Topical analgesics for acute and chronic pain in adults

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Abstract

This is the protocol for a review and there is no abstract. The objectives are as follows:

To provide an overview of the analgesic efficacy and associated adverse events of topical analgesics (primarily NSAIDs, rubefacients, capsaicin, lidocaine, and opioids) for the treatment of acute and chronic pain in adults.

BACKGROUND

Description of the condition

Topical analgesic drugs are used to treat a variety of painful conditions. Some might be regarded as acute pain (pain lasting less than 3 or 6 months), which are typically strains or sprains, tendonitis, or muscle aches. Others would be regarded as chronic pain, like osteoarthritis of the hand or knee, or certain types of neuropathic pain. Other conditions are more difficult to classify, and here one might include topical opioids for painful cutaneous ulcers, which can be a shorter or longer duration problem. With such clinical heterogeneity it is not surprising that the choice of a topical therapy is determined largely by the condition.

Description of the interventions

A number of topical analgesics have been tested, and are used. For strains and sprains, the choice would be between topical nonsteroidal anti-inflammatory drugs (NSAIDs) or topical rubefacients.

For arthritis, the choice would be between topical NSAIDs, topical rubefacients, or low dose topical capsaicin.

For neuropathic pain, the choice would be between topical local anaesthetic (lignocaine/lidocaine, for example) or high dose topical capsaicin.

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CONTRIBUTIONS OF AUTHORS SD and RAM will carry out searches, select reviews for inclusion, and carry out assessment of methodological quality, and data extraction. HJM will act as arbitrator if necessary. All authors will be involved in writing.

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For painful cutaneous ulcers, the only likely choice would be topical opioids.

There is potential for other interventions to be examined, though these are without proven analgesic effects (e.g. arnica, comfrey).

How the intervention might work

Topical medications are applied externally and are taken up through the skin. They exert their effects close to the site of application, and there should be little systemic uptake or distribution. This compares with transdermal application, where the medication is applied externally and is taken up through the skin, but relies on systemic distribution for its effect. For a topical formulation to be effective, it must first penetrate the skin.

Individual drugs have different degrees of penetration. A balance between lipid and aqueous solubility is needed to optimise penetration, and use of prodrug esters has been suggested as a way of enhancing permeability. Formulation is also crucial to good skin penetration. Experiments with artificial membranes or human epidermis suggest that creams are generally less effective than gels or sprays, but newer formulations such as microemulsions may have greater potential.

Topical NSAIDs—NSAIDs reversibly inhibit the enzyme cyclooxygenase (prostaglandin endoperoxide synthase or COX), now recognised to consist of two isoforms, COX-1 and COX-2, mediating production of prostaglandins and thromboxane A₂ (Fitzgerald 2001). However, relatively little is known about the mechanism of action of this class of compounds aside from their ability to inhibit cox-dependent prostanoid formation (Hawkey 1999). Systemically, prostaglandins mediate a variety of physiological functions such as maintenance of the gastric mucosal barrier, regulation of renal blood flow, and regulation of endothelial tone. They also play an important role in inflammatory and nociceptive (pain) processes. The rationale behind topical application is based on the ability of NSAIDs to inhibit cox enzymes locally and peripherally, with minimum systemic uptake. Their use is therefore limited to conditions where the pain is fairly superficial, such as joints and skeletal muscle, rather than visceral pain.

Once the drug has reached the site of action, it must be present at a sufficiently high concentration to inhibit cox enzymes and produce pain relief. It is probable that topical NSAIDs exert their action both by local reduction of symptoms arising from periarticular and intracapsular structures. Tissue levels of NSAIDs applied topically certainly reach levels high enough to inhibit COX-2. Plasma concentrations found after topical administration, however, are only a fraction (usually much less than 5%) of the levels found in plasma following oral administration. Topical application can potentially limit systemic adverse events by minimizing systemic concentrations of the drug. We know that upper gastrointestinal bleeding is low with chronic use of topical NSAIDs (Evans 1995), but have no certain knowledge of effects on heart failure, or renal failure, both of which are associated with oral NSAID use.

Topical rubefacients—Rubefacients cause irritation of the skin, and are believed to relieve pain in muscles, joints and tendons, and other musculoskeletal pains in the

extremities by counter-irritation (BNF 2009). The term “counter-irritant” derives from the fact that these agents cause a reddening of the skin by causing the blood vessels of the skin to dilate, which gives a soothing feeling of warmth. The term counter-irritant refers to the idea that irritation of the sensory nerve endings alters or offsets pain in the underlying muscle or joints that are served by the same nerves (Morton 2002). There has been confusion about which compounds should be classified as rubefacients. Some compounds, such as salicylates, are related pharmacologically to aspirin and NSAIDs, but for the form that they are often used in for topical products (often as amine derivatives) their principal action is to act as skin irritants. We will include salicylates and nicotinate esters as rubefacients.

Topical capsaicin—Capsaicin is the active compound present in chili peppers, responsible for making them hot when eaten. It binds to nociceptors (sensory receptors responsible for sending signals that cause the perception of pain) in the skin, releasing pro inflammatory neuropeptides, such as substance P, which cause neurogenic inflammation. There is an initial excitation of the neurons and a period of enhanced sensitivity to noxious stimuli, usually perceived as itching, pricking or burning sensations. Enhanced sensitivity is followed by a refractory (unresponsive) period with reduced sensitivity and, after repeated applications, persistent desensitisation. The mechanisms of desensitisation remain unclear. It is thought that degenerative changes in the primary sensory neuron result in loss of peripheral or central nociceptor-specific macromolecules and receptors, and that these degenerative changes can affect distant parts of the primary sensory neuron (Jancso 2008). The resulting reduction of sensation is associated with degeneration of epidermal nerve fibres, which is at least partially reversible (Nagy 2004; Nolano 1999; Simone 1998). It is the theoretical ability of capsaicin to desensitise nociceptors that is exploited for therapeutic pain relief (Holzer 2008).

Topical lidocaine—Topical lidocaine dampens peripheral nociceptor sensitisation and central nervous system hyperexcitability. It may benefit patients with postherpetic neuralgia or traumatic nerve injury, where its lack of systemic side effects makes it an attractive option. Lidocaine is an amide-type local anaesthetic agent that acts by stabilising neuronal membranes. It impairs membrane permeability to sodium, which in turn blocks impulse propagation, and thus dampens both peripheral nociceptor sensitisation, and eventually central nervous system hyperexcitability. It also suppresses neuronal discharge in A delta and C fibres. Regenerating nerve fibres have an accumulation of sodium channels. When lidocaine binds to such sodium channels it initiates an ‘inactive state’ from which normal activation is unable to occur. Lidocaine reduces the frequency rather than the duration of sodium channel opening. In a small dose it inhibits ectopic discharges, although it does not disrupt normal neuronal function. Lidocaine also suppresses spontaneous impulse generation from dorsal root ganglia, where the postherpetic neuralgia virus remains dormant after initial infection by varicella zoster (chickenpox) (Khaliq 2007).

Topical opioids—Topically applied opioids bind to peripheral opioid receptors on the terminals of nociceptive nerves in damaged and inflamed tissue, with analgesic effects through reduced pain perception and reaction to pain (Stein 2003).

Why it is important to do this overview

Use of topical analgesics is increasing as patients look for alternatives to systemic treatments and their associated adverse events. For topical NSAIDs in particular, evidence exists to show that rare but serious gastrointestinal bleeding is not associated with its use (Evans 1995). The efficacy of topical interventions, together with their reduced incidence of troublesome adverse events, is now widely recognised. There is a need to pull together the best available evidence for all interventions and conditions to facilitate decisions about which interventions are helpful in particular circumstances.

OBJECTIVES

To provide an overview of the analgesic efficacy and associated adverse events of topical analgesics (primarily NSAIDs, rubefacients, capsaicin, lidocaine, and opioids) for the treatment of acute and chronic pain in adults.

METHODS

Criteria for considering reviews for inclusion

All Cochrane reviews assessing RCTs of topical analgesics for pain relief in adults will be considered for inclusion. Cochrane reviews should identify other systematic reviews and agreements and disagreements between them; relevant non-Cochrane reviews should therefore be identified up to the time of publication. We will supplement this with searches for any more recent non-Cochrane reviews. While it is the intention only to use Cochrane reviews in the overview, it would be inappropriate to exclude non-Cochrane reviews that were superior because they were conducted to more stringent quality criteria (Moore 2010a), used more appropriate outcomes, or included significant amounts of more recent data.

Search methods for identification of reviews

We will search the Cochrane Library for relevant reviews. See Appendix 1 for the search strategy. Searches for non-Cochrane reviews will involve free-text searches in PubMed, and using systematic reviews identified in the individual Cochrane reviews as markers of sensitivity. We will involve the trial search coordinator to check search strategies.

Data collection and analysis

Two review authors will independently carry out searches, select reviews for inclusion, and carry out assessment of methodological quality, and data extraction. Any disagreements will be resolved by discussion, involving a third author if necessary.

Selection of reviews—Included reviews will assess RCTs of the effects of topical application of analgesics for pain relief in adults (as defined by individual reviews), compared with placebo or active comparator if available, and include:

- a clearly defined clinical question;
- details of inclusion and exclusion criteria;
- details of databases searched and relevant search strategies;

- patient-reported pain relief;
- summary results for at least one desired outcome.

Data extraction and management—Data will be taken from the included reviews. Original study reports will be used only if specific data are missing.

Information will be collected on the following:

- Number of included studies and participants;
- Intervention (NSAID, rubefacient, capsaicin) and dose;
- Comparator;
- Condition treated: acute (sprains and strains, overuse injuries), chronic (nociceptive, neuropathic);
- Time of assessment.

RR and NNT for the following outcomes sought will include:

- 50% pain relief (patient-reported);
- any other measure of “improvement” (patient-reported);
- adverse events: local and systemic, and particularly serious adverse events;
- withdrawals.

Assessment of methodological quality of included reviews—The methodological quality of included reviews will be assessed using the following criteria (adapted from AMSTAR; Shea 2007):

1. Was an a priori design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Were published and unpublished studies included irrespective of language of publication?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of studies appropriate?
10. Was the conflict of interest stated?

The question on likelihood of publication bias assessment was not included because statistical tests for presence of publication bias have been shown to be unhelpful (Thornton

2000), but we will use methods that assess the potential for publication bias to influence results (Moore 2008).

The strength of evidence for each outcome will be assessed according to the total number of participants contributing data, and the methodological quality of, and degree of clinical heterogeneity (pain condition mix) in, the primary studies, as reported in the reviews. For chronic pain, we will use recently-established criteria that identified additional potential for bias in chronic pain studies (Moore 2010a).

Data synthesis—It is unlikely that additional quantitative analyses will be required, since only results from properly conducted (predominantly Cochrane) reviews will be considered. The aim is to concentrate on specific outcomes like the proportion of participants with at least 50% pain relief, all-cause or adverse event discontinuations, or serious adverse events, for example, and to explore how these can be compared across different treatments for the same condition. Care will be taken to ensure that like will be compared with like, for example in duration, which can be an additional source of bias (Moore 2010b). Importantly, issues of low trial quality, inadequate size, and whether trials were truly valid for the particular condition, will be highlighted in making between-therapy comparisons.

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Internal sources

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Appendix 1. Search strategy for Cochrane Library

1. MESH descriptor Anti-Inflammatory Agents, Non-Steroidal OR (non-steroidal anti-inflammatory):ti,ab,kw
2. MESH descriptor Capsaicin OR capsaicin:ti,ab,kw
3. MESH descriptor Lidocaine OR lidocaine:ti,ab,kw
4. Rubefacient:ti,ab,kw
5. MeSH descriptor Analgesics, Opioid
6. OR 1/5
7. MESH descriptor Administration, Topical OR topical:ti,ab,kw
8. 6 AND 7 in Cochrane Reviews

HISTORY

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** Indicates the major publication for the study*