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# Question: What is the evidence for the use of morphine solution for injection mixed in gel and applied topically?

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## Summary

The transdermal absorption of morphine has not been widely published.[1] Studies and case reports of the efficacy of topical morphine are conflicting.[1] A statistically significant study is required to prove the analgesic efficacy of topically applied opioids.[1] Topical morphine appears to be most effective when used on chronic, open, clean and moist wounds.[1] The Palliative Care Formulary outlines that topical morphine has also been used successfully to relieve otherwise intractable pain associated with cutaneous ulceration, often decubitus ulcers.[2] It is often applied as a 0.1% (1mg/mL) gel.[2] Intrasite® or Instillagel® are commonly used to administer topical morphine. The amount of gel applied varies according to the size and the site of the ulcer, but is typically 5–10mL applied twice or three times daily.[2] The topical morphine gel is kept in place with either a non-absorbable pad or dressing, e.g. Opsite® or Tegaderm®, or gauze coated with petroleum jelly.[2]

## Choice of Gel

- **Intrasite®**

Intrasite is a hydrogel dressing that is used to facilitate gentle, effective autolytic debridement to prepare the wound bed in all types of wounds.[3] The Martindale advises that “when mixed with about 8 g of Intrasite gel, morphine sulfate, in a concentration of

1.25 mg/mL, remained chemically stable over a 28-day period stored at 4 degrees or at room temperature, irrespective of light exposure. However, unless prepared under sterile conditions, the mixture should be used within 7 days because of the risk of microbial contamination once the gel has been opened."[4] A monograph for the preparation of Morphine 0.1% w/w gel using intrasite gel is available from www.extemp.ie.[5]

- **Instillagel®**

Instillagel® is a gel, containing lidocaine hydrochloride and chlorhexidine gluconate as active ingredients, which is marketed as a product used to anaesthetise the urethra prior to catherisation or cystoscopy.[6,7] Lidocaine hydrochloride is an amide type local anaesthesic that produces surface anaesthesia when applied topically.[7] In addition, the topical application of lidocaine hydrochloride has been found to be useful in the treatment of chronic neuropathic pain, such as that associated with postherpetic neuralgia.[7] Chlorhexidine gluconate is an antiseptic and disinfectant that is bactericidal and bacteriostatic against a wide range of Gram-positive and Gram-negative bacteria.[7] At Our Lady's Hospice and Care Services (OLH&CS) morphine and Instillagel® is prepared on the ward by a staff nurse. The preparation is thoroughly mixed immediately prior to use and any unused product is discarded.

**Formulation**

- Morphine 10mg/ml (1ml) is mixed with Instillagel® 11mls
- 10mg of morphine in 12mls of Instillagel® + Morphine
- **0.08% (0.8mg/ml) of Morphine Gel.**

**Factors Which May Affect the Efficacy of Topical Opioids**

Farley evaluated the studies reported to date and found that several factors appear to be important in determining whether a topical opioid will be effective.[1]

- The wound must be chronic. It has been reported that it is inflammation rather than the immediate damage that is responsible for the up-regulating of opioid receptors.[1]
- The wound must be open. Morphine does not penetrate intact human skin readily.[1]

- The wound needs to be clean and moist and without significant eschar. This enables the opioid to penetrate into the wound tissue where its analgesic action can take place.[1]

**Published Studies**

- Bastami et al conducted a study to evaluate the analgesic effect of topically applied morphine on chronic painful leg ulcers.[8] Twenty-one patients were randomly assigned to receive either morphine or placebo in a randomised, placebo-controlled, crossover pilot study.[8] Each patient was treated four times in total. Although an overall, clinically relevant, reduction of pain was observed upon treatment with morphine, the difference was not statistically significant.[8] The difference was statistically significant only 2 hours after dressing on the first treatment occasion.[8] Thus, the study did not demonstrate a consistent and globally significant difference in nociception in patients treated with morphine.[8] However, the relatively small number of patients included in the study and other methodological limitations made it difficult to draw general conclusions regarding efficacy of topically applied morphine as an effective treatment for some painful ulcers.[8] Further studies are warranted to evaluate the value of topically applied morphine in the treatment of patients with chronic painful leg ulcers.[8]
- Farley conducted a review of 100 case reports involving over 100 patients with many different types of chronic superficial wounds, which suggest that the topical application of an opioid in a suitable gel leads to a significant reduction in the level of perceived pain.[1] The author concluded that the overall question of whether topical opioids are effective and safe is still, as yet, unproven.[1]
- Jansen et al reported on a three-way trial with nine patients with arterial leg ulcers.[9] They were administered morphine 0.5% in hydrogel with placebo subcutaneous morphine injection, or placebo gel with active subcutaneous morphine injection or placebo gel with placebo injection.[9] They concluded that topical morphine does not have a clinically relevant analgesic effect in patients with painful arterial leg ulcers.[9]

## References


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