Intravenous lidocaine to treat postoperative pain*

Lidocaína intravenosa no tratamento da dor pós-operatória

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ABSTRACT

BACKGROUND AND OBJECTIVES: Postoperative pain is foreseeable however it is still undermanaged. Multimodal management decreases side-effects and provides adequate pain control. Lidocaine, local anesthetic used for more than five decades, is being intravenously administered aiming at managing pain in different types of surgeries with promising results. This study aimed at reviewing the use of intravenous lidocaine to manage postoperative pain, and its action mechanism.

CONTENTS: This article addresses the use of intravenous lidocaine to manage postoperative pain, its action mechanism and its applicability for different types of surgeries. An active search was carried out in the following databases: Medline via Pubmed (1974-2013), Cochrane Library (1990-2010) and LILACS (1974-2013). Search was adjusted to identify articles addressing postoperative intravenous lidocaine action mechanism and postoperative analgesia. As to language, articles in Portuguese and English were selected.

CONCLUSION: Intravenous lidocaine, due to its low cost, opioid-sparing action and minimum side-effects is an adequate option to manage postoperative pain.

Keywords: Intravenous lidocaine, Multimodal management, Postoperative analgesia, Postoperative pain.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A dor pós-operatória é previsível, no entanto continua sendo inadequadamente tratada. O tratamento multimodal diminui os efeitos colaterais e propicia adequado alivio da dor. A lidocaína, anestésico local utilizado há mais de cinco décadas, vem sendo empregada por via intravenosa com o objetivo de tratar a dor em diversos tipos de operação com resultados promissores. O objetivo deste estudo foi fazer uma revisão sobre o uso da lidocaína intravenosa no tratamento da dor pós-operatória e seu mecanismo de ação.

CONTEÚDO: Este artigo aborda o emprego da lidocaína intravenosa no manuseio da dor pós-operatória, seu mecanismo de ação e a aplicabilidade em diversos tipos de procedimentos cirúrgicos**.** Realizada busca ativa através das seguintes bases de dados: Medline via Pubmed (1974-2013), Cochrane Library (1990-2010), LILACS (1974-2013). A busca foi ajustada visando identificar os artigos que pesquisaram o mecanismo de ação e a analgesia pós-operatória da lidocaína intravenosa. Quanto à limitação do idioma, foram selecionados artigos nas línguas Portuguesa e Inglesa.

CONCLUSÃO: A lidocaína intravenosa, pelo baixo custo, ação poupadora de opioides e mínimos efeitos colaterais, tem se mostrado adequada opção no tratamento da dor pós-operatória.

Descritores: Analgesia pós-operatória, Dor pós-operatória, Lidocaína, intravenosa, Tratamento multimodal.

INTRODUCTION

Assuring adequate pain management should be part of the perioperative approach to surgical patients, and anesthesiologists may use different available drugs for intravenous infusion, matching their pharmacodynamic features to different types of surgical procedures and to the particularities of each patient.

Among drugs to manage postoperative pain POP), intravenous lidocaine is gaining importance[1]. This local anesthetic was intravenously used for the first time to promote postoperative analgesia during the 1960's and recent studies have proven such analgesic effect especially in abdominal surgeries[1].

However, notwithstanding the practicality of administering intravenous lidocaine as part of multimodal pain management[2], its action mechanism is still not totally understood, especially with regard to analgesia duration.

An active search was carried out in the following databases: Medline via Pubmed (1974-2013), Cochrane Library (2000-2010) and LILACS (1974-2013). Search was adjusted to identify articles studying intravenous lidocaine action mechanism and postoperative analgesia. As to language, articles in Portuguese and English were selected.

This study aimed at reviewing the use of intravenous lidocaine to manage POP and at discussing possible action mechanisms of this analgesic drug.

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POSTOPERATIVE PAIN

POP is a foreseeable and well-known type of acute pain and its management decreases postoperative morbidity, provides adequate incision healing and decreases costs[2,3]. In addition, it promotes less postoperative cognitive changes and decreases the risk of chronic or persistent postoperative pain[4,5]. However, more than 50% of patients submitted to surgical procedures experience moderate to severe pain[6] indicating that, notwithstanding the development of new drugs and the use of new analgesic techniques, POP is still undermanaged[7,8]. Possible justifications for its high prevalence might be: individual sensitivity and inadequate choice of drugs and doses[9].

PHARMACOLOGICAL ASPECTS OF INTRAVENOUS LIDOCAINE

Intravenous lidocaine in the perioperative period promotes important postoperative analgesia resulting in less pain intensity and use of opioids[10-12]. Recent studies have proven that intravenous lidocaine promotes fast return of intestinal transit in patients submitted to colonic surgeries[12] and decreases cytokines production and release[13-16]. Lidocaine analgesic effect on surgical trauma is due to neuronal transmission block at the injury site, to its intrinsic systemic anti-inflammatory property and, depending on the dose, it may decrease cytokine-induced cell injury through mechanisms involving mitochondrial potassium channels sensitive to adenosine triphosphate (ATP)[4,16,17].

It is important to stress that its analgesic property persists even after plasma levels are decreased, thus favoring the theory of nervous conduction block[14]. On the other hand, even in low doses, it suppresses C fibers evoked potential resulting in analgesia[18-21].

Among the advantages of this drug, one may highlight low cost and good effectiveness[18] (Table 1). It is important to stress that doses used to manage acute or chronic pain are in general based on patients' weight, which is not different with lidocaine. However, there is dissociation between analgesic effect and plasma concentration of lidocaine and of its active metabolite[22].

Table 1. Advantages of intravenous lidocaine for postoperative pain

Low cost
Effective in abdominal surgeries
Decreases opioid consumption
Minimizes ileus
Decreases hospital stay and nausea and vomiting
Decreases the incidence of postoperative chronic pain

Lidocaine is metabolized in the liver by the microsmal enzyme system (cytochrome P450), with clearance rate of 0.85L/kg/h. It is converted by oxidation into monoethylglycinexylidine, part of which is hydrolyzed to glycinexylidine. Such metabolites are active and have been implied in cases of intoxication after repeated doses and continuous intravenous infusion. It is excreted by the kidneys, with a fast excretion phase of 8 to 17 minutes and a slow phase of 87 to 108 minutes[22]. Less than 10% of lidocaine is found unaltered in the urine[22-26].

There is a question about lidocaine metabolites: would they also be responsible for the analgesic action of this drug? Possibly not, because lidocaine-induced analgesia goes beyond the half-life of such metabolites.

Intravenous lidocaine has been used in different surgical procedures[1,12,27]. When intravenously administered, it is initially distributed to richly perfused organs, such as skin, skeletal muscle and fat. It has a large distribution volume (91L/kg), its oil/water partition coefficient is 366 and its potency is intermediate. Approximately 60% of its molecules bind to plasma proteins, especially to acid alpha1-glycoprotein[22]. Approximately 40% of intravenous lidocaine is temporarily extracted during its first passage through the lungs where pH is lower as compared to plasma. Lidocaine protein binding associated to pulmonary extraction decreases the chances of systemic intoxication.

Lidocaine action mechanism

Voltage-dependent sodium channels (Nav) are classic lidocaine action targets and nine different forms (isoforms) of subunits have already been identified in voltage-dependent sodium channels of mammals (Nav 1.1 to 1.9), being that some of them are related to neuropathic pain (Nav 1.3, 1.7, 1.8 and 1.9) and others to inflammatory pain (Nav 1.7, 1.8 and 1.9)[28]. After crossing the neural membrane, under the action of intracellular pH there is the conversion of lidocaine to its ionized form and this acts reversibly in the portion S6 of the domain 4 of the alpha subunit within voltage-dependent sodium channels[25,28].

As the anesthetic action is developed, the threshold for electric excitability is gradually increased and action potential peak decreases neuronal impulse conduction. Lidocaine affinity for sodium channels varies with the channel position being higher when the channel is open (activated or inactive) and lower when the channel is closed (turned off or at rest). So, the higher the frequency of neuronal stimulation, more ionized lidocaine molecules have access to action sites and the higher is the blockade level (use-dependent or frequency-dependent block)[18].

In addition to acting on voltage-dependent sodium channels (Nav), present in inflamed tissues nociceptors[29], lidocaine also acts on receptors coupled to protein G (RAPG), on N-methyl-D-aspartate receptors (NMDA) and on A-delta and C channels[30-33]. This local anesthetic also seems to indirectly block NMDA receptors[34-36] by inhibiting protein kinase C (PKC)[35], thus highly influencing postoperative hyperalgesia and tolerance to opioids[10,35]. In addition, this drug through its action on RAPG[37], interferes with sensitization, lysosomal degranulation of neutrophils, production of oxygen free radicals and cytokines production by macrophages and glial cells providing anti-inflammatory action[14,37,38].

Lidocaine also acts on voltage-dependent potassium and calcium channels, however with less affinity as compared to blockade produced in sodium channels. This calcium channel inhibition in pre-synaptic nervous terminals is highly involved with the release of neurotransmitters and, as a consequence, interferes with painful impulse propagation[34]. With regard to potassium channels, it is supposed that acting on such channels, lidocaine decreases cell injury secondary to tissue ischemia[18], decreases inflammatory response and promotes pain intensity decrease.

Intravenous lidocaine adverse effects and contraindications

Lidocaine-triggered toxic manifestations seem to occur when plasma concentrations of 5**μ**g/mL are reached. However, in the clinical practice, doses vary from 2 to 5mg/kg, resulting in plasma concentration of 2**μ**g/mL, that is, below toxic doses, promoting a safety window for lidocaine administration. This safety allows the drug to be used in different forms for pain management (solution, eye drops and cream) and by different administration routes (epidural, spinal, intrapleural, muscular, intra-articular, topic and intravenous)[22,25], each one with its established indication.

Adverse effects intensity depends on the dose, velocity and site of administration, as well as on patients' general status with regard to age, clinical conditions and pregnancy[25]. As lidocaine concentration increases in systemic circulation several signs and symptoms appear especially in systems: central nervous system (CNS) and cardiovascular system. When serum levels are below 5μg/mL there is analgesia and cortical motoneurons are inhibited, which explains its anticonvulsant activity[24]. When serum levels go beyond 5μg/mL symptoms are variable and severity depends on lidocaine blood concentration[25] (Table 2).

Table 2. Adverse effects according to serum levels[2,22,26]

Adverse effects	Serum levels	Symptoms
Mild	3-8μg/mL	Numbness and tingling in fingers and toes, perioral numbness, visual disorders, tinnitus, dizziness and confusion.
Moderate	8-12μg/mL	Nausea and vomiting, shivering, hearing impairment, changes in blood pressure and heart rate and mental confusion
Severe	>12μg/mL	Confusion, loss of consciousness, muscle shivering, seizure, arrhythmia and heart arrest

With regard to CNS, seizure might be the first indication of severe intoxication[26] and may be caused by the inhibition of inhibitory neurons through GABA receptors (gamma-aminobutyric acid) in the amygdala[25,27]. In general, there is seizure with plasma concentrations above 8μg/mL but it may be seen with lower serum levels in the presence of hypercarbia[23]. As to cardiovascular toxicity, there might be bradycardia, increased PR interval and QRS complex enlargement[25]. Finally, one should not forget allergy to amino-amine derivatives, however this is an extremely uncommon event being estimated in less than 1% of recorded reactions[25].

Intravenous lidocaine should not be used in patients with arrhythmia, heart failure, coronary disease, Adams-Strokes or heart block and may be used with caution in patients with liver failure, sinusoidal bradycardia and incomplete branch block[29].

Most common side-effects are in general mild and related to CNS[22]. Patients may present with: sleepiness, dizziness, metal taste, headache, blurred vision, paresthesia, dysarthria, euphoria and nausea[22,29]. Higher doses rapidly administered may cause tinnitus, shivering and agitation. Cardiovascular changes are in general minimal with usual doses (Table 1).

In the presence of lidocaine intoxication, management should involve support measures with oxygenation, hydration, vasopressors, inotropics, anticonvulsants and anti-arrhythmic drugs. For non-responsive cases, intravenous lipid infusion should be considered in initial dose of 1.5mL/kg of 20% solution, which may be repeated every 3-5 minutes to the maximum dose of 8mL/kg[29,30].

Intravenous lidocaine analgesic action

Intravenous lidocaine analgesic action is peripheral and central by the following mechanisms: sodium and potassium channels block, glycinergic action, NMDA receptors block and decreased substance P[18]. In low concentrations, lidocaine inhibits abnormal activity in primary afferent fibers, especially C fibers, promotes sympathetic block, vasodilation and decreases painful stimulation[18]. On the other hand, sodium channels block results in inhibition of spontaneous and evoked neuronal activity[9,25], as well as decreases neuronal activity, resulting in pain relief[31]. In therapeutic concentrations, lidocaine decreases hyperexcitability without affecting nervous conduction. Intravenous lidocaine promotes medullar sensitivity decrease[31], decreasing medullar neurons activity and also decreasing NMDA receptors-mediated post-synaptic depolarization[32].

Higher susceptibility of hyperexcitable neurons to lidocaine may be explained by changes in sodium channels expression when there is nervous injury. This change makes these channels subject to blockade by lidocaine and results in ectopic discharges suppression[33], with consequent decrease in hyperalgesia, mechanical alodynia[4,33], paroxysmal and dysestesic pain[34,35], fact which explains intravenous lidocaine analgesic action on neuropathic pain.

It is also important to highlight that preferential blockade for inactivated sodium channels promoted by lidocaine assures that only hyperexcitable neuron channels are blocked, such as those with post-nervous injury ectopic activity[35]. However, for nociceptive pain results are in disagreement with regard to such preferential block[36,37,39].

Still with regard to the analgesic effect, it seems to be dose-dependent, and 5mg/kg for a period of 30 minutes has promoted more consistent analgesic response[36]. With regard to maximum plasma concentration and maximum pain relief, a correlation between both has been reported[33]. This fact may explain the variation of analgesia obtained with different doses. It has been shown that low intravenous lidocaine doses (plasma concentra-

tion below 5µg/mL) attenuate pain induced by different injuries without interfering with normal nervous conduction and with low incidence of adverse effects[16,37,38].

The effective lidocaine dose to manage POP has not yet been defined[38] and this is possibly due to differences in central and peripheral sensitization of different surgical types and sites[38]. Its analgesic effects are more pronounced when infusion is started in the preoperative period[39] and continued for days or weeks[29,38]. This particularity suggests that intravenous lidocaine acts on other targets different from voltage-dependent sodium channels.

With regard to analgesia, it has been reported that intravenous lidocaine produces three different pain relief stages: the first is during infusion and 30 to 60 minutes after its end; the second is a transient stage approximately 6h after infusion; and the third stage appears 24 to 48h after infusion and continues for 21 to 47 days[29].

Intravenous lidocaine analgesic effect may be evaluated in surgeries by different routes. In videolaparoscopic cholecystectomy there has been additive effect on POP and a synergistic effect on intestinal transit recovery when 3mg/kg/h were compared to 40mg muscular dextromethorphan[39].

There has been postoperative pain and morphine consumption decrease after abdominal surgeries with possible prevention of central hyperalgesia when intravenous lidocaine (1.5mg/kg bolus followed by 1.5mg/kg/h infusion) was administered before surgical incision and continued to up to 60 minutes after skin suture completion, especially in the 36th postoperative hour[10].

For conventional cholecystectomies 2mg/kg bolus intravenous lidocaine before incision and 3mg/kg/h infusion until surgery completion have promoted major pain relief and faster return of intestinal function, have decreased volatile anesthetic and opioids consumption and have attenuated the production of interleukins-1 AR (receptor antagonist), 6 and 8 (IL-1AR, IL-6 and IL-8) for a period of 72h[12]. Similarly, its analgesic effect has also been shown in patients submitted to videolaparoscopic colectomy[41]. On the other hand, intravenous lidocaine in 1.5mg/kg bolus and intraoperative infusion of 1.5mg/kg/h up to 60 minutes after surgical wound suture has not produced analgesic improvement and has also not changed pain thresholds secondary to touch and pressure after total hip arthroplasty[41].

In breast cancer surgeries, authors have observed that this perioperative lidocaine infusion regimen has decreased the area of hyperalgesia as compared to placebo, but postoperative analgesia at rest was superior only in the 4th postoperative hour[42]. Another author using the same lidocaine dose, however limiting end of infusion to skin closure in male patients submitted to subtotal gastrectomy, has observed no difference in analgesia in the first 3 postoperative days as compared to placebo[43].

Based on the above, some questions arise: which is the ideal dose to obtain postoperative analgesia? Is continuous infusion better than bolus injection? Which is the best time to start lidocaine infusion before incision? For how long should lidocaine infusion be maintained? Would less need for intra and postoperative opioids decrease the incidence of persistent POP in patients using lidocaine? Would lidocaine analgesia be more prominent for visceral pain as compared to somatic pain? Is lidocaine plasma dosage mandatory?

Some studies tried to answer such questions[10,11,23,36,39,40]. With regard to intravenous lidocaine dose as part of multimodal POP management, one may mention the dose suggested by Pasero[44], which is 4mg/mL solution (0.4% solution) without preservative, prepared in the hospital pharmacy with 2g in 500mL of diluent solution. A 1.5mg/kg bolus is initially administered followed by continuous infusion of 1.33mg/kg/h in the PACU and for more 24h. It is worth stressing that other infusion rules using slightly higher doses (1.5mg/kg/h and perioperative infusion of 1.5mg/kg/h up to 60 minutes after wound suture) are unable to produce postoperative analgesia different from placebo. The difference between both protocols is that Pasero[44] maintains lidocaine infusion for 24h and its maintenance during the first postoperative day seems to be the differential because voltage-dependent calcium channels block is maintained and neurotransmitters release and inflammatory responses are inhibited.

A meta-analysis[45] on the use of intravenous lidocaine in abdominal surgeries reports that with regard to infusion dose, beginning and duration there is still not a consensus. In studying postoperative opioid consumption, recent studies have evaluated the prevalence of post-mastectomy painful syndrome (PMPS) in patients submitted to breast surgeries and have found association between higher perioperative opioid consumption and the presence of such syndrome[46,47]. A study on post-surgical chronic pain (PSCP) has identified[48] a relationship between POP intensity and the presence of PSCP in different types of surgeries. So, pharmacological strategies (such as intravenous lidocaine) that decrease perioperative pain intensity and opioid consumption may decrease the incidence of chronic pain.

To answer the question about lidocaine action on visceral and somatic pain, since both have nociceptive origin, it was to be expected that the analgesic action of the drug would be similar. However, studies on POP have shown that in surgeries with visceral pain (colectomies, cholecystectomies)[12], analgesic results are promising, what is not true for surgeries resulting in somatic pain (arthroplasties and mastectomies). A study on palliative care[32] has observed that lidocaine is able to promote analgesia regardless of the etiology of pain.

So, clinical studies using the same doses and the same infusion regimen are needed to evaluate the postoperative analgesic action of lidocaine in different types of pain (Table 3).

As to lidocaine systematic plasma dosage, a recent study evaluating 15 patients submitted to initial dose of 1.5mg/kg followed by 2mg/kg/h continuous infusion has shown concentrations below 4.6µg/mL 24h after drug infusion[41]. This plasma concentration is related to the presence of mild and tolerable symptoms (Table 1)[16,30,37,38].

Lidocaine plasma dosage, although not mandatory, provides further safety in cases where the infusion will continue in the postoperative period[40].

Table 3. Lidocaine dose and infusion time, its relationship with opioid consumption and postoperative pain intensity.

References	Types of studies	Lidocaine dose	Infusion time	Opioid consumption	Postoperative pain intensity
Lauwick et al.[11]	RCT	Bolus 1.5mg/kg Infusion 2mg/kg/h	Until surgery completion	Decreased in the lidocaine group	Similar at rest for both groups
Kaba et al.[40]	RCT	Bolus 1.5mg/kg Infusion 2mg/kg /h	24 postoperative hours	Decreased in the lidocaine group	Decreased with movement in the lidocaine group
Kang et al.[43]	RCT	Bolus 1.5mg/kg Infusion 1.5mg/kg/h	Until the end of skin suture	Equal for both groups	Similar at rest for both groups
Grigoras et al.[42]	RCT	Bolus 1.5mg/kg Infusion 1.5mg/kg/h	Up to one hour after skin suture	Equal for both groups	Decreased at rest in the 4thh

RCT: randomized clinical trial.

CONCLUSION

Intravenous lidocaine with analgesic purposes in the perioperative period is a promising possibility. However, placebo-controlled studies are needed to evaluate its safety, its ability to promote POP relief for somatic and visceral pain as well as its ability to prevent chronic pain.

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