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The Efficacy of Systemic Lidocaine in the Management of Chronic Pain: A Literature Review

Fardin Yousefshahi,[1,2] Oana Predescu,[3] and Juan Francisco Asenjo[4,*]

[1]Department of Anesthesiology, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
[2]Brain and Spinal Cord Injury Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran
[3]Assistant Professor, Department of Anesthesia, McGill University Health Centre, Montreal, QC, Canada
[4]Professor, Department of Anesthesia, McGill University Health Centre, Montreal, QC, Canada

[*]*Corresponding author*: Juan Francisco Asenjo, Montreal General Hospital, 1650 Cedar Avenue, D10-144, Montreal, QC, Canada. E-mail: jfasenjog@yahoo.com

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Abstract

Context: Despite recent advances in the understanding of the chronic pain concept, its diagnosis and management remains a daily challenge for clinicians and patients. Based on the published literature, this review discusses and tries to organize the current knowledge and the up-to-date clinical experience about the efficacy and safety of the use of intravenous lidocaine in treatment and prevention of chronic pain.

Evidence Acquisition: To prepare this narrative review, we performed an in depth literature review using the PubMed searching engine. We extracted all relevant articles published in English, up to April 2016.

Results: Lidocaine, administered as transdermal patch or intravenous lidocaine, is a safe and effective modality in the treatment of post-herpetic neuralgia (PHN), complex regional pain syndrome, as well and for prevention of chronic pain. It may be effective in the management of neuropathic pain syndromes, chronic pain, post-operative pain, and refractory cancer pain.

Conclusions: Intravenous lidocaine and lidocaine patch are effective and safe for the treatment of several chronic or neuropathic pain syndromes. The use of lidocaine during surgery could prevent the development of some chronic post-surgical pain syndromes.

Keywords: Lidocaine, Chronic Pain, Neuropathic Pain, Post-Herpetic Neuralgia, Complex Regional Pain Syndrome

1. Context

Despite recent advances in the understanding of the concept of chronic pain, its diagnosis and management remains a daily challenge for clinicians and patients (1).

A persistent inflammatory process in the anatomically healed tissues is responsible for the transition from acute to chronic pain (2, 3). Inflammatory mechanisms are involved in both neuropathic and somatic, inflammatory pains (4-6). A continuous inflammatory stimulation and response results in hyper-excitability and remodelling in the peripheral and central nervous system, that is mediated by the increase in the N-methyl-D-aspartic acid (NMDA) receptor activity, the activation of microglia and astrocyte cells in the dorsal horn of spinal cord. The increase in pro-inflammatory cytokines and analgesic mediators causes chronic pain (2, 4, 7, 8).

Lidocaine is an amide local anesthetic that in pain medicine, is widely used for local or regional infiltration in different settings to manage or prevent acute or chronic pain (9, 10). Lidocaine hydrochloride has an elimination half-life of 1.5 to 2 hours after an intravenous bolus dose.

Lidocaine is a short acting local anesthetic; its pharmacologic effect is limited to few times of medication half-life.

A long lasting analgesic effect is reported after single shot use of Lidocaine. This effect is more than a simple local analgesic effect, and seems to be the result of a continuous active biological response to lidocaine (11). The possible mechanism might be an anti-inflammatory effect (11-13). Based on this, clinical trials administering lidocaine before or during the surgery suggest a reduction in postoperative pain quantified by a concomitant reduction in pro-inflammatory cytokines (14).

Reviewing the literature, there is still limited data regarding the indications, safety and effectiveness of lidocaine in chronic pain.

This review tries to discuss and organize our current knowledge and experience regarding the efficacy and safety of the use of intravenous lidocaine in preventing and treating the chronic pain.

2. Evidence Acquisition

We performed an exhaustive literature review using the PubMed searching engine. We extracted all the relevant human studies articles, published in English, without time limitation until the end of April 2016.

Our relevant searching terms were intravenous, lidocaine, chronic, pain, and CRPS in following combinations; Lidocaine (title) and pain (title) and chronic (title/abstract), AND, Lidocaine (title) and pain (title) and intravenous (title/abstract) OR Lidocaine (title) and pain (title) and IV (title/abstract), limited to human studies and also, Lidocaine (title) and CRPS (title/abstract).

Our reference manager software was EndNote X7 version. Duplicate references were omitted.

The relevant articles to be used in this review were chosen by agreement between 2 independent literature reviewers (FY and FA). Further searches were performed to realize special issues during the review or to find document source for referred issues.

2.1. Historical Aspects

The first mention of the effectiveness of intravenously administered lidocaine in the treatment of postoperative pain was in 1961 by Bartlett and Hutaserani (15).

In 1976, Iwane et al. (16) use with success the intravenous lidocaine for the intractable pain.

10 years later, a small placebo study by Person et al. (17) reports significant improvement in 78% chronic pain patients after administration of iv. Lidocaine.

In Person's study, the pain relief effect lasted between 2 hours and 25 days, whereas a later study by Sjogren (18) does not prove the long term effect of intravenous lidocaine on cancer pain.

2.2. Mechanism of Action

An extensive review by Van der Wal et al. in 2016 (19), gives emphasis to the different mechanisms involved in the effect of intravenous lidocaine on acute and chronic pain. The authors concluded that intravenous lidocaine is effective in the management of some neuropathic pain syndromes by modulating the ectopic neuronal discharges, thus decreasing hyperalgesia and the inflammatory response. This effect is obtained through inhibition of the voltage-gated sodium channels (VGSC), voltage-gated calcium channels (VGCC), various potassium channels, NMDA receptors, glycine system and G protein pathways.

Using PET (positron emission tomography), Chana et al. (20) suggests that persistent pain relief obtained after repeated intravenous lidocaine infusion may be accompanied by changes in the thalamic regional blood blow.

2.3. Systemic Lidocaine and Post-Herpetic Neuralgia

In 1999, FDA approves lidocaine 5% patch as the specific treatment against post herpetic neuralgia (PHN). Five years later the literature review performed by Davies et al. concludes that the patch of 5% lidocaine is safe and effective in relieving tactile allodynia related to PHN (21). Since covering the whole painful area with patches is almost impossible, the effect of lidocaine patch is most likely achieved through systemic absorption, rather than a local effect.

Using functional magnetic resonance (fMRI), Gaha et al. (22) describe in PHN patients responding to the lidocaine patch treatment the occurrence of changes in the affective and sensory-discriminative areas of brain.

2.4. Systemic Lidocaine for Other Neuropathic Pain Syndromes

There are several publications that address the successful use of systemic lidocaine (administered as patch or intravenously) in the management of different neuropathic pain syndromes.

A 3 days treatment with lidocaine 5% patch for chronic pain may show improvement for 12 weeks (23-25) and sometimes up to 3 - 5 years (26).

The administration of intravenous lidocaine in low to mid antiarrhythmic doses, was assessed by Dirks et al. (27). The authors found that the chosen dose of intravenous lidocaine was not effective for the treatment of acute nociceptive pain, but had a selective, limited effect on secondary hyperalgesia.

The effect of intravenous lidocaine on allodynia and hyperalgesia secondary to traumatic or post-herpetic peripheral nerve injury, was assessed by Attal et a in a double blind placebo controlled study of 22 patients They reported a significant decrease in pain for up to 6 hours after injection, therefore the authors suggest the use of lidocaine as a treatment for patient suffering mechanical allodynia (28). Similar results were reported in patients with peripheral neuropathic pain, who have received 5mg/kg/h lidocaine infusion, and the effect lasted up to 4 hours after the infusion (29). Carroll et al, found that patients with "heavy" neuropathic pain sensation respond better to intravenous lidocaine (30).

In our literature review we did not find any articles studying the possible long lasting effect of a single dose of lidocaine vs. repeated doses of intravenous lidocaine, in patients with chronic neuropathic pain.

2.5. Systemic Lidocaine and Osteoarthritis and Musculoskeletal System

Gale et al published a nonrandomized prospective trial on the effect of lidocaine patch on low-back pain (LBP), assessed using the Neuropathic Pain Scale (NPS). They enrolled 77 patients with either acute, short-term chronic (3 - 12 months history of LBP), or chronic LBP. The authors found significant improvement in all 4 NPS composite

measures, in patients with moderate to severe LBP, over the 2 to 6 weeks assessment period. The patients tolerated the treatment well, with only very few side effects (31). A randomized double-blind study on 30 patients suffering of chronic back pain showed that the lidocaine patch has similar effect to placebo at 6 hours and 2 weeks after treatment (32). In this study, patients were not followed beyond 6 weeks.

In his multicenter open label study on 20 patients with osteoarthritis, Galer et al assessed the efficacy and safety of lidocaine patch as single pain treatment modality. The study patients had significant improvement in the level of pain, stiffness, and functional capacity (33). A similar study done on 100 patients suffering of knee osteoarthritis found a significant improvement in all the common neuropathic pain descriptions (sharp, hot, dull, deep) with only 3 patients developing mild side-effects to topical lidocaine (34).

2.6. Systemic Lidocaine in Different Chronic Pain Syndromes

In a multicenter pilot clinical trial, 5% lidocaine patch was not only effective in the treatment of PHN, but also in other categories of chronic pain like low back pain and diabetic neuropathy. In 107 patients, the lidocaine was added to other co-analgesic medications, and the results were safe and significant decrease in pain with consecutive increase in the walking and working abilities, as well as return to normal sleep and social life relationships (35, 36).

There is a case report about the effectiveness of Intravenous lidocaine in opioid resistant visceral pain (37).

Mooney et al reported a 76% pain relief after series of lidocaine infusion in 15 young patients. Patients who were suffering from moderate to severe pain, and patients who had three or more lidocaine infusions had a better response. There were minimal adverse reactions reported (38).

It seems that administration of repeated doses of intravenous lidocaine may result in a longer-term effect.

2.7. Intra-Operative Lidocaine and Development of Chronic Pain

Application of EMLA cream in breast cancer patients was reported to decrease the incidence and severity of the development of chronic pain (12).

More studies support the idea of chronic pain prevention due to pre-emptive lidocaine administration.

A randomized, double-blinded study by Grigoras et al enrolled 36 breast cancer surgery patients who intraoperatively received intravenous either lidocaine or normal saline. Lidocaine was not effective on early postoperative pain, but it was effective and safe to reduce the severity of persistent postsurgical pain as measured 3 months later (39).

In order to evaluate the effect of intravenous lidocaine on the development of chronic post-surgical pain, Terkawi et al enrolled 61 mastectomy patients in a valuable placebo-controlled, double blind, randomized trial. They followed their patients for 6 months after surgery. After performing multivariate analysis, the authors conclude that administration of intravenous lidocaine decreases 20 times the relative risk of the occurrence of post-surgical chronic pain. The relative risk is increased 16 times after replacement of breast implant and 29 times if the patient received radiotherapy (40).

A recent meta-analysis performed by Chang et al examines the effect of intravenous lidocaine on acute and chronic pain after breast surgery. Their results are consistent with previous studies: there is no beneficial effect of lidocaine for the treatment of acute pain, but it decreases the risk of the development of post-surgical chronic pain (41).

In a randomized, placebo control trial of 116 complex spine surgery patients who received either intravenous lidocaine or placebo for up to 8 hours, the authors found a significant difference in pain scores and opioids requirement in first 48 hours after surgery. The lidocaine group had non-statistically significant less complications at 30 days postoperative, and statistically significant higher SF-12 scores at 1 and 3 months postoperative (42).

These results are suggestive of beneficial effect of systemic administration of lidocaine as a prophylactic measure for development of chronic pain.

2.8. Lidocaine and Post-Operative Pain

The benefits of intravenous lidocaine are not limited to the prevention of the development of chronic pain. There are several reports favouring the use of intraoperative lidocaine for improving the early postoperative pain control (14, 42-48). By reducing the release of pro-inflammatory cytokines (14, 44), it reduces the opioid consumption (42-44, 46, 48, 49) facilitating the return of bowel function (44, 45, 47), therefore decreasing the hospital length of stay (45, 47). Lidocaine seems to be effective when administered intraperitoneally (46, 48), or via epidural (43, 45). As mentioned, not all the studies prove the efficiency of lidocaine on reducing immediate postoperative pain (39, 41).

The most recent Cochrane review of all randomized controlled trials involving perioperative intravenous lidocaine concludes that there is enough evidence regarding the effectiveness of lidocaine in reducing the postoperative pain for up to 24 hours after abdominal surgeries. There is no evidence that lidocaine decreases postoperative pain after other types of surgeries, nor 48 hours after abdominal surgeries. It does not seem to be good evidence

for the effect of lidocaine in improving the bowel function (50).

2.9. Lidocaine and Cancer Pain

High incidence of adverse effects of opioids (51), mandate use adjuvants for opioids. There is spare and controversial literature regarding the administration of systemic lidocaine in the management of cancer pain. A double blinded, randomized controlled trial studied the effect of single infusion of lidocaine vs. placebo, in 50 patients with refractory cancer pain. The study demonstrated significant analgesic effect up to 9 days post infusion (52), whereas the 2014 multicenter French RCT did not prove the efficiency of lidocaine in similar type of cancer patients with intractable pain (53). Vosoughian et al reported a shorter duration of lidocaine neuraxial anesthesia in opium abusers (54). The mechanism of this observation is not clear, but the important possibility of cross-tolerance to opioids should be considered, as suggested in animal studies (55).

2.10. Complex Regional Pain Syndrome

Beside other recommended or possible treatments (56, 57), intravenous regional anesthesia (Bier block) is the most used modality of lidocaine administration for the treatment of CRPS. Whether lidocaine is used alone (58-60) or in combination with guanetidine (61), after the Bier block, the patients successfully improved their motor function.

In a double-blinded, randomized, crossover study, Eckmann et al reported only short term relief in CRPS pain after regional intravenous administration of ketorolac and lidocaine (62). The five years follow up of 168 upper extremity CRPS-1 patients who were treated with a mean of 4.8 session of regional intravenous lidocaine and methylprednisolone, finds that 88% of the patients report mild or no pain at the end of the study (63).

There is one study, a small RCT, which did not prove the benefits of the Bier block in controlling the CRPS pain, neither for short, nor for long term (64).

In the treatment of CRPS, different routes of lidocaine administration have been tested. A report of nine patients in with CRPS types I and/or II, after continuous subcutaneous infusion of 10% lidocaine for four to eight weeks the patients reported significant improvement in pain with increasing range of motions and beneficial skin changes (65).

In a small RCT, intravenous lidocaine was more effective than placebo in managing the CRPS pain. Other study of intravenous lidocaine infusion in CRPS patients describes less spontaneous pain although pain threshold remains intact (66).

After 5 sessions of intravenous lidocaine infusion, a retrospective study of 49 CRPS patients reports significant beneficial effect on thermal and mechanical allodynia for up to 3 months after the treatment, but minimal effect on the motor and inflammatory components of the pain (67).

There are case reports of the use and efficacy of lidocaine patch or ointment in the management of CRPS (68-70).

2.11. Doses and Treatment Protocols

The efficient dose of lidocaine in the treatment of neuropathic pain varies widely in different studies, with a plasmatic level from 0.62 to 5.0 mcg/mL (15, 43, 65).

Despite using the same protocol of administering the lidocaine - 5 mg/kg over 30 minutes infusion, Sjogren et al. (18). and Attal et al., (28) obtained different results. The former does not prove the effect of lidocaine in the treatment of pain, whereas the later finds the same dose of lidocaine as being effective in the treatment of mechanical allodynia due to peripheral nerve injury, an effect that would last for at least 6 hours post infusion.

In a report of successful use of subcutaneous lidocaine in the management of CRPS, the lidocaine serum levels were maintained between 0.09 - 8.06 μg/mL, with an average of 3.7 μg/mL (65).

In other report, low to mid-antiarrhythmic doses of lidocaine infusion were ineffective in treating the acute nociceptive pain, but had a selective, limited effect on secondary hyperalgesia (27).

Kipper et al found that a dose of 1.5 mg/kg/h of lidocaine started in the preoperative period and continued intraoperatively and then up to one hour after surgery, with a mean lidocaine plasmatic levels of 1.9 μg/mL during surgery, was effective in controlling the postoperative pain control for up to 72 hours after surgery (43).

In an interesting study aiming to determine the concentration-effect of lidocaine in 13 patients with neuropathic pain, Ferrante et al. administered 500 mg of lidocaine over 60 minutes. The authors conclude that the pain scores abruptly decrease when a plasmatic level of 0.62 μg/mL of serum lidocaine is achieved. The analgesic effect was more correlated with total concentration of lidocaine than the concentration of free lidocaine. There was a narrow effective range of lidocaine that could be the theoretical reason why some studies found lidocaine unsuccessful in the treatment of chronic pain (71). In the report of pain Carroll et al reported in their study that for each 1 μg/mL increase in the plasmatic level of lidocaine, the pain report on the visual analog scale (VAS) is reduced with 0.24 (95% CI 0.05 - 0.43) (30).

2.12. Safety

The systemic administration of lidocaine is reported as being a safe therapeutic method for the chronic pain patients (21, 26, 31, 33, 35, 36, 39, 42, 50); the side effects are minor (34, 38), most often there are dermal reactions following the application of the lidocaine patch (34).

3. Summary and Conclusion

Systemic lidocaine was introduced in management of chronic pain more than half of a century ago, but little is still known about its efficacy, indications and mechanism of action.

It's suggested that different biochemical and anti-inflammatory pathways are involved in mediating the anti-hyperalgesic effects of systemic lidocaine.

There is evidence supporting the effectiveness of 5% lidocaine for treatment PHN and other neuropathic pain syndromes.

There are several reports about the efficacy of intravenous lidocaine administered over few hours period for the neuropathic pain syndromes.

Lidocaine patch might be effective in the management of low back pain and osteoarthritic pain, but further research is required in order to establish the evidence.

Lidocaine patch and repeated doses of intravenous lidocaine seem to be effective in long term management of chronic pain patients.

Intravenous lidocaine used during the surgery has established effect in preventing the occurrence of post-mastectomy chronic pain syndrome, and it might improve the quality of life after spine surgery.

In acute post-operative phase, intravenous lidocaine is effective in reducing the postoperative pain; it might improve bowel function, decrease postoperative nausea and opioid requirements, and decrease the hospital length-of-stay.

There are case reports of lidocaine use in refractory cancer pain patients.

There is supporting evidences for lidocaine use in the treatment of CRPS, whether administered as Bier block, continuous intravenous or transdermal patch.

4. Future Studies

As described, there are encouraging studies with optimistic results in what concerns the use of lidocaine in the management of chronic pain syndromes.

A better understanding of the lidocaine mechanisms of action, required doses and modality of administration, as well as lidocaine clinical use, will help prevent the occurrence of chronic pain, will improve the pain and the quality of life of patients suffering of chronic pain.

Therefore, further research involving local anaesthetics in different clinical scenarios needs to be performed.

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Footnotes

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