Research Paper

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

Jian Fransén [a,*], Salumeh Bastami [b], Folke Sjöberg [c], Srinivas Uppugunduri [d],
Fredrik R.M. Huss [a,e]

[a] Department of Surgical Sciences, Plastic Surgery, Uppsala University, Sweden
[b] Department of Medical and Health Sciences, Division of Drug Research, Linköping University, Linköping, Sweden
[c] Department of Hand-, Plastic-, and Burn Surgery, University Hospital of Linköping, Linköping, Sweden
[d] Department of Clinical Chemistry and Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden
[e] Burn Center, Dept of Plastic- and Maxillofacial Surgery, Uppsala University hospital, Uppsala, Sweden

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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

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
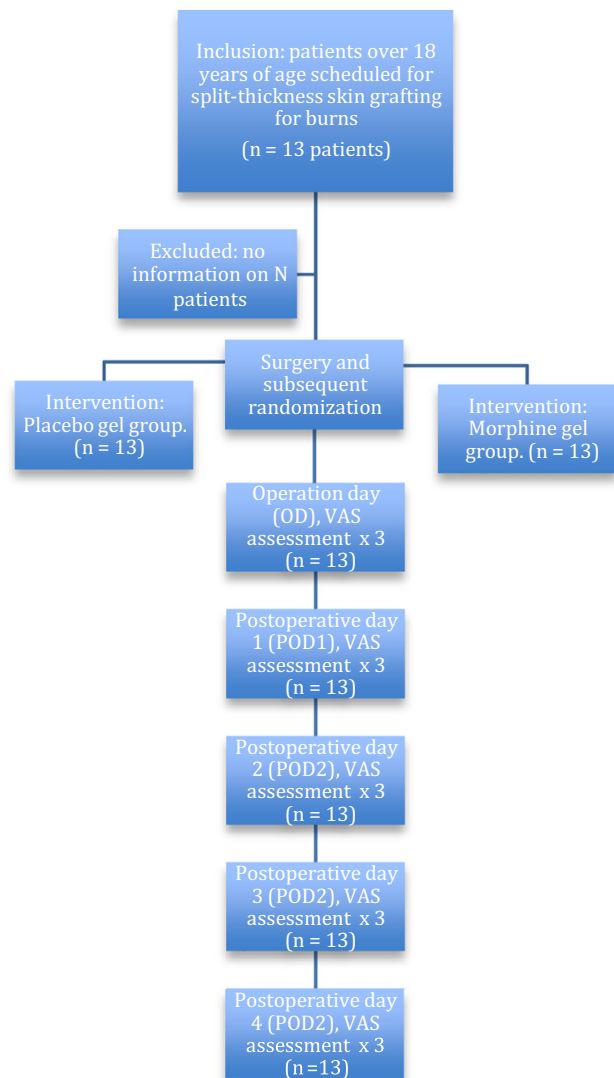

Fig. 1. Flow diagram of study design and execution.

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

Table 1
Clinical data on patients. No adverse events were reported.

Patient no.	Sex	Age	Placebo	Morphine
1	F	23	L, med.	L, lat.
2	F	81	L, ant.	R, ant.
3	M	74	R, lat.ant.	R, med.ant.
4	M	63	R, med.	R, lat.
5	M	85	L	R
6	M	82	R	L
7	M	38	R, lat.	R, med.
8	F	20	R, lat.	R, med.
9	M	51	L, ant.	L, post.
10	M	39	lat.	med.
11	M	63	L, med.	R, lat.
12	M	36	L	R
13	M	38	L, post.	R, post.
Mean	3 F, 10M	53.3		

normality and subsequent paired *t*-tests also showed no significant differences between the groups. We found no significant differences when we compared AUC using non-parametric comparison tests (Table 2, Fig. 2). This was the case for all days or split into individual days. Clinical confounders could not be verified or discarded because of the small sample size.

4. Discussion

Pain at STSG donor sites is an important clinical problem. It is often described as being more severe than at the grafted site [1–3] [16] and empirical observations from our burns centre support this. Data were considered normally distributed but normal *t*-tests, non-parametric tests, and comparison of AUC showed no significant differences. We had to modify AUC comparisons through interpolation, as missing values increase bias. The modification lowered

the risk for bias but was not fully satisfactory [38]. There was no difference between the groups after operation or during the 4 postoperative days. It could be speculated that a larger study with more patients might show significant results. No previous power calculation was made to estimate sample size (Table 2, Figs 2 and 3).

4.1. Molecular mechanisms and clinical deductions

Studies have shown that the proximal perineural application of opioids along non-injured nerves does not produce reliable analgesic effects. To obtain a pronounced and sustained analgesic effect, a combination of injured nerves and endogenously-released peptides is required [34,35]. It is generally thought that nerves in the skin are cut or damaged, or both, when the upper part of the epidermal and dermal layers are harvested, which led us to speculate about the use of topical morphine for pain relief. However, we found that it had no significant effect.

Topical opioids might also have anti-inflammatory effects. The number of peripheral opioid mechanisms of pain control increases with the duration and severity of inflammation, and inflammation further contributes to the antinociceptive effects of opioids through multiple intracellular and extracellular signalling effects [34,35]. Paradoxically, this might indicate that topical morphine has a limited effect immediately after injury but a better effect later on in the healing process, so we continued to assess pain for 5 consecutive days. However, we did not observe any delayed analgesic effect.

4.2. Potential pain-relieving effects of gels and systemic treatment of pain

In contrast to our own clinical experience, we report less pain from the donor sites regardless of treatment. Our results show that the patients reported a VAS of 3 or more in only 17.8% of all time

Table 2
Visual analogue scores (VAS) for use of morphine gel and placebo gel, divided by groups.

	Observations	Mean Placebo	Mean, morphine gel	Mean difference	Wilcoxon paired sign-rank test, p =	AUC comparison using Wilcoxon paired sign-rank test, p =
All	129	1.95	1.48	0.47	0.26	0.22
OD	17	2.14	1.02	1.17	0.09	0.33
POD 1	32	2.08	1.75	0.33	0.5	0.17
POD 2	30	1.85	1.47	0.28	0.28	0.12
POD 3	30	1.67	1.31	0.37	0.48	0.49
POD 4	20	2.89	2.19	0.7	0.08	0.08

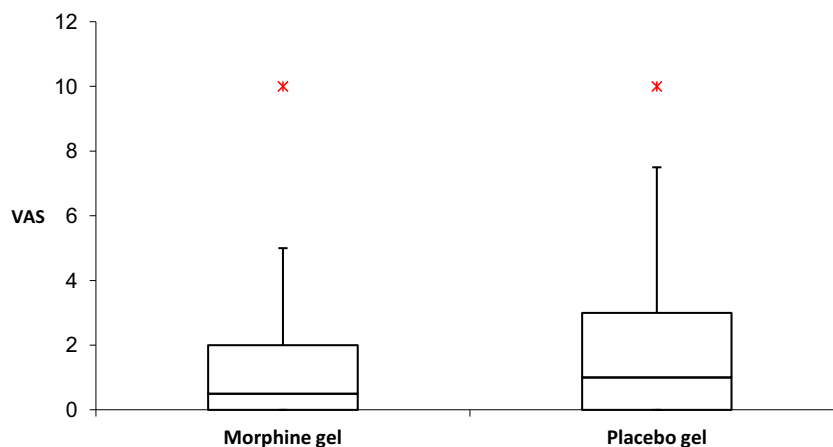OD, operative day; POD, postoperative day.

Fig. 2. Box plot comparing VAS pain scores of morphine gel compared with placebo gel showing different quintiles and outliers.
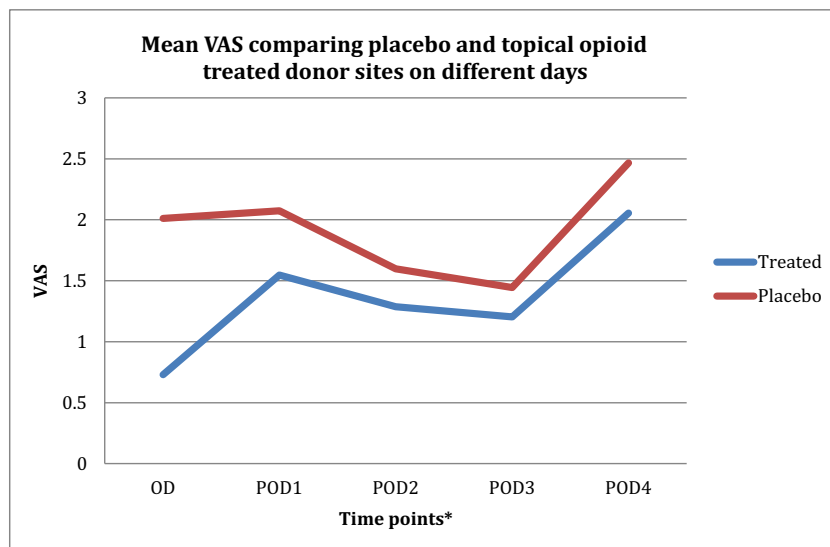
Fig. 3. Line chart comparing VAS pain scores for use of morphine gel versus placebo gel over 5 days.

points. It could be argued that the inert gel-base could be involved in the reduction of pain but a more plausible explanation is the use of concurrent systemic analgesia (the dosage was not documented). Using only polyurethane foam on donor sites (mean area of 68.8 cm^2), Lauchli et al. reported a mean VAS of 0.75 on day 1 and 0.53 on day 5 [14]. Weber et al. used the same polyurethane foam as we did and reported a mean VAS of 0.8 on day 1 and 2.0 on day 5 with a mean donor site area of 89.2 cm^2 [15]. In comparison, these results measuring donor site pain are not considerably higher than those reported in our study.

4.3. Intensity of pain at the donor site

The intensity of pain at the donor site is a matter of debate as it is clinically perceived to be high in comparison with the extent of surgical trauma. However, to our knowledge few clincal studies have focused on pain and have compared different wound dressings instead. Weber et al. showed that the VAS for donor sites dressed with polyurethane foam was lower than that for the operative site [15]. Arigova et al. compared Acticoat (Smith and Nephew) with Allevyn (mean VAS 2.33 and 3.33, respectively, at day 4). They reported higher mean pain scores than those in our study but the VAS had been measured when the dressings were changed [4]. Barnea et al. compared Aquacel (ConvaTec) with paraffin gauze (VAS 3.5 and 2.4, respectively at day 1) and reported higher pain scores than those in our study [1]. When Akan et al. compared conventional harvesting of grafts with use of overlying skin flaps, they reported pain scores with a mean VAS of 5.87 on day 1, which is considerably higher than our findings and more in line with that which is clinically perceived [2]. In a study of wounds dressed with Surgicel (Ethicon) or fine meshed gauze treated with Furacin (GlaxoSmithKline), Uysal et al. reported no pain in 50% and 18.7%, respectively, of the groups [3]. Simultaneous use of systemic pain relief or the choice of anaesthetic during operation are important confounders in studies on pain at donor sites and are not always reported in detail.

4.4. Study limitations and final remarks

In a randomised, placebo study in which different uniform doses of 0.25 mg, 0.75 mg, and 1.25 mg/100 cm^2 were given, there was no significant difference between morphine and placebo [13]. Further

studies need to be done to evaluate the optimum dosage/cm^2 or whether it should be based on the surgeon's preference.

We did not collect data on healing time with or without use of the gel, or patients' coexisting conditions, which might affect healing and the subjective evaluation of pain. Given the rapid action of morphine, closer time points for measurement might give more detailed information on its effects. Also, it would be interesting to study the effects of repeated applications over several days.

We did not detect any adverse events, but more studies need to be done with a larger sample and over longer periods of time to confirm the reliability and non-toxicity of the morphine gel.

5. Conclusions

We found that topical opioid gel does not reduce pain significantly at the donor site after harvest of STSG, and its pain-relieving effects up to 4 days after operation are not significantly better than placebo. Future studies are needed (preferably with larger sample size) to examine the effect of topical opioids and to further our understanding of pain at the donor site.

Ethical Approval

This prospective, paired, randomised, double-blinded, placebo-controlled trial was approved by the regional local ethics committee (Linköping University, Dnr 00-047).

Author Contribution

Jian Fransén: Author of article, analysis and interpretation of data, drafting the article and revising it critically for important scientific content.
Salumeh Bastami: Synthesis of morphine and placebo gel, analysis and interpretation of data, drafting the article and revising it critically for important scientific content.

Folke Sjöberg: Acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important scientific content.

Srinivas Uppugunduri: Acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important scientific content.

Fredrik Huss: Author of article, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important scientific content.

Conflict of interest

The authors declare no conflicts of interest.

Guarantor

The guarantor for this article is Fredrik Huss.

Research registration

The Research Registration UIN is 933.

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