectomy in a randomized prospective study.[15]Lauwick S. et al. discovered in their study that the total postoperative analgesic consumption was considerably lower in the lignocaine infusion group compared to the control group. [16]

Studies on the postoperative analgesic needs after intravenous lignocaine have been done, and the results were inconsistent. No difference was seen after laparoscopic renal surgery [17], however after ambulatory laparoscopic surgery, analgesic needs were dramatically reduced in lignocaine group. [18]

Contrary to lignocaine, intraoperative low-dose ketamine infusion in the current trial was failed to reduce postoperative diclofenac consumption. Similar findings were made by Dullenkopf A et al. who discovered that intraoperative intravenous ketamine did not lessen the need for postoperative morphine. [19]

In patients undergoing laparotomy for benign gynecologic diseases, Bilgin H et al. showed that ketamine infusion decreased postoperative morphine consumption relative to a single preoperative dose. This finding contrasted with the present study.[20]

The differences in these studies might be due to variation in surgical procedures, study medication dosages, duration of study drug infusions, and difference in study protocols.

In the postoperative period, the VNRS score was significantly lower in the lignocaine infusion group compared to the ketamine infusion group. Similarly, in a randomised, placebo-controlled trial, Yardeni IZ et al. found that the lignocaine infusion group experienced less pain during coughing episodes and at rest in the first 4 and 8 hours following a hysterectomy under general anaesthesia. [21]

Additionally, Grigoras A et al. found that intravenous lignocaine infusion significantly decreased pain scores during breast surgery when compared to the control group. Systemic lignocaine appears to be likely to stop the induction of central hyperalgesia during the intraoperative period. [22] In the current study, ketamine infusion also failed to lower the VNRS score during the postoperative period. According to one study by Katz et al., ketamine infusion during radical prostatectomy did not significantly lower incidence or intensity of pain and pain scores, when compared to the control group. [23]

In the current study, reduced postoperative rescue analgesic and pain scores, indicate the benefits of lidocaine infusion in modified radical mastectomy under general anesthesia. These characteristics are crucial from a clinical perspective for postoperative recovery.Intravenous lignocaine acts through various mechanisms of action, like it inhibits glycine and NMDA receptors, releases endogenous opioids, blocks presynaptic muscarinic receptors, and increases acetylcholine levels in the cerebrospinal fluid.[24]Anti-nociceptive, anti-hyperalgesic and anti-inflammatory properties explain the prolonged effect of lignocaine after an infusion. [25-28]

In our study lignocaine and ketamine infusion provided stable haemodynamics throughout the study period. Talebi F et al. concluded that ketamine prevents hemodynamic variations at a particular dose and acts as a haemodynamic stabilizer.[29]

In the ketamine group, two patients had nausea and vomiting and no one required any treatment. None of the patients in lignocaine group had experienced any adverse events. Similarly, a meta-analysis and Cochrane review analysis that was conducted by Vigeant et al. [14,30]also found no overall significant difference in adverse events between both the study groups.

The limitations include the need for a large patient sample to draw conclusions about negative effects. Second, because the study only involved one center, it cannot be generalized. Thirdly, we did not assess the lignocaine plasma concentration and we were unable to identify any appreciable impact of either study medication on the intraoperative fentanyl needs. So future research is required to examine the effects of different dosage of lignocaine and ketamine on intraoperative analgesia.

CONCLUSION

Based on the results of this study, lidocaine infusion is more effective to reducethe postoperative analgesic consumption and pain scores and comparable effect for intraoperative opioids consumption when compared to low-dose ketamine infusion in patients undergoing modified radical mastectomy surgeries.

REFERENCES

1. Mishra AK, Afzal M, Mookerjee SS, Bandyopadhyay KH, Paul A. Pre-emptive analgesia:Recent trends and evidences.IndianJPain2013;27:114-20.
2. KissinI.Pre-emptiveanalgesia.Anaesthesiology2000;93:1138-43.
3. Kehlet H, Holte K. Effect of postoperative analgesia on surgical outcome. Br J Anaesth2001;87:62-72.
4. Garg R. Regional anaesthesia in breast cancer: Benefits beyond pain. Indian J Anaesth2017;61:369-72.
5. Carstensen M, Moller AM. Adding ketamine to morphine for intravenous patient-controlled analgesia for acute postoperative pain: a qualitative review of randomized trials. Br J Anaesth2010;104:401-6.
6. BonnetF, MarretE. Postoperative pain management and outcome after surgery. Best Pract ResClin Anaesthesiol2007;21:99-107.
7. Chelly JE, Ploskanych T, Dai F, Nelson JB. Multimodal analgesic approach in corporating paravertebral blocks for open radical retro pubic prostatectomy: arandomized double-blind placebo-controlledstudy. CanJAnaesth2011;58:371-8.
8. Lavand'homme P. Perioperative pain. Curr OpinAnaesthesiol2006;19:556–61.
9. Lauretti GR. Mechanisms of analgesia of intravenous lidocaine. Rev BrasAnestesiol2008;58:280-6.
10. Becker DE, Reed KL. Essentials of local anesthetic pharmacology. Anesth Prog 2006;53:98-110.
11. Bell RF, Dahl JB, Moore RA, and Kalso E. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev 2006;25(1):CD004603.
12. Welters ID, Hafer G, Menzebach A, Muhling J, Neuhauser C, Browning P, et al. Ketamine inhibits transcription factors activator protein 1 and nuclear factor-kappaB, interleukin-8, production, as well as CD11b and CD1 expression: studies in human leukocytes and leukocytic cell lines. AnesthAnalg2010;110:934–41.
13. Lavand'homme P, De Kock M, Waterloos H. Intraoperative epidural analgesia combined with ketamine provides effective preventive analgesia in patients undergoing major digestive surgery. Anesthesiology2005;103:813–20.
14. Bell RF, Dahl JB, Moore RA, and Kalso E. Peri-operative ketamine for acute post-operative pain: a quantitative and qualitative systematic review (Cochrane review). Acta Anaesthesiol Scand 2005;49:1405-28.
15. Kang JG, Kim MH, Kim EH, Lee SH. Intraoperative intravenous lidocaine reduces hospital length of stay following open gastrectomy for stomach cancer in men. J Clin Anesth2012;24:465–70.

16. Lauwick S, Kim Do J, Michelagnoli G, Mistraletti G, Feldman L, Fried G, et al. Intraoperative infusion of lidocaine reduces postoperative fentanyl requirements in patients undergoing laparoscopic cholecystectomy. Can J Anaesth2008;55:754–60.
17. Wuethrich PY, Romero J, Burkhard FC, Curatolo M. No benefit from perioperative intravenous lidocaine in laparoscopic renal surgery: a randomised, placebo-controlled study. Eur J Anaesthesiol2012;29:537–43.
18. De Oliveira GS Jr, Fitzgerald P, Streicher LF, Marcus RJ, McCarthy RJ. Systemic lidocaine to improve postoperative quality of recovery after ambulatory laparoscopic surgery. AnesthAnalg2012;115:262–7.
19. Dullenkopf A, Muller R, Dillmann F, Wiedemeier P, Hegi TR, Gauche S. An intraoperative pre-incision single dose of intravenous ketamine does not have an effect on postoperative analgesic requirements under clinical condition. Anaesth Intensive Care 2009;37:753–7.
20. Bilgin H, Ozcan B, Bilgin T, Kerimoglu B, Uckunkaya N, Toker A, et al. The influence of timing of systemic ketamine administration on postoperative morphine consumption. J Clin Anesth2005;17:592–7.
21. Yardeni IZ, Beilin B, Mayburd E, Levinson Y, Bessler H. The effect of perioperative intravenous lidocaine on postoperative pain and immune function. AnesthAnalg 2009;109:1464-9.
22. Grigoras A, Lee P, Sattar F, Shorten G. Perioperative intravenous lidocaine decreases the incidence of persistent pain after breast surgery. Clin J Pain 2012;28:567-72.
23. Katz J, Schmid R, Snijdelaar DG, Coderre CJ, McCartney L, Wowk A.Pre-emptive analgesia using intravenous fentanyl plus low-dose ketamine for radical prostatectomy under general anesthesia does not produce short-term or long-term reductions in pain or analgesic use. Pain 2004;110:707-18.
24. Hahnenkamp K, Durieux ME, Hahnenkamp A, Schauerte SK, Hoenemann CW, Vegh V, et al. Local anaesthetics inhibit signalling of human NMDA receptors recombinantly expressed in Xenopus leavis oocytes: role of protein kinase C. Br J Anaesth 2006;96:77–87.
25. Dunn LK, Duriex ME. Perioperative use of intravenous lidocaine. Anesthesiology2017;126:729-37.
26. Meaney ED, Reid L, Srivastava D. A survey on the use of intravenous lidocaine infusion for acute pain in Scottish Hospitals. Br J Pain 2020;2:98-103.
27. Hermanns H, Hollmann MW, Stevens MF, Lirk P, Brandenburger T, Piegeler T, et al. Molecular mechanisms of action of systemic lidocaine in acute and chronic pain: a narrative review. Br J Anaesth2019;123:335-49.
28. Eipe N, Gupta S, Penning J. Intravenous lidocaine for acute pain: an evidence-based clinical update. BJA Education 2016;16:292-8.
29. Talebi F, Mojaveraghili SB, Hesari Z, Kor F, Chavoshi T, Rayeji F, et al. Effects of intraoperative low dose ketamine on hemodynamic changes and postoperative opioid consumption in patients undergoing laparoscopic cholecystectomy.Arch anesthesiol crit care 2023;9:52-8.
30. Vigneault L, Turgeon AF, Zarychanski R, Cote D, Lauzier F, Moore L, et al. Perioperative intravenous lidocaine infusion for postoperative pain control: A meta-analysis of randomized controlled trials. Can J Anaesth2011;58:22–37.