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Intravenous Lidocaine for Perioperative Use

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Abstract

Introduction and Background: Lidocaine was recognised only as a local anesthetic and anti-arrhythmic drug for past decades. Nonetheless, more recently its utility in perioperative setting is being appreciated globally. This review aims to analyse its work beyond its traditional use when employed intravenously in perioperative setting and overall impact on postoperative period. **Content:** A total of 41 articles were selected for study while 13 of them were chosen for data presentation. Databases such as CENTRAL, MEDLINE/Pubmed, LILACS, Ovid and Scielo were used to search the articles using keywords like Intravenous lidocaine, local anesthetics, perioperative analgesia or postoperative pain. A bolus dose of 1.5 mg/kg and maintenance dose of 2 - 3 mg/kg/h of intravenous lidocaine was used to bring out its analgesic effect and its positive impact on postoperative stage in nearly all the selected studies. Its anti-inflammatory, antinociceptive and immunomodulatory effects were also addressed. **Conclusion:** Perioperative implication of systemic lidocaine not only lessens pain perception but also assures early return of bowel function, lower incidence of postoperative nausea and vomiting, opioid sparing effect and shorter length of hospital stay. Thus, implementation of lidocaine as a part of perioperative approach should be seriously considered. Its role in surgeries other than abdominal needs more detailed study. In spite of current results encouraging, it may be too early to claim its similar impact in other types of surgeries.

Keywords

Intravenous Lidocaine, Local Anaesthetics, Postoperative Analgesia, Postoperative Pain

1. Introduction

Pain is undoubtedly the most anticipated part of postoperative experience [1]. According to World Health Organisation, more than 300 million surgeries are performed each year globally and more than three-quarters of the patients un-

dergoing surgery suffer postoperative pain. However, it continues to remain under-managed producing undesirable surgical outcomes thereby, increasing morbidity and mortality in many cases. In fact, it has a negative impact on quality of life, functional recovery and financial liability of a patient [2]. Thus, effective management of pain should be part of perioperative approach. With this concept, many perioperative interventions and management strategies for controlling pain have emerged [3]. Among these, the use of intravenous lidocaine as perioperative analgesia is enormously growing in popularity. This could be attributed to its pharmacological properties including effective postoperative analgesia and lack of side-effects associated with traditionally used analgesics such as opiates, which will be discussed in this article [4].

Lidocaine, 2-diethylaminoaceto-2',6'-xylidide ($C_{14}H_{22}N_2O$), is an amide local anesthetic and a class 1b antiarrhythmic agent. It was first synthesized in 1942, came to use in 1948, and approved by Food and Drug Administration in 1949 [5]. Previously it was used as antiarrhythmic and local anaesthetic agent but more recent studies suggest that it has significant analgesic, anti-nociceptive, immuno-modulating, and anti-inflammatory properties. Several studies document a decrease in incidence of postoperative chronic pain, nausea, vomiting, ileus, opioid consumption and duration of hospital stay with the use of this anaesthetic agent. It was also established that these effects were rather limited to abdominal surgeries [6]. Nevertheless, lately more promising results have been observed in different types of surgeries like spinal [7] or brain surgery [8].

2. Methodology

Active research was carried out electronically. The method adopted was to review scientific journals, peer reviewed articles, clinical trials and meta-analysis. Databases such as CENTRAL, MEDLINE/Pubmed, LILACS, Ovid and Scielo were used to search the articles using MeSH terms and free text like intravenous lidocaine, local anaesthetics, perioperative analgesia or post operative pain as key words. Furthermore, references listed in the retrieved articles were also checked for relevant studies. A total of 213 articles dating from 1990 to 2017 were scanned independently by two reviewers based on the above search results, howbeit, only 60 articles were selected during primary screening mainly on the basis of study design, as randomised control trial was prioritized. Rest were discarded due to various reasons like variation in the type of study, irrelevancy to the subject matter or dates, 20 of which were discarded due to duplicity and inaccessibility of full text. After thorough discussion between the two reviewers, 41 articles were finalized. Any disagreement between the two was sorted out by consulting a third reviewer. In addition, sample size, description of pharmacology of lidocaine and language used were taken into consideration while finalizing the articles. Articles those published in language other than English with no availability of translation were discarded. Bearing in mind the type of study and outcome of the study according to the determinants like post-operative pain, nausea

and vomiting or length of hospital stay, ultimately 13 studies were employed for data presentation (Figure 1).

3. Pharmacokinetics

The pharmacokinetic process of lidocaine, to a large extent, depends on the total dose, route of administration and the vascularity of the site of injection. When given intravenously, distribution occurs at a rate of 0.6 - 4.5 L/kg, [5] primarily in well-perfused organs such as kidney, brain and heart, and then to lesser perfused organs like skin, skeletal muscles fat and peripheral organs [1]. Its absorption begins within 1 to 5 minutes after local infiltration and 5 to 15 minutes after peripheral nerve blockade. However, irrespective of its site of administration serum levels reach its peak at 20 to 30 minutes following injection while its action lasts for 10 to 20 minutes. The elimination half-life of lidocaine is 60 to 120 minutes. Around 60% to 80% of its molecules are protein bound, with approximately 70% of the binding to alpha-1 glycoprotein alone. The anaesthetic agent is metabolized mainly to active metabolites like monoethylglycinexylidide (MEGX) and glycinexylidide by cytochrome P450 in liver [5]. Furthermore, both the agent and the metabolites are cleared via renal route at a rate of 10 - 20 ml/min per kilogram [5] with a fast excretion phase accounting for 8 to 17 minutes and slow excretion phase for 87 to 108 minutes. Less than 10% of lidocaine remains unchanged in urine [1].
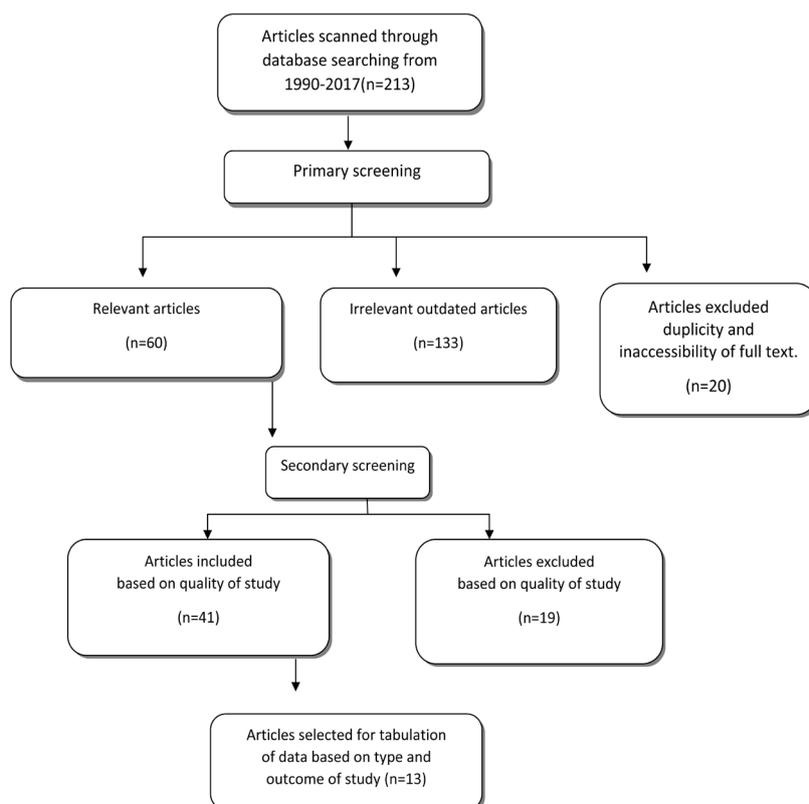

Figure 1. Flow diagram.

4. Pharmacodynamics

Being an amide-based local anesthetic agent, lidocaine acts by blocking voltage-gated Na⁺ channels (VGSC) in neuronal tissues [9]. VGSC is composed of a subunit of 260 kDa associated with β subunits of 33 - 36 kDa. α subunits have four homologous domains (I to IV) containing six transmembrane α helices (S1, S6). The S4 segments serve as voltage sensors and move outward to initiate activation. The S5 and S6 segments and the short membrane-associated loops between them form the pore. Fast inactivation is mediated by closure of an inactivation gate formed by intracellular loop between domains III and IV. Lidocaine blocks the pore of Na⁺ channels by binding to a receptor site in segment S6 in domains III and IV [4] causing a conformational change that prevents the transient influx of sodium and, thus depolarisation. Also, it has more affinity for opened ionic channel which occurs during depolarisation. Although all potentially excitable membranes are affected, sensory fibres are blocked preferably as they are thinner, unmyelinated and more easily penetrated [10].

Apart from its classical action, its analgesic activity could be evoked through systemic use. When administered intravenously, there is an increase in the concentration of the neurotransmitter acetylcholine in cerebrospinal fluid (CSF) which stimulates the inhibitory descending pathways causing analgesia by binding to muscarinic receptors M3, inhibition of glycine receptors and release of endogenous opioids. When it reaches spinal cord, it reduces the post-synaptic depolarisation mediated by N-methyl-D-aspartate (NMDA) and neurokinin receptors consequently altering pain stimuli. NMDA blockade inhibits protein kinase C, thereby minimising hyperalgesia and postoperative opioid tolerance [11].

Additionally, the agent exhibited antinociceptive effects, involving glycinergic mechanisms, in systemic usage. This was demonstrated in an experiment conducted in rat's astrocytes and frog's oocyte where the function of glycine transporter 1 (GlyT1) was studied. Lidocaine itself reduced glycine, a major inhibitory neurotransmitter, uptake only at toxic concentration whilst its metabolites MEGX, glycinexylidide and N-ethylglycine markedly reduced glycine uptake at a clinically relevant concentrate increasing extracellular glycine concentration. This rise in the level of extracellular glycine at the synaptic cleft through the blockade of GlyT1, suppress the pathologically increased conduction of excitation signals in glutamate and NMDA receptors responsible for pain stimuli, securing antinociceptive effect [12].

With regards to surgical impact on pro and anti-inflammatory systems in the body, perioperative infusion of lidocaine weakens the pro-inflammatory effects of surgery such as pain, ileus or organ failure as revealed by several studies. It acts on various steps of inflammation cascade. One of the major action recognised is blocking of priming, a process where exposure of cells to certain mediators leads to an exaggerated response like the release of cytokines and reactive oxygen species [ROS] such as superoxide anion when the cells are subsequently activated by a second mediator, of polymorphonuclear granulocyte (PMN). Moreover, PMN production of ROS much higher during trauma or

surgery. This raised level of ROS, in turn damages the endothelium leading to vascular and organ injury. Lidocaine blocks PMN priming when cells are exposed to lidocaine at minimal concentration for prolong period of time. It has also been proposed that the same mechanism is implicated in the inhibition of specific intracellular G-protein signalling molecule (Gq). The number of studies also confirmed dose-dependent and reversible inhibition of leukocyte adhesion and migration through endothelium by inhibiting intercellular adhesion molecules, modifying the cytoskeleton, or attenuating the release of chemotactic factors. It also decreases circulating interleukin (IL) 6, phospholipase A2 levels, and production of thromboxane B2 all of which contributes to anti-inflammatory effect [13] [14].

5. Adverse Effects

Like any other local anesthetic agent, lidocaine is also not free of side-effects although extremely rare. Evidence suggests that its toxicity begins once its serum level goes beyond 5 mcg/ml while low serum concentration is enough to induce desired clinical outcomes. Convulsive seizure which is a potentially life-threatening complication associated with the use of lidocaine, occurs when its plasma level exceeds 8 mcg/ml through selective depression of depression of central inhibitory tracts. It is noteworthy that when level of carbon dioxide increases in the body, it can trigger convulsions even at lower doses. In addition, it peripherally causes vasodilation, and thusly hypotension at very large doses [15]. The intensity of toxicity depends on factors like dose and speed of injection, site of administration, blood supply of the area of injection and general status or the underlying disease condition of the patient such as hepatic or renal impairment. The adverse effects of lidocaine according to serum concentrations could be summarised as below:

- Mild (serum levels 3 - 8 mcg/mL): Numbness and tingling in the fingers and toes, numbness and unusual sensations around and inside the mouth (perioral numbness), metallic taste, ringing in the ears, light-headedness, dizziness, visual disturbances, confusion.
- Moderate (serum levels 8 - 12 mcg/mL): Nausea and vomiting, severe dizziness, decreased hearing, tremors, changes in blood pressure and pulse, confusion.
- Severe (serum levels > 12 mcg/mL): Drowsiness, confusion, muscle twitching, convulsions, loss of consciousness, cardiac arrhythmias, cardiac arrest.

6. Clinical Studies

Various clinical trials, meta-analysis and reviews favour the perioperative use of intravenous lidocaine to facilitate better surgical outcomes. Its role as analgesic, antinociceptive, anti-inflammatory and immunomodulatory agent that makes it capable of reducing postoperative pain, lowering opioid requirement, postoperative nausea and vomiting, minimising ileus and shortening duration of hospital stay, is evident in the following clinical studies (Table 1).

Table 1. Effects of intravenous lidocaine (IV) infusion.

Reference	Type of study	Type of surgery	Sample size	Lidocaine IV infusion	Outcome
Farag *et al.* [7]	RCT	Complex spine surgery	116	IV lidocaine 2 mg/kg/h with maximum of 200 mg/h during induction of anesthesia and continued until discharge from post anesthesia care unit for maximum of 8 hours	IV lidocaine significantly improved post-operative pain after complex spine surgery however, post-operative nausea and vomiting and the during of hospitalization did not differ significantly.
Insler *et al.* [16]	RCT	CABG (Coronary Artery Bypass Surgery)	100	IV lidocaine 1.5 mg/kg bolus followed by 30 µg/kg/min during surgery 48 hours post operatively	Low dose lidocaine did not significantly reduce post-operative pain. Also, it had no impact on time of extubation, ICU stay or hospital length of stay.
Kang *et al.* [17]	RCT	Subtotal gastrectomy	48	IV lidocaine 1.5 mg/kg bolus 20 minutes before incision followed by a continuous infusion of 1.5 mg/kg/h until the end of surgery	Intraoperative lidocaine decreased opioid consumption and length of hospital stay after gastrectomy. No differences were noted between the groups in pain intensity or duration of ileus.
Kyoung-Tae *et al.* [18]	RCT	Lumbar microdiscectomy	51	IV lidocaine 1.5 mg/kg bolus followed by a 2 mg/kg/h infusion until the end of surgery	Lidocaine decreased pain perception and hence, also the consumption of opioid and the severity of postoperative pain that further contributed to shortening of hospital stay.
Kim *et al.* [19]	RCT	Laparoscopic appendectomy	68	IV lidocaine 1.5 mg/kg bolus followed by a continuous infusion of 2 mg/kg/h throughout surgery	Lidocaine reduces pain and fentanyl consumption. The shoulder tip pain and post-operative nausea and vomiting were also reduced.
Lauwick *et al.* [20]	RCT	Laparoscopic prostatectomy	40	IV lidocaine 2 mg/kg/h during surgery, 1 mg/kg/min for the first 24 hrs after surgery	Lidocaine infusion attenuated the deterioration in functional walking capacity and hand an opioid sparing effect.
Martin *et al.* [21]	RCT	Total Hip arthroplasty	60	IV lidocaine 1.5 mg/kg 30 min before surgical incision followed by continuous infusion of 1.5 mg/kg/h. The infusion ended 60 min after skin closure	The study didn't show any benefit of perioperative administration of low dose IV lidocaine in terms of post-operative analgesia and functional recovery after total hip arthroplasty.
Oliveira *et al.* [22]	RCT	Laparoscopic bariatric surgery	50	IV lidocaine 1.5 mg/kg bolus + 2 mg/kg/h till the end of surgical procedure	Systemic lidocaine reduced opioids (morphine) consumption and thereby, improving the quality of post-operative recovery.
Peng *et al.* [8]	RCT	Supratentorial tumor surgery	94	IV lidocaine 1.5 mg/kg bolus followed by continuous infusion of 2 mg/kg/h until the end of surgery	Systemic lidocaine profoundly reduced the proportion of patients with acute pain after surgery.
Striebel *et al.* [23]	RCT	Elective tonsillectomy (1992)	40	IV lidocaine 1.5 mg/kg 30 min before the surgery followed by 2 mg/kg/h over 6 hr and 0.5 mg/kg/h for another 18 h	Intravenous lidocaine did not significantly reduce postoperative pain after tonsillectomy in the dosage used.

Continued

Vigneault *et al.* [24]	Meta-analysis of 29 papers	7 cardiac, 3 gynecology, 1 thoracic, 2 urology, 1 otorhinolaryngology, 14 abdominal surgery, 1 orthopedic surgery	1754	IV lidocaine bolus prior to infusion (infusion rate ≤ 3 mg/kg/h)	IV Lidocaine infusion reduced post-operative pain during rest and during movement. It also reduced opioid requirement, nausea, vomiting, time to first flatus, time to first feces and length of hospital stay abdominal surgery was strongly associated with these outcomes.
Wuethrich *et al.* [25]	RCT	Laparoscopic renal surgery	64	IV lidocaine 1.5 mg/kg/hr bolus during induction followed by intraoperative infusion of 2 and 1.3 mg/kg/h for 24 h post operatively	Lidocaine did not influence the length of the hospital stay readiness for discharge opioid consumption, return of bowel function or inflammatory and stress responses after laparoscopic renal surgery.
Wongyinsinn *et al.* [26]	RCT	Laparoscopic colorectal surgery	60	IV lidocaine 1 mg/kg/h + PCA (patient controlled analgesia) morphine for the first 48 h after surgery	Both IV lidocaine and thoracic epidural analgesia (TEA) had similar impact on restoration of bowel function; however, TEA provided better analgesia in patients undergoing rectal surgery. Time out of bed dietary intake and hospital stay were similar.

Farag and colleagues conducted a trial in 116 patients undergoing complex spine surgery by randomly infusing lidocaine at 2 mg/kg/h for induction (maximum of 200 mg/h) which was continued for maximum of 8 hours post-operatively, to some and placebo to others. The group that received lidocaine reported substantial improvement in postoperative pain as compared to the placebo group. Postoperative nausea and vomiting and the duration of hospital stay did not differ significantly [7].

Insler and his associates carried out a study of in 100 subjects who were undergoing coronary artery bypass grafting (CABG) for the first time. The subjects were given intravenous lidocaine 1.5 mg/kg/min during surgery and 48 hours postoperatively. Low dose lidocaine had no impact on postoperative pain. Also, it had no influence on time of extubation, Intensive Care Unit (ICU) stay or length of hospital stay [16]. Similarly, studies conducted by Martin [21], Striebel [23], as well as Wuethrich [25] and associates with similar dose of lidocaine but different type of surgeries, did not show any considerable benefits of lidocaine over placebo solution.

Kang and colleagues evaluated 48 patients submitted to gastrectomy under general anesthesia with intravenous lidocaine in bolus dose of 1.5 mg/kg at induction and same dose in continuous infusion until the end of surgery. This technique significantly diminished the opioid postoperative consumption and time of hospital stay, although this study didn't show any improvement of pain levels and return of bowel function [17].

Fifty-one patients subjected for lumbar microdiscectomy were studied by **kyoung-Tae and colleagues** to evaluate the analgesic effect of lidocaine infusion

on postoperative pain. Preoperatively and throughout the surgery, one group received lidocaine infusion (1.5 mg/kg bolus followed by 2 mg/kg/h infusion until the end of surgical procedure) and the other group received normal saline infusion as placebo. Intraoperative intravenous lidocaine lessened pain perception during surgery subsequently decreasing opioid requirement and duration of hospital stay [18]. In similar fashion with similar dosage, Peng with his colleagues analysed 94 subjects enrolled for supratentorial craniotomy. Intravenous lidocaine greatly reduced acute pain after surgery [8].

Again with the same induction and maintenance dose of lidocaine, a randomised control trial was carried out in 68 patients subjected to laparoscopic appendectomy by **Kim and collaborators**. However, this time the samples were divided in three groups; 1) Group IP (the intravenous group) receiving intraperitoneal instillation of lidocaine and intravenous normal saline injection 2) Group IV (the intravenous group) receiving intravenous lidocaine injection and intraperitoneal instillation of normal saline 3) Group C (the placebo controlled group) receiving normal saline both intravenously and intraperitoneally. Intravenous lidocaine was found as effective as peritoneal instillation for decreasing pain and fentanyl consumption [19].

Lauwick and associates randomised forty patients undergoing laparoscopic prostatectomy to receive an intravenous infusion of either lidocaine 2 mg/kg/hour during surgery and 1 mg/kg/min for the first postoperative period or an equivalent volume of normal saline to assess the postoperative functional walking capacity, as a measure of surgical recovery. Lidocaine attenuated functional walking capacity and had opioid-sparing effect [20]. Clinical trial performed by **Dr Oliveria and teammates** in fifty patients being admitted for laparoscopic bariatric surgery also established positive results [22].

Vigneault and collaborators did a meta-analysis of 29 RCT of different types of surgeries. A bolus dose prior to infusion was given in all the trials (≤3 mg/kg/h). It not only reduced postoperative pain but also decreased opioid consumption, nausea, vomiting, time to first flatus, time to first defecation, and length of hospital stay. These effects were more pronounced in abdominal surgeries [24].

Wongyingsinn examined 60 patient scheduled for laparoscopic colorectal surgery to test the efficiency of systemic lidocaine 1.5 mg/kg (maximum 100 mg) for induction and 2 mg/kg/h for maintenance in comparison to thoracic epidural analgesia in terms of restoration of bowel function in postoperative period. The impact of intravenous lidocaine on the return of bowel function was similar to thoracic epidural analgesia when an enhanced recovery program was implemented [26].

To sum up, Therapeutic level of lidocaine was achieved with bolus dose of 1.5 mg/kg and maintenance dose of 2 or ≤3 mg/kg/h in almost all the clinical trials. Contrary to previous belief that advantages of its perioperative use is only evident in abdominal surgeries, trials conducted by **Farag, kyoung-Tae and Peng** provided promising results in other surgeries. Furthermore, while assessment

done by **Wongyingsinn and Kim** gives hope of its future use as an alternative in cases where intraperitoneal or thoracic epidural routes are contraindicated [7] [8] [18] [19] [26] (**Table 1**).

7. Conclusion

Lidocaine is safe and has obvious advantages in perioperative use. Whether these merits are only associated with abdominal surgeries is still a subject that demands more exploration and vigorous research. However, the outcomes yielded by more recent studies are not disheartening. Moreover, its clinical implication as an alternative to thoracic epidural analgesia or anti-inflammatory agent could be another field of future interest. It would be safe to assume that this local anesthetic agent can be used at a low dose without fear of toxicity as adverse reactions are very rare and commence only at and above a plasma level of more than 5 mcg/ml. Finally, it is also convenient and cost-effective which provide a basis for its use in a wide range.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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