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Research Paper

Evaluating topical opioid gel on donor site pain: A small randomised double blind controlled trial

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ABSTRACT

Background: Autologous donor skin harvested for transplantation is a common procedure in patients with burns, and patients often feel more pain at the donor site than is justified by the extent of trauma. Topical morphine gels have been thought to have an effect on peripheral opioid receptors by creating antinociceptive and anti-inflammatory effects, which could potentially reduce the systemic use of morphine-like substances and their adverse effects.
Methods: We therefore did a paired, randomised, double-blind placebo study to investigate the effect of morphine gel and placebo on dual donor sites that had been harvested in 13 patients. Pain was measured on a visual analogue scale (VAS) 15 times in a total of 5 days.
Results: The mean (SD) VAS was 1.6 (2.3) for all sites, 1.5 (2.2) for morphine, and 2.0 (2.5) for placebo. The pain relieving effects of morphine gel were not significantly better than placebo.
Conclusion: The assessment of pain at donor sites is subjective, and more systematic and objective studies are needed.

1. Background

Autologous split-thickness skin grafts (STSG) harvested with a dermatome are widely used for transplantation in deep burns, large wounds, cell harvesting for keratinocyte retransplantation and other reconstructive procedures. Numerous studies have been published on the optimal dressing and management of pain at donor sites [1–15]. Clinical experience has suggested that patients often feel more pain than is justified by the extent of trauma [1–3,16]. Pain can give rise to adverse effects such as hypertension and agitation, and can impair wound healing [16,17]. High doses of analgesics such as morphine or morphine-like substances are often used to alleviate it. Unfortunately, the systemic use of opioids can cause many adverse effects such as respiratory depression, nausea, pruritus, and constipation [18,19].

1.1. Topical treatment for peripheral pain control

Topical treatments are available as gels, creams, ointments, lotions, solutions, pastes, sprays or patches [20]. Non-opioid treatment for pain at donor sites has focused on analgesics such as lignocaine or bupivacaine with some success [5,7,8,17]. Authors have suggested that some dressings not only affect healing, but also reduce pain at the donor site better than others [1,4,6,9–12,21,22]. Topical opioids applied to wounds in the cornea, the oral mucosa, and to various types of wounds in the skin have had mixed results [23–30]. Although most pain-relieving topical treatments are intended to induce analgesia locally, it can sometimes be difficult to distinguish peripheral effects from systemic effects [13,24,29,31–33].

1.2. Molecular mechanisms of peripherally applied opioids

Since the discovery and characterisation of peripheral opioid receptors, many studies have shown that the analgesic effects of opioids can also be mediated by peripheral receptors. After diffusion through the skin, topical opioids produce analgesia by their agonistic effects on opioid receptors on injured peripheral sensory neurons. This creates conformational changes that allow the intracellular

Abbreviations: OD, operation day; POD, postoperative day; RCT, randomised controlled studies; STSG, split-thickness skin graft; VAS, visual analogue scale.

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coupling of signalling proteins to the receptors and their subsequent interaction with ion channels in the membrane. In turn this reduces the excitability of nociceptive neurons and lessens the release of pronociceptive neuropeptides. All these events lead to antinociceptive and anti-inflammatory effects [34,35].

1.3. Study rationale

We aimed to study the efficacy of topically applied morphine gel on pain at the donor site. In a previous randomised study that examined the use of topical opioid gel at donor sites, no significant differences were found, but it did not address the issue of potential antinociceptive effects that last for more than 24 hours postoperatively [13]. The potential anti-inflammatory effects of topical opioids might contribute to the prolongation of their pain-relieving action [34–37], which creates the need to study pain scores for longer periods after initial application. We therefore conducted a clinical trial to study the possible pain-reducing effect of topically applied morphine gel at the donor sites of split thickness skin grafts (STSG) for 5 days after operation.

2. Material and methods

This prospective, paired, randomised, double-blinded, placebo-controlled trial was approved by the regional local ethics committee (Linköping University, Dnr 00–047), and it conforms to the Helsinki Declaration of 1975 (revised in 2000). It is also designed to try to adhere to CONSORT criteria for randomised controlled studies (RCT). The study included male and female patients over 18 years of age with burns who were listed for STSG with planned harvest of skin from the thigh at Linköping University Hospital Burn Center. Informed consent had been obtained orally and in writing. Those with known severe adverse effects to morphine or other opioid-like substances were excluded. Grafts were harvested with a dermatome according to clinical routine. Donor sites with similar sizes were paired and located either on each leg or, if only one leg was used, medially and laterally or ventrally and dorsally. Donor sites were randomised for active or placebo treatment. Each patient was given one application of active or placebo gel of 2 ml each in syringes marked 1 and 2 directly after skin graft harvesting. The gel was not visually distinguishable from each other; both patient and caregiver were blinded to the study. The wound was then dressed with a polyurethane foam dressing (Allevyn, Smith and Nephew) and elastic wrap. Patients then assessed the intensity of pain from each donor site 3 times a day for 5 consecutive days using a visual analogue scale (VAS) (0: no pain at all to 10: worst pain imaginable). Systemic analgesics (oral or parenteral, or both) were given when needed (Fig. 1).

The gel was obtained from Apoteket Production and Laboratories (APL) (Stockholm, Sweden) as a sterile hydrogel containing hydroxypropyl methylcellulose (a semisynthetic, inert viscoelastic polymer) and morphine hydrochloride 1 mg/ml. The placebo gel was made in a similar way using the same components except morphine. The gels were sent from the hospital pharmacy in identical syringes labelled “Gel 1” and “Gel 2”.

2.1. Statistical analysis

To analyse the differences in VAS between the 2 groups, we used Wilcoxon signed-rank test, normality tests, and paired Student’s *t*-test. Box plots, descriptive statistics, and bar charts were done using Stata SE for Mac OS (Version 12.0, StataCorp College Station, USA). Area under the curve (AUC) measurement was done using Microsoft Excel for Mac OS (Version 14.0.0, Microsoft Redmond Campus, Washington, US) and was constructed using the trapezoid method with linear interpolation of missing values between 2 valid points. The

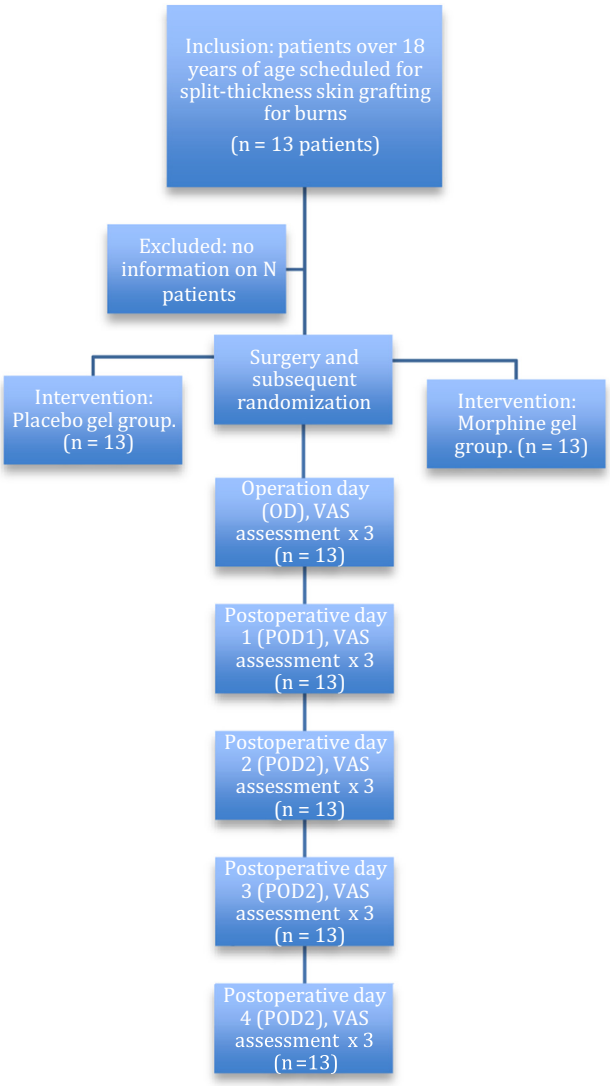

Fig. 1. Flow diagram of study design and execution.

Wilcoxon signed-rank test was done to compare the mean of the 2 groups. Probabilities are two-tailed and those of less than 0.05 were considered significant. Results were analysed daily and for the whole group. Data are presented as mean (SD) if not otherwise specified.

3. Results

We used data from 13 patients (3 women and 10 men), mean age 53.3 years (range 20–85) (Table 1, Fig. 1). Analysis was made for originally assigned groups. The donor site was measured during operation to be about 8–9 cm wide and 15–20 cm long. The graft was about 10–12/1000″ inches thick. No individual measurements were collected for analysis. No adverse events were reported. Some VAS assessments were missing, and blank time points were excluded from paired mean comparison tests. Missing values outside valid points were ignored.

Mean values were calculated for each time point for each patient. The mean (SD) VAS was 1.6 (2.3) for all sites, 1.5 (2.2) for morphine, and 2.0 (2.5) for placebo. The Wilcoxon signed-rank test showed that differences in the assessment of pain between the 2 groups were not significant (Table 2, Fig. 2). Data were tested for