Perioperative Intravenous Lidocaine Infusion for Postoperative Pain Control in Open Nephrectomies at the National Kidney and Transplant Institute: A Randomized, Double-Blind, Placebo Controlled Trial*

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ABSTRACT

***Background**:* Postoperative Pain control in Open Nephrectomy is one of the leading concerns of patients who underwent the procedure. Many efforts were made to determine the most efficient concoction for pain control, and studies have shown that opioids were the most efficient in reducing pain; however, it was observed that these opioids would produce side effects which hinders the goals of Enhanced Recovery after Surgery (ERAS). Lidocaine Intravenous infusion on the other hand, has been introduced as an adjunct as an opioid sparing alternative. It has been reported that it is effective in managing pain in different types of surgeries with promising results.

Objective: To determine the effectiveness of perioperative intravenous lidocaine infusion as an adjunct in postoperative analgesia in patients undergoing open nephrectomy.

Methodology: This is a randomized, double-blind, placebo-controlled study among patients admitted at The Institution, who underwent Elective open nephrectomy. Randomization into two treatment groups was done via draw lots. Both groups received treatment 30mins prior to cutting time wherein induction of anesthesia using Midazolam 1mg IV, Fentanyl 50mcg/dose IV, Propofol 1% 1mg/kg IV, with sevoflurane were used and adjusted accordingly. Rocuronium 0.6mg/kg IV was used as muscle relaxant. During induction, Group A received Lidocaine 2% (200mg) diluted to D5W in a 50ml syringe and infused intravenously via Target controlled infusion (TCI) with a maintenance rate of 40mcg/kg/min infusion intra-operatively at the start of cutting time. On the other hand, Group B will receive PNSS in a 50ml syringe. Postoperative outcome measured for this study includes numeric pain scores at 1, 2, 12, and 24 hours post operatively, number of morphine rescue doses and presence of adverse drug reactions.

***Results*:** Patients who received lidocaine had significantly lower mean pain scores across all time periods (7.6±1.2 at 1 hr, 3.4±1.3 at 2 hrs, 2.5±0.8 at 12 hrs, and 1.5±2.0 at 24 hrs) compared to those who received placebo (5.4±1.6 at 1 hr, 5.4±1.6 at 2 hrs, 4.9±1.1 at 12 hrs, and 3.5±1.5 at 24 hrs) (p-value=0.0021).

The mean pain scores of both groups significantly decreased starting from 1 hour to 24 hours after surgery (p-value=0.0000). Patients who received lidocaine had significantly lower mean number of rescue morphine (1.9±2.1) compared to those who received placebo (5.6±2.9) (p-value=0.0001). No patients had significant adverse reactions from the lidocaine group, while 6 patients (33.3%) had nausea from the placebo group (p-value=0.019).
Conclusion: Peri-operative intravenous Lidocaine Infusion (IVLI) is effective in reducing post-operative pain during the first, second, twelfth and twenty-fourth hours after nephrectomy. Also, the administration of perioperative IVLI significantly lowered the number of needed rescue morphine.

Keywords: *Intravenous Lidocaine Infusion, Pain Management, Open nephrectomy*

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INTRODUCTION

Open Nephrectomy is a common surgical procedure at the Institution second only to the trending laparoscopic nephrectomies. In the annual reports from the Institution's Medical Records, A total of 242 and 212 open nephrectomies were done in 2016 and 2017 respectively. Due to the nature of the surgical approaches, specifically, flank incision (~8-10 inches) and lateral decubitus position, it encounters problems postoperatively such as: pain, delayed gastrointestinal function, nausea and vomiting, and prolonged hospital stay. Among these, postoperative pain is notorious and of great concern not only for the patients but for the surgeons and anesthesiologists as well. Numerous studies have been conducted to resolve this problem, hence adjunct medications were introduced and one of these medications is lidocaine.

Lidocaine is part of a multi-modal protocol designed to provide optimal perioperative care particularly in patients with abdominal surgery by maximizing perioperative pain control, reduce opiate requirements and adverse events. In fact, the Enhanced Recovery after Surgery (ERAS) protocol included lidocaine infusion as a good pain control agent and good opioid sparing adjunct.[1]

Lidocaine as Postoperative pain adjunct has not yet been established as part of the protocol for pain management practice at the Institution. Furthermore, the growing interest in some centers and several published international studies related to the efficacy of lidocaine has piqued the interest of the proponents of this study to provide better and safer post-operative pain control in open nephrectomy, and to provide local data for further related studies.

SIGNIFICANCE OF THE STUDY

Post-operative pain is the major concern in open nephrectomies. The usual practice in this Institution for postoperative pain control in open nephrectomies are combined intravenous opioid infusion with or without epidural analgesia. While it may be effective in pain control, prolonged opioid use may result in several side effects including: Ileus, nausea and vomiting, urinary retention, respiratory depression, hyperalgesia and dizziness. This research aims to study the opioid sparing effect of lidocaine IV infusion as an adjunct in controlling postoperative pain. Upon searching at Pubmed, Clinical key and google scholar, no local studies have been published regarding continuous Lidocaine IV infusion. Thus, this study hopes to provide local factual data that may contribute in the advancement and influence the current practice of pain management at the Institution.

REVIEW OF RELATED LITERATURE

Lidocaine is a local anesthetic, amide-type that works as a sodium channel blocker in neural tissues by interrupting neuronal transmission. It is a widely used local anesthetic that promotes anti-hyperalgesic properties that improves acute post-operative pain control.[2] Numerous studies supported intravenous (IV) lidocaine as an effective adjunct for opioid sparing use, and for pain control in chronic pain.[3] According to G. Lauretti, author of the Updated Journal for Mechanisms of Analgesia of Intravenous lidocaine, the differential action of intravenous lidocaine in central sensitization and the analgesic and cytoprotective actions of different doses of lidocaine IV is multifactorial. The central sensitization is secondary to a peripheral anti-hyperalgesic action on somatic and central on neuropathic pain which result on blockade of central hyperexcitability. It is noted too that IV lidocaine should not exceed the toxic dose of plasma concentration of 5mcg/ml.[4]

According to J, Adams et. al., on Emergency medicine: Clinical Essentials, the maximum dose of lidocaine is 4 to 4.5mg/kg but is increased to 7mg/kg when lidocaine is given with epinephrine. Signs of toxicity are dived into three levels, Mild (tingling and numbness in fingers and toes, light headedness, vertigo, tinnitus, metallic taste in mouth, and confusion), Moderate (nausea and vomiting, decreased hearing, tremors, hypotension, bradycardia, dysarthria) and Severe (Drowsiness, loss of consciousness, muscle twitching,

convulsions, cardiac arrhythmias and cardiac arrest). Therapeutic concentrations of lidocaine can be 5.5mg/L whereas a plasma level of 8-12mg/L and higher is associated with Central nervous system and Cardiorespiratory toxicity. In cases of lidocaine toxicity, The American Society of Regional Anesthesia and Pain Medicine recommends an initial bolus of 1.5mg/kg of 20% intravenous lipids followed by a continuous infusion of 0.25ml/kg/min., infusion of intravenous lipids can be doubled to 0.5ml/kg/min if cardiac stability is not restored. [5] Drug interactions that may affect the increase in serum levels of lidocaine are Cimetidine and Propanolol, Beta blockers with other anti-arrhythmics can increase cardiac depression. Phenytoin has additive cardiac effects, and Acetazolamide, Loop diuretics and Thiazides that cases hypokalemia may antagonize lidocaine.[6]

A. Kaba M.D. et al, on clinical investigations on IV lidocaine infusion noted that lidocaine has properties on analgesia, anti-hyperalgesia and anti-inflammatory which has been reported to speed the return of bowel function post operatively. [7]

Opioids

In modern medicine, opioids were discovered as the most potent pain killers used for perioperative and post-operative pain control. It is classified as natural, semisynthetic or synthetic opioids. Nociception and perception of noxious stimulus are modified by opioids in a manner that exerts its action in the brain, specifically the cortex and limbic system, affecting the cholinergic systems, resulting in changes in pain and arousal perception. Although opioids are potent and has good pain control properties, it can induce hyperalgesia, promotes tolerance and can cause numerous untoward side effects such as: Respiratory depression, nausea and vomiting, delayed gastric emptying, constipation, bowel distention, paralytic ileus, spasm of sphincter of oddi, urinary retention, histamine release, muscle rigidity, sedation, drowsiness, dizziness, light headedness and euphoria.[8] Opiates do not alter pain threshold of afferent nerve endings to noxious stimuli, nor do they affect the conductance of impulses along peripheral nerves. Analgesia is mediated through changes in the perception of pain at the spinal cord (mu_2, delta, kappa-receptors) and higher levels in the CNS (mu1, kappa3 receptors). There is no ceiling effect of analgesia for opiates. [9]

Morphine is a potent mu-opiate receptor agonist; Receptors include mu, kappa and delta.[10] Stimulation of mu-receptors produces analgesia, euphoria, respiratory depression, miosis, decreased gastrointestinal motility, sedation, somnolence, and physical dependence. [11] Kappa-receptors produces analgesia, miosis, respiratory depression, dysphoria and some psychomimetic effects. [11] There is no predictable relationship between morphine serum concentrations and analgesic response but may vary from patient to patient due to several factors: age, medical condition and emotions. There is no relationship between morphine concentrations and incidence of adverse events, although higher concentrations are associated with more adverse events. [12]

Flank Incisions are preferably used in uncomplicated open nephrectomies because this allows access to the retroperitoneum while avoiding the entry into the peritoneum. Post-Operative pain from flank incisions may be significant, especially during deep inspiration. Pain may be long term due to neuritis or entrapment of an intercoastal nerve in the suture or surrounding scar tissue.[13] The physiopathology of acute surgical pain is described by inflammatory cell infiltration which activates the pain pathways in the spinal cord and the reflexive muscle spasms. Inadequately controlled acute postoperative pain may result in chronic pain.[14]

OBJECTIVES OF THE STUDY

General Objective

The study is designed to determine the effectiveness of perioperative intravenous lidocaine infusion as an adjunct in postoperative analgesia in patients undergoing open nephrectomy.

Specific Objective

1. To describe the socio-demographics and clinical profile of patients undergoing open nephrectomy according to the following characteristics:

a. Age
b. Sex
c. Height
d. Body Mass Index (BMI)
e. American Standard of Anesthesiologist (ASA) Classification

2. To compare the postoperative numerical pain scores during the first, second, twelfth and twety-fourth hour postoperatively for patients receiving lidocaine (Group A) versus the group given placebo (Group B).
3. To compare the total number and mean of rescue doses of opioid (Morphine) for patients receiving lidocaine (Group A) and Placebo (Group B).
4. To determine the mean dose of lidocaine given to patients in group A.
5. To determine safety of the drug through the proportion of patients with adverse drug reactions in both treatment arms.

METHODOLOGY

Study Design

This will be a prospective, randomized, double blind, placebo-controlled research. The anesthesiologist-in-charge and patients are not aware of the treatment. Only the investigator will know which treatment will be handed to the anesthesiologist. The participants of the study will be divided into two groups: Group A consists of the IV lidocaine infusion as the variable, and NSAIDs and Morphine as constants. Group B will be the placebo group, it consists of IV PNSS infusion as the variable and NSAIDs and Morphine as constants. Randomization will be done through a master list by listing the numbers 1 to 36, where in each number corresponds to either Group A or B. Patients will be randomly listed in the master list by draw lots, wherein a number will be drawn, and it will correspond to the number of the specific patient all throughout the study. Upon randomization, the anesthesiologist in charge will draw a number and that number will correspond to the treatment group. Only the Investigator will know the treatment group and will prepare the corresponding regimen. The investigator will also be responsible in keeping the master list.

Study Population

The study participants are patients admitted at the Institution who will undergo an elective Open Nephrectomy procedure.

Inclusion Criteria

1. All patients who will undergo elective open nephrectomy
2. Age 18 to 60 years old
3. Male or Female
4. ASA I-III
5. Creatinine level: 0.6- 1.2mg/dL (males); 0.5-1.1mg/dL (females)

Exclusion Criteria

1. Patients diagnosed with Metastatic Renal Cell Carcinoma
2. Patients with cardiac Problems such as: arrhythmias, AV blocks, CAD, recent MI, heart failure
3. Patients with previous cardiac, hepatic and renal surgeries (I.e. angioplasty, CABG, Hepatectomy, liver and kidney transplant)
4. Patients with seizure disorders
5. Patients with electrolyte imbalance
6. Patients with liver diseases and cardio-renal problems
7. Patients with known lidocaine allergy
8. Patients on medications such as: Cimetidine, Propanolol, Anti-arrhythmic drugs, Phenytoin, Acetazolamide, Loop diuretics and Thiazides

Patient Enrollment

This research protocol was submitted to the Department of Anesthesia and the Institutional Review board. Patients will be recruited from both

Pay and Service, if they consented for the procedure.

Enrollment Period

Enrolment of patients in the study will be done a day prior to the proposed surgery during preoperative evaluation.

Treatment Period

Duration of the treatment period will begin on the day of the surgery and will terminate on the 24th hour post-operative day.

Study Period

The study will be conducted with a duration of 6-8months, from May 2019 to December 2019.

MATERIALS AND METHODS

Sample Size Estimation

This is a Prospective study which includes 36 subjects. Sample size needed for the study was computed using G-Power software for repeated-measures ANOVA with 4 time periods. Alpha was set to 0.05, medium effect size= 0.5, correlation = 0.7 and target power of 0.90. The resulting sample size is 36 or 18 per treatment arm.

F tests – ANOVA: Repeated measures, between factors		
Analysis:	A priori: Compute required sample size	
Input:	Effect size f	= 0.5
	α err prob	= 0.05
	Power (1-β err prob)	= 0.90
	Number of groups	= 2
	Repetitions	= 4
	Corr among rep measures	= 0.7
Output:	Noncentrality parameter λ	= 11.612903
	Critical F	= 4.130018
	Numerator df	= 1.000000
	Denominator df	= 34.000000
	Total sample size	= 36
	Actual power	= 0.911505

Method Sampling

The study will include 36 adult patients, ASA I-III, ages 18 to 60 years old, scheduled for elective open nephrectomy under general anesthesia with continuous intravenous infusion of either lidocaine or placebo, depending which Group the patient was randomly assigned.

Data Collection Procedure

A. Preoperative:

An informed consent and patient information sheet will be given to all the research subjects who are going to participate in the study. This will include patient participants only.

B. Intra-Operative:

1. Patients of both arms will be hooked to the standard American Society of Anesthesiologists (ASA) monitors such as ECG, Pulse oximeter, ETCO2, and non-invasive blood pressure.

2. In Group A (Experimental group), treatment will start 30mins prior to cutting time. Induction of anesthesia will make use of the following: Midazolam 1mg IV, Fentanyl 50mcg/dose IV, Propofol 1% 1mg/kg IV, Volatile anesthetic: Sevoflorane maintained at least MAC 2 will be used and adjusted accordingly, and Rocuronuim 0.6mg/kg IV for muscle relaxant. Lidocaine 2% (200mg) will be diluted to D5W in a 50ml syringe, making a concentration of 4mg/ml will be used for infusion via Target controlled infusion (TCI) with a maintenance rate of 40mcg/kg/min. Infusion intraoperatively will start at cutting time. Rate will be decreased to 2mg/hr at the end of surgery and is continued at a constant rate of 2mg/hr until 24 hours post operatively via IV easy pump. Acetaminophen 1g IV will be given prior to cutting time. The medications will be prepared by the investigator prior to surgery and will be handled to the anesthesiologist in charge prior to induction. Syringes will be labeled as the number corresponding to the master list. No drug name will be placed on the syringe, but a standard dose preparation of 4mg/ml will be placed regardless if it is Group A or B.

3. In group B (placebo group), a 50ml syringe containing PNSS will be prepared and handled to the anesthesiologist in charge prior to induction. Treatment will start 30 mins prior to cutting time with the same induction of anesthesia as Group A regimen. Placebo continuous intravenous infusion will be used via TCI with the same maintenance rate of 40mcg/kg/min intra-operatively. Rate will be decreased to 2mg/hr at the end of surgery and is continued at a constant rate until 24 hours post-operation.

4. A standby 20% lipid intravenous solution will be prepared intraoperatively in case of local anesthetic toxicity would occur. An initial bolus of 1.5mg/kg followed by a continuous infusion of 0.25ml/kg/min. will be used for reversal of toxicity. Intravenous lipids can be doubled to 0.5ml/kg/min if cardiac stability is not restored.

A. Post-Operative:

A record sheet for numeric pain score will be provided for each patient. Frequency of rescue doses will be determined from the treatment sheet provided in the chart. Data obtained from PACU monitoring during the first two hours post-operatively, and 24 hours continuous monitoring will be noted. A standard opioid, Morphine at 1mg IV every hour as needed for pain will be used as rescue IV bolus, and a constant NSAID (Acetaminophen) of 1g IV every 6 hours round the clock will be given and Ketorolac 30mg IV every 8 hours round the clock for both treatment group.

During the entire course of the study, the incidence and the types of adverse events will be recorded and managed according to the standards of medical care. The following adverse events were to be noted namely: Nausea and/or vomiting, dizziness, hypersensitivity reactions, bradycardia, cardiac arrhythmias, hypotension, myocardial depression, restlessness, seizures, tachycardia, tremors or cardiac arrest. These will be assessed by the investigator who has knowledge on local anesthetic system toxicity (LAST). The nurse-in charge shall inform the investigator for occurrence of any of the above events. After assessment, appropriate treatment shall be given accordingly, and if deemed necessary, an immediate referral to other disciplines such as urology or internal medicine shall be made. If there are life-threatening adverse events, the patient's participation will be terminated, and appropriate interventions will be given. The occurrence of any adverse events shall be recorded by the investigator and noted in the data gathering sheet and will be reported to the Institutions' Adverse Event Committee.

Definition of Terms:

ASA - American Society of Anesthesiologist Classification

Nephrectomy - surgical removal of Kidney

NSAID- Non Steroidal Anti-inflammatory Drugs

Arrythmias- problem with rate or rhythm of heartbeat

Bradycardia- heart rate <60 beats per minute

Tachycardia- heart rate >100 beats per minute

MI- Myocardial Infarction (heart attack)

CAD- Coronary Artery Disease

AV Block- Atrio-ventricular block

ETC02- end tidal carbon dioxide

LAST- Local Anesthetic System Toxicity

PACU- Post Anesthesia Care Unit

OUTCOME MEASUREMENTS AND DATA COLLECTION

Primary Endpoint

Numeric Pain Score- Measured ranging from 0= no pain, to 10= worst pain imaginable at 1, 2, 12, and 24 hours post operation. Pain will be standardized while patient is at rest at supine position.

Secondary Endpoints

1. Rescue Doses- Measured by the number of times the patient was given morphine intravenously from 0 to 24 hours post operation.

2. Adverse drug reactions- systemic toxicity such as light headedness, tinnitus and numbness of tongue and other rare but possible side effects that may be related to lidocaine include anaphylactoid reactions, bradycardia, cardiac arrhythmias, cardiac arrest, myocardial depression, respiratory arrest, restlessness, seizures, tachycardia and tremors. It shall be emphasized that the amount of drug used in this study is the maximum recommended dose to avoid systemic toxicity.

DATA HANDLING AND ANALYSIS

All subjects enrolled in the study will be assigned with a number code (1-36). Each data will be recorded in a pre-designed research data collection form. The demographics and biomedical date of each patient will be encoded in Microsoft excel 2007, together with the baseline characteristics.

Statistical Analysis

Descriptive statistics using frequencies and proportion will be used to summarize categorical variables (e.g. Sex, ASA classification, proportion of patients with adverse drug reactions). Mean and standard deviation will be used to describe quantitative continuous variables (e.g. Age, Height, BMI, Numerical pain scores, number of rescue doses of morphine).

Repeated measures of ANOVA will be used to determine if significant different exists in numerical pain scores between patients receiving lidocaine (group A) and the group given placebo (Group B) across the four time periods. T-test will be used to determine if significant different exists in the total number and dosage of lidocaine between patients receiving lidocaine (Group A) and the group given placebo (Group B). T-test will also be used to determine if there is significant difference in the number and dosage of morphine between the two groups. Test for homogeneity among groups will be done and Shapiro-Wilk test will be used to determine if outcome variables are normally distributed.

Finally, Chi-square test will be done to determine if there is significant difference in the proportion of patients with adverse drug reactions in both treatment arms. Significance level will be set at $p<0.05$ for all statistical analysis and Stata SE version 12 software will be used.

Ethical Considerations

The study protocol was submitted to the Department of Anesthesia and the Institutional Review Board. The informed consent shall be explained in a dialect easily understood by the patient and will be done prior to patient enrollment. The study will be conducted in compliance with the protocol and regulatory requirements. Patient's name will not be disclosed, only their corresponding number will be shown in the data. All patients' data will be kept in confidentiality by the principal investigator, and if the patient would want to have a copy of their participation, they will be provided with a copy of their data only. No other parties will know the patient's name or initials to ensure anonymization, privacy and confidentiality.

The 24hrs monitoring of the patient will be done at the Recovery room post operation. Budget allocation for this was approved by the Ethics committee with study protocol number: R-2018-019 which allows to waive the recovery room fee of approximately Php 4,500 per patient.

RESULTS

The mean age of the patients was 44.8 years old (SD=12.6). There is equal distribution of males and females in the study. The mean height was 160.2cm (SD=5.9) and mean BMI was 23.1 (SD=3.1). More than half of the patients were classified as ASA II (63.9%). All patient characteristics did not differ significantly between the two treatment groups.

Table 1. Characteristics of Study Population				
	Total (N=36)	Group A, Lidocaine n=18	Group B, placebo n=18	Independent T-test / Chi-square p-value
Age (mean, ± SD)	44.8±12.6	45.3±12.3	44.3±13.2	0.8158
Sex (n, %)				
Male	18 (50.0)	10 (55.6)	8 (44.4)	0.505
Female	18 (50.0)	8 (44.4)	10 (55.6)	
Height in cm (mean, ± SD)	160.2±5.9	160.8±6.3	159.6±5.5	0.5661
Body Mass Index (mean, ± SD)	23.1±3.1	22.5±2.3	23.7±3.8	0.2503
ASA (American Standard of Anesthesiologists) Classification (n, %)				
I	13 (36.1)	4 (22.2)	9 (50.0)	0.083
II	23 (63.9)	14 (77.8)	9 (50.0)	

Patients who received Lidocaine had significantly lower mean pain scores across all time periods compared to those who received placebo (p-value=0.0021). The mean pain scores of both groups significantly decreased starting from 1 hour to 24 hours after surgery (p-value=0.0000).

Table 2. Comparison of Postoperative Numerical Pain Scores Between Lidocaine and Placebo Group					
	1 hour	2 hours	12 hours	24 hours	Repeated-measures ANOVA (F-test, P-value)
Group A, Lidocaine (mean, ± SD)	7.6±1.2	3.4±1.3	2.5±0.8	1.5±2.0	Within groups: F=170.0, p-value=0.0000
Group B, placebo (mean, ± SD)	8.7±1.0	5.4±1.6	4.9±1.1	3.5±1.5	
Independent T-test (p-value)	0.0060	0.0002	0.0000	0.0028	Between groups: F=10.0, p-value=0.0021

Patients who received Lidocaine had significantly lower mean number of rescue morphine compared to those who received placebo (p-value=0.0001).

Table 3. Comparison of Use of Rescue Medications Between Lidocaine and Placebo Group			
	Group A, Lidocaine n=18	Group B, placebo n=18	Independent t-test (p-value)
Number of rescue morphine (Mean ± SD)	1.9±2.1	5.6±2.9	0.0001
Dosage of rescue morphine (Mean ± SD)	1.9±2.1	5.6±2.9	0.0001

The incidence of ADR differed significantly between the two groups (p-value=0.019). No patients had nausea from the Lidocaine group while 6 patients (33.3%) had nausea from the placebo group.

Table 4. Comparison of Occurrence of Adverse Drug Reaction Between Lidocaine and Placebo Group			
	Group A, Lidocaine	Group B, placebo	Chi-Square Test (p-value)
Occurrence of Adverse Drug Reaction (Nausea)			
Yes	0 (0.0)	6 (33.3)	0.019
No	18 (100.0)	12 (66.7)	

DISCUSSION

Among the different strategies that has been recommended for control of post-operative pain, intravenous lidocaine infusion (IVLI) gained the attention. The results of the current study supported the use of perioperative IVLI for management of post-operative pain. One strength of this study is the use of randomization to allocate patients into treatment groups which minimized selection bias. Performance and detection biases were also minimized by doing a double-blinded design. The use of a placebo-controlled trial wherein the patient characteristics were similar in both the treatment and placebo groups also strengthened the validity of the results and resolved the issue of possible confounding. The results were also consistent with previous studies which showed the effectiveness of IVLI.

Vigneault and colleagues (2010) presented an evaluation of effectiveness of the analgesic and its safety during general anesthesia. MEDLINE EMBASE, Cochrane and SCOPUS databases, with addition of grey literature, were used to perform the systematic review[16(12)] The review comprised of all randomized controlled trials that use placebo or any comparator and assessed IVLI throughout general anesthesia for any type of surgery (29 studies consisting of 1754 patients). The I2 index was used to assess heterogeneity and random effects models. Six hours after operation, IVLI decreased pain at rest (weighted mean difference [WMD]= -8.70, 95% confidence intervals [CI] -16.19 to -1.21), during cough movement (WMD= -11.19, 95% CI -17.73 to -4.65), and during movement (WMD= -9.56, 95% CI -17.31 to -1.80). There were also decreased opioid requirement (morphine) due to IVLI (WMD= -8.44 mg, 95% CI -11.32 to -5.56), time to first flatus (WMD= -7.7.62 hr, 95% CI -10.78 to -4.45), time to first bowel movement (WMD= -10.71 hr, 95% CI -16.14 to -5.28), nausea/ vomiting (risk ratios= 0.71, 95% CI 0.41 to 0.07). Incidence of cardiac and neurologic adverse events was comparable in the 12 studies that systematically screened adverse events. The authors concluded that IVLI is an anesthesia auxiliary throughout general anesthesia and has the capacity to improve post-operative analgesia and the effectiveness of care, primarily in the context of abdominal surgeries. IVLI safety cannot be established in the study given that it is linked with potentially serious adverse event and insufficient studies of adverse events evaluation. The authors recommended further research particularly on optimal dose treatment and intervention safety.[15]

More recently, a systematic review on the effectiveness of perioperative lidocaine infusion (IVLI) in postoperative pain and recovery in various surgery patients was done by Weibel et al (2016) consisting of 45 trials with 2802 participants. [20] Randomized controlled trials until May 2014 were searched in CENTRAL, MEDLINE, EMBASE, and CINAHL databases and ClinicalTrial.gov and congress proceedings for comparative studies of patients who did or did not receive continuous perioperative IVLI. Meta-analysis suggested that lidocaine decreased postoperative pain (visual analog scale 0 to 10 cm) at 1-4 hours (MD= -0.84, 95% CI -1.10 to -0.59) and at 24 hours (MD= -0.34, 95% CI -0.57 to -0.11) post-surgery, but not at 48 hours (MD= -0.22, 95% CI -0.47 to 0.03). Trial sequential analysis and subgroup analysis proposed decreased pain for abdominal surgery patients who underwent laparoscopic or open abdominal, but not for those who had other surgeries. Evidence were insufficient for positive effects of lidocaine on postoperative gastrointestinal recovery, opioid requirements, postoperative nausea and vomiting and duration of hospital stay. The authors concluded that there is limited evidence on intravenous lidocaine infusion when compared with placebo on pain scores, especially in the early phase of post-operation.[20]

CONCLUSION

Peri-operative intravenous lidocaine infusion (IVLI) is effective in reducing post-operative pain during the first, second, twelfth and twenty-fourth hours after nephrectomy. Also, the administration of perioperative IVLI significantly lowered the number of needed rescue morphine post operation. It is considered safe as no adverse events were observed. Given this, the use of perioperative IVLI is highly recommended.

REFERENCES:

1. Y. Cerantola, M. Valero, B. Persson, et. Al: *Guidelines for perioperative care after Radical Cystectomy for bladder cancer: Enhanced Recovery after Surgery (ERAS) society recommendations*, Elsevier Clinical Nutrition. September 2013. 879-887
2. N.Eipe,MBBS MD., S. Gupta MD FRCPC, J. Penning MD FRCPC., *Intravenous Lidocaine for acute pain: an evidence-based clinical update.* BJA Education, Volume 16, Issue 9, 1 September 2016, Pages 292–298,https://doi.org/10.1093/bjaed/mkw008
3. L. Dunn, M.D. Ph.D., M. Durieux, M.D. Ph.D. *Perioperative Use of Intravenous Lidocaine*, Department of Anesthesiology and Neurosurgery, University of Virginia, Charlottesville, Verginia. American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Anesthesiology 2017; 126:729-37
4. G. Lauretti, *Mechanisms of analgesia of Intravenous Lidocaine.*Anestesiol. Vol.58 no.3 Campinas May/June 2008,http://dx.doi.org/10.1590/S0034-709420080000300011
5. J. Adams, et.al, *Emergency Medicine: 2nd edition*: *Local and Regional Anesthesia.* 2013 by Saunders, an imprint of Elsevier Inc. 188, 1578-1586.e1
6. Medscape, *Lidocaine (Rx)*. The heart. Org. 1994-2020 by WebMD LLC, http://reference.medscape.com/drug/lidocaine-cv-lidopen-342302#91
7. A. Kaba, MD, et.al.*Clinical Investigations: Intravenous Lidocaine infusion facilitates Acute Rehabilitation after Laparoscopic Colectomy.* American Society of Anesthesiologist, Inc. Lippincott Williams and Wilkins, Inc. Anesthesiology 2007; 11-8
8. P. Barash, MD, et.al, *Clinical Anesthesia: 8th edition.* Lippincott Williams & Wilkins, a Wolters Kluwer business, Philadelphia 2017
9. ARYMO ER, Astramorph PF, et. al. *Drug monograph :Morphine*. Elsevier ClinicalKey 2020. https://www.clinicalkey.com/#!/content/drug_monograph/6-s2.0-416?scrollTo=%23top
10. Harrison C, Smart D, Lamber DG. Stimulatory effects of opioids. Br J Anaesth 1998;81-20-8.
11. MS Contin (Morphine sulfate extended-release tablets) package insert. Stanford, CT: Purdue Pharma L.P.;2019 Oct.
12. Morphine sulfate tablet package insert. Eatontown, NJ: West-Ward Pharmaceuticals Corp: 2019 Oct.
13. E. Nelson, M.D., C. Evans, M.D., *Complications of Nephrectomy.* (2010). *Complications of Urologic Surgery, 387–400.* doi:10.1016/b978-1-4160-4572-4.00033-9
14. I. Alper, M.D., E. Yuskel, M.D., *Comparison of Acute and Chronic Pain after Open Nephrectomy versus Laparoscopic Nephrectomy: A prospective clinical trial.* Wolters Kluwer Published online Apr 22, 2016. doi: 10.1097/MD.0000000000003433
15. Vigneault L, Turgeon A, Côté D et al. Perioperative intravenous lidocaine infusion for postoperative pain control: a meta-analysis of randomized controlled trials. Canadian Journal of Anesthesia/Journal canadien d'anesthésie. 2010;58(1):22-37. doi:10.1007/s12630-010-9407-0
16. Zhao J, Li Y, Wang Y et al. Intravenous lidocaine infusion for pain control after laparoscopic cholecystectomy. Medicine (Baltimore). 2018;97(5):e9771. doi:10.1097/md.0000000000009771
17. Baral B, Bhattarai B, Rahman T, Singh S, Regmi R. Perioperative intravenous lidocaine infusion on postoperative pain relief in patients undergoing upper abdominal surgery. Nepal Medical College Journal. 2010. https://www.nmcth.edu/images/gallery/Editorial/8AjuUb_kharal.pdf. Accessed December 7, 2019.
18. Cui W, Li Y, Li S, Wang R, Li J. Systemic administration of lidocaine reduces morphine requirements and postoperative pain of patients undergoing thoracic surgery after propofol–remifentanil-based anaesthesia. Eur J Anaesthesiol. 2010;27(1):41-46. doi:10.1097/eja.0b013e32832d5426
19. McCarthy GC e. Impact of intravenous lidocaine infusion on postoperative analgesia

and recovery from surgery: a systematic review of randomized controlled trials. - PubMed - NCBI. Ncbi.nlm.nih.gov. https://www.ncbi.nlm.nih.gov/pubmed/20518581. Published 2010. Accessed December 7, 2019.

20. Weibel S, Jokinen J, Pace N et al. Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery: a systematic review with trial sequential analysis † †This review is an abridged version of a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2015, Issue 7, DOI: CD009642 (see www.thecochranelibrary.com for information).1 Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review. Br J Anaesth. 2016;116(6):770-783. doi:10.1093/bja/aew101

21. R. Werdenhausen M.D., D.Kramer,M.D. et al., *Lidocaine Metabolites Inhibit glycine Transporter 1: A novel mechanism for tha analgesic action of Systemic Lidocaine.* American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Anesthesiology 2012: 116:147-58

22. P. Tauzin-Fin, O. Bernard, et.al.*Benefits of Intravenous Lidocaine on post-operative pain and acute rehabilitation after laparoscopuc Nephrectomy*. Journal of anesthesiology clinical Pharmacology. 2014 july-September; 30(3): 366-372

23. B. Hasan, et.al *Lidocaine-induced systemic Toxicity: A case report and Review of Literature*. Department of Internal medicine, University of Missouri Kansas City. Cureus. May 2017; 9(5): e 1275, doi: 10.7759/cureus.1275

APPENDIX A

DATA GATHERING SHEET

1. GENERAL DATA

Patient No.	Patient Initials	Age	Sex	Weight (Kg)	Height (cm)	BMI (kg/m2)	ASA Classification
1							
2							
3							
4							
5							
6							

PACU MONITORING SHEET

TIME FROM POST OP	PAIN SCORE	RESCUE DOSE(morphine) 1mg q1 prn	Additional Medications given if any	Adverse Effect
1hr				
2hrs				
12hrs				
24hrs				

Total Amount of Morphine____

Adverse Drug Reactions noted within 24 hours: PUT A CHECK MARK FOR YES or NO and write the name of rescue medications and total dose given if indicated

REACTIONS	YES	NO	NAME OF RESCUE MEDICATION/S (IF GIVEN)	TOTAL DOSE OF RESCUE MEDICATION/S (IF GIVEN)
NAUSEA				
VOMITING				
DIZZINESS				
ANAPHYLACTOID REACTIONS				
BRADYCARDIA				
CARDIAC ARREST				
CARDIAC ARRHYTHMIAS				
MYOCARDIAL DEPRESSION				
RESPIRATORY ARREST				
RESTLESSNESS				
SEIZURES				
TACHYCARDIA				
TINNITUS				
TREMORS				