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Transdermal Lidocaine for Perioperative Pain: a Systematic Review of the Literature.

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Abstract

Purpose of Review: The purpose of this review is to provide a summary of the perioperative studies that have examined transdermal lidocaine (lidocaine patch) as an analgesic and put the evidence in context of the likely overall benefit of transdermal lidocaine in the perioperative period.

Recent findings: Several randomized controlled trials have been published in the past 4 years that concluded transdermal lidocaine can reduce acute pain associated with laparoscopic trocar or cannula insertion.

Summary: Transdermal lidocaine may reduce short-term pain after surgery in selected surgery types and has a low risk of toxicity but its overall clinical utility in the perioperative setting is questionable. Transdermal lidocaine does not consistently reduce opioid consumption after surgery and has not been shown to improve patient function.

Introduction

Recent data have shown that the risk of taking chronic opioids after surgery increases after about 5 days of postoperative opioid therapy [1]. Alternatives to opioids are desirable, especially those with few or no systemic adverse drug effects (ADEs), and transdermal lidocaine is one such perioperative multimodal agent that has been used clinically for decades. Lidocaine as a local anesthetic was first described in the 1940s [2]. Although transdermal lidocaine has mostly been studied in neuropathic pain, where it is one of only two approved topical agents [3], it has a role in the management of postoperative pain in some patients based on its cost, availability, and safety. Lidocaine is an amide local anesthetic whose mechanism of action is blockade of voltage-gated sodium channels and because of its relatively low potency compared to other local anesthetics it is less toxic at clinically relevant doses than others, such as bupivacaine and ropivacaine [4]. When used in recommended doses, transdermal lidocaine has minimal systemic absorption and has proven efficacy and safety in postherpetic neuralgia and is recommended as a first-line treatment [5]. During the perioperative period when gastrointestinal absorption may be altered and oral medications are not first-line agents immediately after surgery, parenteral and transdermal formulations may be preferred. Because of the publication of several recent studies, a review focusing on the analgesic benefits of perioperative transdermal lidocaine is warranted. We therefore performed a systematic review of the literature to determine the overall benefit of transdermal lidocaine on perioperative pain.

Methods

Literature Search Details

We conducted the review protocol using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (see supplemental file)[6]. During the month of December 2018, we conducted searches of PubMed and Scopus databases looking for randomized controlled trials (RCTs) that studied the efficacy of lidocaine patch in patients undergoing surgery. The last date searched was December 19, 2018. There were no date limitations placed on the searches in either database. We used the following search protocol in PubMed: ("lidocaine patch"[All Fields] OR "transdermal lidocaine"[All Fields]) AND ("postoperative pain"[All Fields] OR "acute pain"[All Fields]) and limited results to the English language.

Our search protocol for Scopus included the following: (ALL ("lidocaine patch") OR ALL ("transdermal lidocaine") AND ALL ("postoperative pain") OR ALL ("Acute pain")) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (LANGUAGE , "English")).

Inclusion Criteria

Studies involving patients who were undergoing surgery and were given either transdermal lidocaine, placebo, or active comparator in the perioperative period with the primary endpoint of improvement in pain were included in the analysis. Only RCTs were included.

Exclusion Criteria

Studies that were prospective but did not include a placebo group or comparative treatment group were excluded, as were studies in which patients were not randomized. Studies that were not conducted in adults (>17 years of age), as well as studies conducted in animals, were not included. Finally, studies that did not provide an assessment of pain control, those that studied patients who did not have surgery, and those that studied patients outside of the perioperative period were all excluded.

Review Protocol, Evidence Grading, and Assessment of Bias

Evidence quality was assessed using the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) approach (Table 1) [7]. Using this approach, studies are classified as high, moderate, low, or very low quality of evidence.

All articles were first reviewed independently by J.S. and A.C. and assessed for inclusion in the review. If the determination could not be made from reading the article title, the abstract was reviewed, and if ambiguity remained after that, the full article was subsequently downloaded and reviewed. Discrepancies were resolved by discussion between J.S and A.C, with M.R. having the tie-breaking vote if needed.

The risks of bias related to sequence generation, allocation concealment, blinding of personnel and participants, blinding of outcome assessment, and handling of incomplete outcome data were evaluated using the Cochrane Collaboration's tool for assessing bias in randomized trials [8].

Results

Included Studies

Initial search of the literature yielded 265 articles (Figure 1). Because of the overlap between PubMed and Scopus databases, there were 4 duplicates. Reasons for exclusion are shown in Figure 1. The most common reasons for exclusion were that transdermal lidocaine was not studied (n=151), and that studies were not perioperative studies (n=47). A total of 7 studies were included in the final review. Meta-analysis was deemed inappropriate given the heterogeneity between studies and endpoints.

Primary Outcome

A total of 7 RCTs that studied the use of transdermal lidocaine in the setting of the perioperative period were included in the review (Table 1). All included studies compared transdermal lidocaine to placebo, with 2 studies also having an IV lidocaine comparison group [9, 10]. The type of surgery was not homogenous and included robotic cardiac valve surgery, laparoscopic gynecological surgery, gynecological surgery via laparotomy, laparoscopic appendectomy, "elective operations," and radical prostatectomy. The primary outcome for 4 studies was the mean visual analog scale (VAS) pain rating [9, 11-13]. Another study's primary outcome was the pain disability index [14]. A single study used the 4-point categorical verbal rating scale [10] and in the last study the primary outcome was pain rating on the 11-point verbal rating scale (VRS) [15].

Overall, 5 out of the 7 studies analyzed reported lower pain ratings in the lidocaine group compared to placebo [9-11, 13, 15]. Three out of the 4 studies that used VAS as primary endpoint reported that transdermal lidocaine decreased postoperative pain ratings at rest, which remained reduced for 6 hours [13], 24 hours [11], and 72 hours [9], although the pain ratings with movement were no different in two of them [11, 13]. The remaining VAS study found no difference [12]. The study that used pain disability index found no improvement in acute or chronic pain with transdermal lidocaine [14]. The study whose primary outcome was the 4-point scale reported that the incidence of

cannula-induced pain was lowest in the transdermal lidocaine group compared to both placebo and intravenous lidocaine groups [10]. In the single study that used the 11-point VRS, pain at rest for up to 12 hours and with coughing for up to 24 hours was reduced in the transdermal lidocaine group [15].

Secondary Outcomes

All but 1 study by Hong et al [10] reported opioid consumption in the study groups. In 4 studies there was no difference in opioid consumption between treatment and placebo groups [11, 13-15] and opioid consumption was not reported in another [10]. Meperidine use was reduced a small amount of uncertain clinical significance in the transdermal lidocaine group in the study by Lee et al [12] and in the study by Elhafz et al [9] opioid use was reduced the same amount by both transdermal lidocaine and IV lidocaine.

Although patient satisfaction is typically an important secondary outcome, only 2 of the studies reported on this. Vrooman et al [14] reported no difference between transdermal lidocaine group and placebo, while Habib et al [15] found that patients who received transdermal lidocaine rated overall pain control quality better and reported less interference with walking, breathing, and mood.

Study Quality and Consistency and Assessment of Bias

The studies reviewed ranged from very low to moderate quality according to the GRADE recommendations for rating study quality (Table 1) [7]. Heterogeneity in end points as well as study protocols was a problem throughout the literature. For example, some studies examined pain at rest and with movement [9, 11, 12, 15], some reported global pain ratings [13, 14], and others focused on pain at specific sites [10]. Some studies used the VAS [9, 11-13] while others used the 11-point VRS [15] or 4-point Likert scale [10] and the final study used a pain disability index [14]. The dose of lidocaine used in the treatment group varied between studies. Lau et al [11] used a single lidocaine patch while Lee et al used 2 patches on either side of the trocar site [12]. Hong et al [10] used a single patch that

was applied to venous cannulation site and then removed prior to cannulation, while Vrooman et al [14] and Kwon et al [13] used an entire 700-mg lidocaine patch at the surgical site. Habib et al [15] used a single patch, the dose of which was unclear, and cut it in half and applied to either side of the wound, and Elhafz et al [9] used 3 lidocaine patches. Overall, the studies had a low risk of bias in all areas, with the exception of the study by Elhafz et al (Tables 2 and 3) [9].

Safety and Adverse Events

None of the 7 studies reported any adverse events related to transdermal lidocaine, although none of them were adequately powered for that outcome. Elhafz et al [9] stated that there were no "adverse events of local anesthetic toxicity," while patients who received transdermal lidocaine in the study by Lee et al [12] experienced no nausea, vomiting, erythema, rash, contact dermatitis, hypotension, bradycardia, cardiovascular instability, headache, or dizziness. Vrooman et al [14] described an equal number of transdermal lidocaine and placebo patients with various adverse events, none of which was attributed to the treatment assignment.

Discussion

This review demonstrates that transdermal lidocaine may provide a modest improvement in pain ratings in the perioperative period but the number of studies was limited and the duration of benefit is limited. Although 5 out of 7 studies showed a decrease in pain ratings with transdermal lidocaine, this reduction was typically only observed at rest and often did not translate to decreased opioid consumption, making the overall clinical benefit questionable.

A previous review in 2015 of transdermal lidocaine for acute and postoperative pain concluded that it did not improve pain, reduce opioid consumption, or reduce length of stay and questioned the overall efficacy of transdermal lidocaine as an analgesic adjunct [16]. Two of the most recently published studies included in our review [10, 12] focused on pain at cannula and trocar sites and were published after that review. One study found that transdermal lidocaine did not decrease pain at the site of peripheral IV cannula insertion [10], while the other did report a brief but statistically significant decrease in pain at the site of trocar insertion [12]. In the latter study the overall VAS pain ratings were low at all time points except the initial rating immediately after surgery, so it is not clear that the reported differences would translate to changes in treatment.

In 3 of the 5 studies with positive results, transdermal lidocaine decreased pain at the site of either a cannula or trocar [9, 10, 13]. This may represent the most logical use of the patch, which is approved at this time only for use in postherpetic neuralgia [3], a condition in which the varicella zoster virus may damage sensory nerves and dermatomal pain occurs [5]. The conceptual basis for lidocaine's efficacy in postherpetic neuralgia is that neuronal cell injury leads to the development of abnormal sodium channels, which are a target for transdermal lidocaine [5]. Tissue trauma that occurs in laparoscopic surgery is mostly limited to discrete areas of trocar insertion and a topical treatment like transdermal lidocaine is logical for neuropathic pain in a limited distribution such as this.

It was interesting to note that only 2 of the 7 included studies reported a decrease in opioid consumption in the lidocaine groups. Our interpretation of this finding is that while transdermal

lidocaine may have a role in decreasing localized pain for a short period of time, such as during insertion of a cannula or trocar, it does not provide substantial and lasting relief that actually affects analgesic use. It would be easy to dismiss this type of ephemeral relief as unimportant but patient satisfaction remains a key driver of hospital reimbursement [17], with patient perception of pain management a major factor in that overall rating. Seemingly small details, such as pain experienced during brief procedures, may contribute to patient perception of overall pain control. The cost of one lidocaine patch 5% at our institution as of July 2019 is $2.25, which is relatively inexpensive when considering the potential costs of poor patient satisfaction ratings on surveys such as the HCAHPS (Hospital Consumer Assessment of Healthcare Providers and Systems) in the pay-for-performance model currently used by the Centers for Medicare and Medicaid Services [18].

Future studies are needed examining the use of transdermal lidocaine for specific procedural pain indications, such as placement or removal of chest tubes, extracorporeal membrane oxygenation (ECMO) cannula placement, or dressing changes. It is unlikely given the effect sizes observed in this review and overall lack of difference in opioid consumption that additional perioperative studies in laparoscopic or open abdominal surgery would provide new information.

This review has some limitations. First, there may be unpublished studies or studies only available on other search engines that we did not find in our searches, and these are more likely to be negative studies. Second, despite using 2 different authors to perform literature searches and using 2 search engines for the searches, we might have missed some studies that used terminology not detected in our search queries.

In conclusion, transdermal lidocaine may have a limited role in reducing perioperative pain but the magnitude of the improvement is likely small and has not thus far been associated with a reduction in opioid consumption or other patient-centered outcomes.

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