Effectiveness of topical administration of opioids in palliative care: a systematic review
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CRD summary
The review provided support for the effectiveness of topical opioids in controlling pain in palliative care, but did not provide clear recommendations for clinical practice regarding the ideal opioid, dosage, interval of administration, carrier, or identification of wounds that were most suitable for treatment. The limitations of the evidence provided imply that the authors' conclusions should be interpreted with caution.

Authors' objectives
To evaluate the effectiveness of topical opioids in controlling pain in palliative care.

Searching
The databases MEDLINE, EMBASE, CINAHL, CANCERLIT, St Christopher's Hospice Library database, www.controlled-trials.com, and Evidence-Based Medicine Reviews were searched to August 2006. Search terms were reported. Bibliographies of each retrieved article, relevant reviews, selected journals, grey literature, conference proceedings and research trials registers were searched for additional studies. Abstracts were excluded. The search was for publications in English and German.

Study selection
Primary studies on the effectiveness of topical opioids in the palliative care setting were eligible for inclusion. Studies where topical opioids were administered by more invasive routes (usually outside the typical palliative care setting), such as intrapleural, intravesical, or intra-articular, were excluded. The primary outcome was pain relief. The secondary outcome measures were time to onset of analgesia, duration of analgesia, and side effects (either local or systemic).

The included studies were randomised controlled trials (RCTs), case series and case reports. The opioids used in the included studies were diamorphine, morphine (sulphate and hydrochloride), methadone, oxycodone, and meperidine (pethidine). The opioids were applied every two to three hours in trials on mouthwashes, and one to six times daily to skin wounds. A variety of carriers were used, but in most studies IntraSite gel or another hydrogel were used. Details of the comparator interventions were not reported. The ulcers treated included both malignant and non-malignant wounds, and oropharyngeal mucositis. No details of the age or sex of the participants were reported. Most studies used objective measures to evaluate pain relief, including numerical rating scores (0 to 10 or 0 to 4), visual analogue scales, and percentage pain relief.

The authors did not state how many reviewers performed the selection.

Assessment of study quality
The methodological quality of the RCTs was assessed using the method developed by Jadad et al.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Three reviewers extracted data using a structured form. It was unclear whether it was done independently.

Methods of synthesis
A narrative synthesis was provided due to the heterogeneity of the studies, providing more detail for the RCTs than the case series and case reports.

Results of the review
Nineteen studies (number of participants unclear) were included: six RCTs (range 5 to 26 participants), six case series, and seven case reports. The included RCTs were all small and inadequately powered, with high attrition rates; three trials had a high quality score of 4 or 5 and two trials were not blind.
All but one of the 19 studies (an RCT) suggested beneficial effects of topical opioids on pain relief. However, only six studies (including five RCTs) reported a statistically significant beneficial effect on objective outcome measures. Three RCTs found that a morphine and diamorphine gel was effective for painful pressure ulcers. Two RCTs of mucositis found an analgesic benefit with topical morphine mouth washes, where a concentration of 2% was more beneficial than 1%. An RCT of painful skin (mainly leg) ulcers did not show statistically significant pain relief.

Authors’ conclusions
The evidence from the small RCTs provided support for the use of topical opioids in controlling pain in palliative care, but did not permit clear recommendation for clinical practice for the ideal opioid, the starting dose, the interval of administration, methods of titration, the carrier, and the identification of wounds that are most suitable for treatment. There is a deficiency of higher quality evidence on the role of topical opioids, and more robust primary studies are required to inform practice recommendations.

CRD commentary
The review addressed a clear question with inclusion criteria defined in terms of intervention and participants, but study design and relevant outcomes were broadly defined. Relevant databases were searched in English and German, but unpublished studies were not considered, so there was a possibility of language and publication bias. The initiation date for the searches was not given but the earliest included paper was from 1995. Publication bias was not assessed. The study quality of the RCTs was assessed using suitable criteria, but the quality of the case series was not assessed. It was not clear whether efforts were made to reduce error and bias in the review process. Limited study details were reported and there was no numerical or statistical data. No details were reported of the comparator interventions in the RCTs. A narrative synthesis was provided due to the heterogeneity of the included studies. No meta-analysis was performed. The potential limitations arising from the review process, the limited evidence, and the limited study details reported, implies that the authors’ limited conclusions should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors stated that there was not enough evidence to make recommendations for clinical practice.

Research: The authors identified a need for RCTs with more power, with other opioids (particularly fentanyl) versus active placebo (hydrogel), with results stratified for different wounds and ideally stable levels of systemic analgesics, throughout the trials. Topical opioids might also be particularly well suited for ‘n-of-1’ trials.

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