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Is systemic administration of local anesthetic agents effective for relieving neuropathic pain? A Cochrane Review summary with commentary

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Abstract.
BACKGROUND: The role of systemic use of local anesthetics in the treatment of neuropathic pain (NP) is still unclear.
OBJECTIVE: To assess the efficacy and safety of systemic local anesthetics for NP.
METHODS: To summarize and to discuss the rehabilitation perspective on the published Cochrane Systematic Review "Systemic administration of local anesthetic agents to relieve neuropathic pain" by Challapalli V et al.
RESULTS: The review included 30 RCTs including patients with NP treated with iv lidocaine, oral mexiletine, lidocaine and mexiletine, or oral tocainide. Low-to-moderate quality of the evidence suggest that intravenous lidocaine or oral mexiletine may slightly reduce NP vs placebo, but the efficacy of these drugs is comparable to anticonvulsants or morphine.
CONCLUSIONS: Systemic administration of local anesthetics is not supported by scientific evidence for pain relief as well as for functional improvement.

Keywords: Neuropathic pain, Cochrane Systematic Review, local anesthetics, lidocaine

The aim of this commentary is to discuss in a rehabilitation perspective the published Cochrane Review "Systemic administration of local anesthetic agents to relieve neuropathic pain" [1] by Challapalli, Tremont-Lukats, McNicol, Lau, & Carr[1], under the direct supervision of Cochrane Pain, Palliative and Supportive Care Group. This Cochrane Corner is produced in agreement with NeuroRehabilitation by Cochrane Rehabilitation.

1. Background

Neuropathic pain (NP) is defined as pain resulting from a lesion or disease of the somatosensory system, including peripheral fibers (Aβ, Aδ, C) and central nervous system (CNS) (Colloca et al. 2017). Several international guidelines have addressed the pharmacological treatment of NP, including antidepressants, gabapentinoids, opioids, botulinum toxin, and topical

[1]This summary is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2019, Issue 10, Art. No.: CD003345. DOI: 10.1002/14651858.CD003345.pub2 (see www.cochranelibrary.com for information). 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.

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medications, such as capsaicin and lidocaine. Analgesic properties of lidocaine mainly depend on the inhibition of ectopic neuronal discharges by modulating of the activation state of voltage-gated sodium channels. Limited safety of long-term use of intravenous lidocaine prompted pain specialists to use its oral analogs, such as mexiletine and flecainide. However, the role of systemic use of local anesthetics in the treatment of NP conditions is still unclear. A Cochrane Review (Challapalli et al. 2019), first published in 2005 (Challapalli et al., 2005) and published again in 2019 without any changes following a search in September 2019 leading to the identification of no potentially relevant trials which could change the results and has been considered stabilised, addressed their role in NP.

Systemic administration of local anesthetic agents to relieve neuropathic pain

Challapalli, Tremont-Lukats, McNicol, Lau, & Carr, 2019

2. Objective

The aims of this Cochrane Systematic Review (CSR) were to assess the efficacy of systemic local anesthetics in relieving NP and their safety and to compare their treatment effects with those of placebo and other control interventions.

3. What was studied and methods

The population addressed in this review included patients of any age affected by NP conditions, including peripheral neuropathies, plexopathy or radiculopathy of unknown, traumatic, infectious, toxic, or infiltrative origin; complex regional pain syndrome type I and II, cerebrovascular lesions or tumors, spinal cord injuries, multiple sclerosis and other demyelinating diseases, trigeminal neuralgia, post-amputation pain, and fibromyalgia. The intervention studied was systemic administration (orally or parenterally) of lidocaine or its analogs. The comparators were placebo or any other medication or non-pharmacological treatment including analgesics, anticonvulsants, antidepressants, acupuncture, TENS, biofeedback, relaxation techniques, regional blockade, or spinal cord stimulation. Studies about topical lidocaine were excluded. The outcomes studied were pain intensity and adverse effects (AEs), defined as any symptom due to the systemic administration of local anesthetics resulting in study withdrawal or in dosage reduction. The latest search date for relevant trials included in the review was May 2004 since the most recent search done in September 2019 did not reveal any trials likely to change the results.

4. Results

The review included 30 randomized, double-blind, controlled trials (RCTs) including patients with NP (mean age 51.7+/– 10.3 years, median number of participants 28, range 8–87), treated with iv lidocaine (1 to 5 mg/kg, 16 RCTs), oral mexiletine (300–1200 mg/die, 12 RCTs), sequential lidocaine and mexiletine (1 RCT), and oral tocainide (20 mg/kg divided daily in three doses, 1 RCT).

The CSR shows that:

- Lidocaine is more effective than placebo in reducing pain [mean change at 0–100 mm Visual Analog Scale (VAS) -11.26 points (–17.3 to –5.22); 11 RCTs, 373 participants]
- Mexiletine is more effective than placebo for pain relief [mean change at 0–100 mm VAS -11.11 points (–16.25 to –5.97), 9 RCTs, 377 participants]
- Higher proportion of responders (patients reporting 30% or greater decrease in pain intensity) was reported with lidocaine or mexiletine administration compared to placebo [OR (Odds Ratio) 3.39 (95% CI 2.08 to 5.55), 14 RCTs, 589 participants]
- No difference between intervention vs other analgesics (carbamazepine, gabapentin, amantadine or morphine) for pain relief [mean difference –0.6 (–6.96 to 5.75)] or AEs [OR 0.78 (0.15 to 3.96)]
- Patients receiving systemic lidocaine or oral analogs have a significant increased risk of AEs, particularly somnolence and lightheadedness, vs placebo [OR 4.6 (3.04 to 6.97)]

5. Conclusions

Systemic lidocaine or oral analogs are more effective than placebo and as effective as other analgesics for NP. Moreover, the safety profile of intervention is comparable to other analgesics in the same population.

6. Implications for practice in neurorehabilitation

This CSR aimed to investigate benefits and harms of systemic administration of local anesthetics in patients affected by NP caused by different conditions. The available evidence suggests that intravenous lidocaine or oral mexiletine may slightly reduce NP compared to placebo, but the efficacy of these interventions is comparable to anticonvulsants or morphine. Moreover, poor safety profile, because of bothersome but not severe adverse effects, negatively affects systemic use of local anesthetics. These considerations raise doubts about the role of these drugs as suitable treatment for patients suffering of NP, according to what is reported by international guidelines (NICE 2013). However, oral analogs of lidocaine are almost never used in clinical practice now.

From a rehabilitation perspective, NP is still a challenging condition resulting in serious impairments, activity limitations and participation restrictions in different functioning domains. In this context, systemic administration of local anesthetics is not supported by scientific evidence for pain relief as well as for functional improvement. It is interesting that potentially relevant studies likely change the results could not have been identified within the period between 2005 and 2019. The effects of interventions on disability is very important for rehabilitation professionals and future research is recommended to use disability relevant outcomes. Moreover, it should be underlined that drug therapy is only a component of a multidisciplinary intervention, commonly recommended to manage NP.

The review did not assess or report on the settings in which IV lidocaine was administered; therefore, the generalizability of the findings on its efficacy and safety to the rehabilitation setting is unknown. Realistically IV lidocaine and its oral analogs are unlikely to find a role in this population.

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Conflict of interest

The author declares no conflicts of interest.

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