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Research Article

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# Systematic literature review of topical local anaesthesia or analgesia to donor site wounds

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## Abstract

**Background:** Topical local analgesic and anaesthetic agents have been used both pre- and immediately post-harvest on split-thickness skin graft (STSG) donor site wounds (DSW). There is no systematic review of their effectiveness in providing post-harvest analgesia, or of the possible toxic effects of systemic absorption. This study is designed to address the question of which agent, if any, is favoured over the others and whether there are any safety data regarding their use.
**Methods:** Systematic literature review of randomised controlled trials of topical agents applied to STSG DSWs, with a view to providing analgesia. Studies identified via search of Cochrane and EBSCO databases. No restrictions on language or publication year. Primary outcomes: pain at the time of (awake) STSG, and post-harvest pain (up to first dressing change). Secondary outcome was serum medication levels relative to published data on toxic doses. Cochrane risk of bias assessment tool utilised in assessment of included studies. At least 2 reviewers screened and reviewed included studies. A narrative review is presented.
**Results:** There were 11 studies meeting inclusion criteria. Overall methodological quality and patient numbers were low. Topical eutectic mixture of lidocaine and prilocaine pre-harvest affords good local anaesthesia in awake STSG harvesting. Topical bupivacaine (5 studies) or lidocaine (1 study) gave significantly better post-harvest anaesthesia/analgesia than placebo. Topical morphine performs no better than placebo. Topical local anaesthetic agents at reported doses were all well below toxic serum levels.
**Conclusions:** Topical local anaesthetics (lidocaine or bupivacaine) provide good analgesia, both during and after STSG harvest, at well below toxic serum levels, but there are no good data determining the best local anaesthetic agent to use. There is no evidence morphine performs better than placebo.

**Key words:** Local anaesthetic, Donor site wound, Topical analgesia, Lidocaine, Bupivacaine, Morphine, split-thickness skin graft, EMLA

## Highlights

- Topical local anaesthetics provide effective donor site wound analgesia following split-thickness skin grafting.
- The most commonly studied are lidocaine and bupivacaine; there are no strong data to recommend one over the other.
- At doses used in randomized controlled trials, measured serum levels fall well short of toxic levels.
- Morphine gel application to donor site wounds performs no better than placebo.

## Background

### Description of the condition

Skin grafting leaves the patient with two wounds—the recipient site and the donor site wound (DSW). In many cases the DSW is more painful post-operatively [1]. This expectation of greater pain at the donor site, compared to the recipient site, was christened Moriarty's sign by Richard Stark in 1962 [2]. Like Stark's reticence to name the sign after himself, clinicians have historically been similarly reluctant to focus on the DSW. Given the known detrimental effects of pain on wound healing, donor site analgesia is an important part of the package of skin grafting. Pre-harvest local anaesthetic (LA) to the donor site may permit awake harvesting in high-risk general anaesthetic patients. Skin grafting is usually done under general anaesthesia, obviating conscious pain and distress during the surgical procedure. LA to the donor site remains important, both during, but particularly following, the anaesthetic. Since the clinician deliberately creates this wound, there is an imperative to minimize any pain associated with it. Methods employed to achieve this vary. Nerve blocks require specialized knowledge. LA infiltration is simpler and topical application simpler still.

### Description of the intervention

**Topical agents used** There are a number of possible topical agents that have been applied historically to the DSW with a view to decreasing pain. Preliminary literature searching suggests these agents fall into a number of categories.

*Local anaesthetics (LAs)* LAs agents are typically water soluble salts or lipid soluble alkaloids [3]. They consist of a hydrocarbon chain with a lipophilic aromatic ring and a hydrophilic amine at opposite ends of the molecule, and either an ester or an amide intermediary bond. Un-ionized LA molecules cross the phospholipid membrane then dissociate into ionized and non-ionized equilibrium. The ionized form binds reversibly to voltage-gated $Na^+$ channels in a concentration-dependent manner [3].

The only locally occurring LA is cocaine, the archetypal ester. The first synthetic ester, procaine, was introduced in 1904. Lidocaine was the first amide, in 1948. Most subsequent LAs, with the exception of tetracaine, are amides also. The increased cardiac toxicity associated with R(+)-isomers has led to the introduction of S(−)-isomers (single optical isomers). The only commercially currently available examples of these are ropivacaine and levobupivacaine. All other LAs are either racemic mixtures or have no asymmetric carbons.

LAs have a wide range of anti-inflammatory, antimicrobial, antiviral and anti-fungal effects through their action on immune system cells and the synthesis and release of inflammatory mediators. The effects of LA on inflammation-induced capillary hyperpermeability could be related to reduced histamine release from macrophages, leukotriene $B_4$ inhibition, cytokine and oxidant release from activated granulocytes, increased prostacyclin synthesis and endothelial cell cytoskeleton synthesis [3, 4].

As LAs have been found to reduce polymorphonuclear adherence, migration and accumulation at the site of inflammation in *in vitro* studies, concerns have arisen that LA might increase infection susceptibility. On the other hand, antibacterial and antiviral effects of LA have also been reported *in vitro* and *in vivo*, the effects of which are only attained with the use of high systemic concentrations not achieved in regional or local anaesthesia. Precise mechanisms of action are unclear but could be related to LA interaction with bacterial wall or macromolecules at the bacterial cellular surface. A theoretical increased risk of infection therefore exists, but this has not been proven *in vivo* [4, 5].

Animal studies have shown that local infiltration of lidocaine and bupivacaine produce significant histopathological changes and influence local inflammatory/proteolytic factors but do not impair the rate of healing [6–8].

Prilocaine and lidocaine are generally considered to have relatively short duration of action (60–120 min), whereas bupivacaine has a longer duration (240–480 min).

*Analgesics* Analgesics such as non-steroidal anti-inflammatory drugs or opiates (e.g. morphine) have differing methods of action and a number are available as topical treatments. The main mechanism of action of non-steroidal anti-inflammatory drugs is cyclooxygenase inhibition and therefore blockage of arachidonic acid conversion to inflammatory mediators such as thromboxanes, prostaglandins and prostacyclins.

Topical opioids may be anti-inflammatory but also have immunosuppressive effects. Opioids act on endogenous opioid receptors, leading to adenylate cyclase inhibition, with subsequent inhibition of cAMP production and protein kinase A activation. Several immunosuppressive effects of opioids have been reported including suppression of phagocytosis mediated by inhibition of reactive oxygen species (ROS) production, decrease in pro-inflammatory cytokines produced by macrophages and impaired immune cell recruitment to the injury site. Early and transient ROS production and macrophage activity is required for regeneration as seen in animal studies. As a result, opioids, via their immunosuppressive effects, may inhibit the regeneration process [9, 10].

*Frost anaesthesia* Freezing with ice or aerosolized cold sprays (such as ethyl chloride, Freon, dichlorotetrafluoroethane) numbs the skin and has been used for skin grafts [11–21]. The most common agent used for this historically appears to be ethyl chloride.

**Regional practice in Australia and New Zealand** A recent Australasian survey of practices with respect to the paediatric DSW has shown the most commonly used method is LA infiltration; either pre-harvest (20/36 responses, 55.6%) or post-harvest (5/36, 13.9%) [22]. Topical LA is the preferred analgesic method for 7/36 (19.4%) of respondents.

### How the intervention might work

Topical local agents can be used pre-harvest and are most appropriate in a population with multiple co-morbidities in

whom a general anaesthetic may carry too high a risk. They may also be appropriate in resource-constrained settings, to permit skin grafting without general anaesthesia.

Topical local agents may also be used post-harvest, as a simple method of prolonging an LA or analgesic effect at the DSW.

### Potential risks of the intervention

Bupivacaine has a systemic toxicity; with myocardial depression, peripheral vasodilation and central nervous system toxicity. The convulsive dose in monkeys is 4.3 mg/kg, corresponding to serum levels with a mean of 5.51 $\mu$g/mL [23]. Serum levels in children who had convulsions following infusions ranged from 2–10 $\mu$g/mL, though other studies report no seizures in children with serum levels <7 $\mu$g/mL [24]. The maximum recommended dose in humans varies from 2–3 mg/kg [25]. Fischer *et al.* studied the absorption of infiltrated bupivacaine at 3 mg/kg in children undergoing split-thickness skin graft (STSG) [26]. In their study of 14 patients none had subsequent serum bupivacaine levels >1.2 $\mu$g/mL, well below toxic levels. The time to maximum blood level was 8.9 ± 1.7 h post-instillation, with 12/14 patients still having measurable levels at 24 h. It is reasonable to expect topical application would result in lower serum levels than subcutaneous instillation.

The toxic level of lidocaine differs between the conscious patient (3–5 $\mu$g/mL) and the anaesthetised patient (10 $\mu$g/mL) because of the protective effect of anaesthesia [27]. A number of studies have examined serum concentrations following topical LA gels (lidocaine, lidocaine/prilocaine) at concentrations from 2–5% to DSWs [27–29]. Levels typically peaked at 5-6 h. A single patient in one study had a peak serum level in the potentially toxic range [28].

Studies appear to show no correlation between serum LA levels and size of the DSW, although numbers are small [28, 30]. A correlation between the surface area treated and urinary excretion of lidocaine has been demonstrated, though again with low numbers [28]. A larger study (146 patients) involving pre-harvest application of a 5% eutectic mixture of lidocaine and prilocaine (EMLA) demonstrated a correlation between both size of the application area and duration of application [29].

### Why it is important to do this research

There are several topical methods described in the literature. Some, such as freezing of local tissues prior to STSG, appear to have fallen out of favour. Others use a variety of LA agents. This study is designed to address the question of which agent, if any, is favoured over the others and whether there are any safety data regarding their use.

### Objectives

To assess the effects of topical agents applied to the DSW with the intention of providing local analgesia.

## Methods

### Criteria for considering studies for this review

**Types of studies** This review includes all randomized controlled trials (RCTs), irrespective of language and publication status. Excluded are quasi-randomized studies (e.g. alternate allocation, allocation by date of birth or by medical record number).

**Types of participants** People of any age in any setting who have a DSW created as a result of harvesting a STSG are included. The DSW may be created as an elective or an emergency procedure. Only studies involving human participants are considered. STSGs may be harvested for any cause (e.g. burns, trauma, pressure ulcers).

**Types of interventions** Included are studies in which any widely available agent is applied to a DSW with a view to promoting analgesia. Anticipated likely comparisons include:

- comparisons of liquids, gels or freezing sprays against each other or against a control
- different strengths compared against each other

**Types of outcome measures** Outcomes are grouped by the following definitions:

- at harvest: pain recorded at the time of awake harvesting of STSG
- post-harvest: pain recorded at least 1 h following harvesting of STSG

### Primary outcome

Donor site pain is the primary outcome. Pain may be recorded during STSG harvest or post-harvest up to first dressing change.

Studies with pain scores that do not distinguish donor site pain from generic pain are excluded. Pain may be measured using validated scales or other objective measures. Patient self-reports of pain only, rather than observer reports, will be analyzed in the first instance.

### Secondary outcome

Serum levels are a secondary outcome. The main outcome of interest is a peak serum level above toxic levels (see above).

### Search methods for identification of studies

**Electronic searches** Relevant trial reports were retrieved from the following databases:

- the Cochrane Wounds Specialized Register
- the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (latest issue)
- EBSCOhost MEDLINE (from 1946 onwards)
- EMBASE
- CINAHL

There were no restrictions of the searches with respect to language, date of publication or study setting. The search strategy for MEDLINE is shown in Figure 1.

The following clinical trials registries were also searched for ongoing studies:

- ClinicalTrials.gov (www.clinicaltrials.gov)
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch)
- EU Clinical Trials Register (www.clinicaltrialsregister.eu/ctr-search/search)

The following databases were searched to identify reports of relevant trials published in conference abstracts and theses:

- ProQuest COS Conference Papers Index (from 1982 onwards)
- ProQuest Dissertations & Theses Global (from 1861 onwards)

**Searching other resources** Reference lists of retrieved included trials were checked to identify other potentially eligible trials or ancillary publications, as well as relevant systematic reviews, meta-analyses and health-technology assessment reports.

### Data collection and analysis

Two reviewers independently screened titles, abstracts and keyword or descriptor terms of the retrieved articles for potential relevance. If initial assessment suggested potential inclusion then full-text copies were obtained. Full articles were retrieved in ambiguous cases and in cases where a single author identified a study for potential inclusion.

Two reviewers then independently further assessed the retrieved articles for final selection. Discrepancies were resolved by discussion and consensus, with a third casting vote where necessary. All data extractors have clinical experience in burns and/or experience in prior systematic reviews. Reasons for exclusion of those studies where full text was retrieved were recorded.

### Data extraction and management

Each reviewer was assigned a share of the included studies (two reviewers per study). A data extraction sheet was used to summarise each study. Duplicated studies had their data recorded once only, with all reports used to maximize data extraction. Where there were missing data from reports, study authors were contacted to request this information. Discrepancies were resolved by discussion and consensus amongst all reviewers. If there was no consensus the majority opinion applied. Where studies had intervention arms that were not eligible, only data from intervention and control arms that met eligibility criteria were extracted.

The following data, by treatment group and for relevant time points where appropriate, was extracted:

- year of publication, or publication status if unpublished
- country of origin and care setting
- trial design (e.g. parallel, cluster)
- study registration
- pre-published protocol
- randomization method and unit of randomization (patient or wound)
- allocation method
- blinding of allocation and/or outcome assessment
- duration of follow-up
- funding source/s
- declarations of potential conflicts of interest
- number of participants or wounds randomized to each trial arm
- unit of analysis (patient or wound)
- type of wound being grafted (e.g. burn, venous ulcer)
- primary and secondary outcome/s, with definitions and time points
- outcome data for primary and secondary outcomes (by group)
- measurement scales used for outcomes and rationale for use
- number of withdrawals (by group)
- intervention received by each group
- duration of treatment
- concurrent interventions

These data were used to populate results tables for individual studies and to facilitate risk-of-bias assessments for each study (Table 1).

### Assessment of risk of bias in included studies

Two reviewers independently applied the Cochrane tool for assessing risk of bias to the included studies [31]. Blinding and the completeness of outcome data were assessed for each outcome separately. A 'risk of bias' table from the available data for each eligible study is presented. Any disagreement was discussed until consensus. If there was no consensus, a third reviewer had a casting vote.

### Assessment of heterogeneity

Preliminary searching revealed such extensive clinical, methodological and statistical heterogeneity that is was apparent at the outset that a meta-analysis would not be possible. A narrative review only was therefore planned. This falls outside the boundaries permitted for pre-registration with PROSPERO. Nonetheless, the study was performed according to standard criteria.

## Results

The PRISMA diagram for the review is shown in Figure 2.

### Risk of bias assessment

Blinding and the completeness of data were assessed for each outcome separately (Table 2). For the majority of studies it was difficult to determine the nature of these, and thus

**#1** MH "Anesthesia, Local" OR MH "Anesthetics, Local"

**#2** analgesia OR anesthetic* OR anaesthetic*

**#3** MH "Administration, Topical"

**#4** topical* OR local*

**#5** TI gel OR TI aerosol OR TI cream or TI lotion OR TI foam OR TI spray OR TI salve

**#6** #1 OR #2 OR #3

**#7** #4 OR #5

**#8** #6 AND #7

**#9** MH "Transplant Donor Site" OR MH "Transplantation, Autologous" OR MH "Skin Transplantation"

**#10** "split thick*" OR "split-thick*" OR "split skin" OR "partial dermal" OR "partial-dermal" OR "partial thick*" OR "partial-thick*"

**#11** (skin N# Graft*) OR ((Skin OR Derm*) N3 transplant*)

**#12** #9 OR #10 OR #11

**#13** #8 AND #12

**Figure 1**. Search strategy for Medline via EBSCOhost for systematic literature review of topical donor site analgesia in split-thickness skin grafting

most have been marked 'unclear' accordingly. No study had a pre-published protocol. No trial was registered in a trials database.

### Summary of included and excluded studies

**Excluded studies after full-text review** Following full-text review, 65 studies were excluded. These studies, and the reason/s for exclusion, are included in the online supplementary material. There were no RCTs investigating the use of a freezing agent. Five studies investigated the use of ketocaine. As this agent is only available in Italy these studies were excluded from analysis.

**Included studies after full-text review** Following full-text review, 11 studies were included (Table 3). There were 6 studies investigating bupivacaine as a topical agent (1 of which compared it to lidocaine) [25, 30, 32–35]. There were 2 EMLA and 2 morphine studies [36–39]. There was a further study comparing lidocaine against a placebo control [40]. There was too much heterogeneity on visual inspection of study methodologies and outcome measures to be able to perform a meta-analysis. Thus a narrative review only was undertaken.

### Primary outcome—donor site pain

Nine of the 11 studies measured donor site pain at time of harvest or post-harvest. Of these, the majority investigated the use of bupivacaine for post-harvest analgesia. There were 2 RCTs investigating the use of morphine for post-harvest analgesia and 2 studies investigating the use of EMLA for

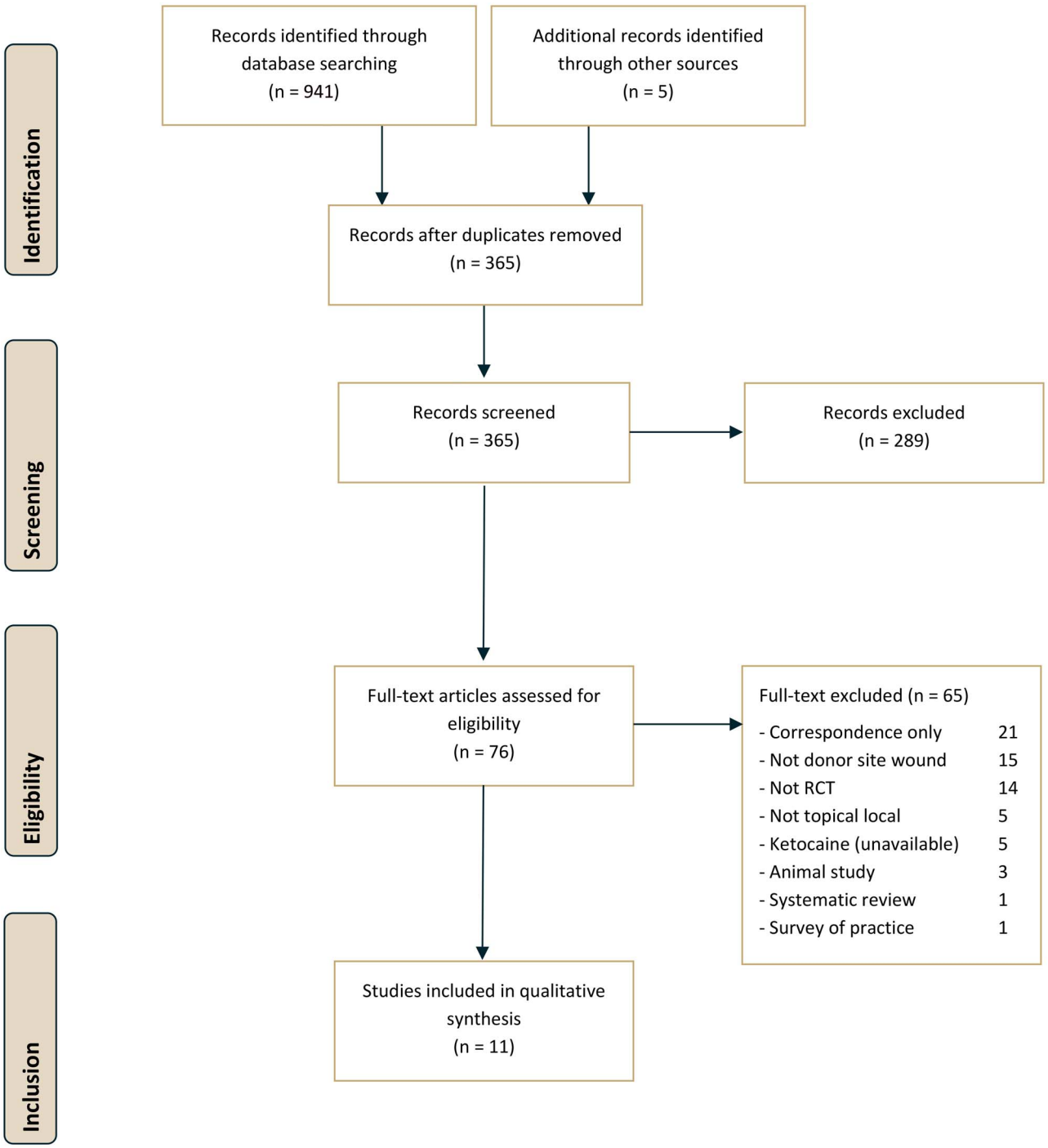



**Figure 2.** PRISMA flow diagram for systematic literature review of topical donor site analgesia

analgesia at the time of awake STSG harvest. There were no RCTs of other agents that met the inclusion criteria.

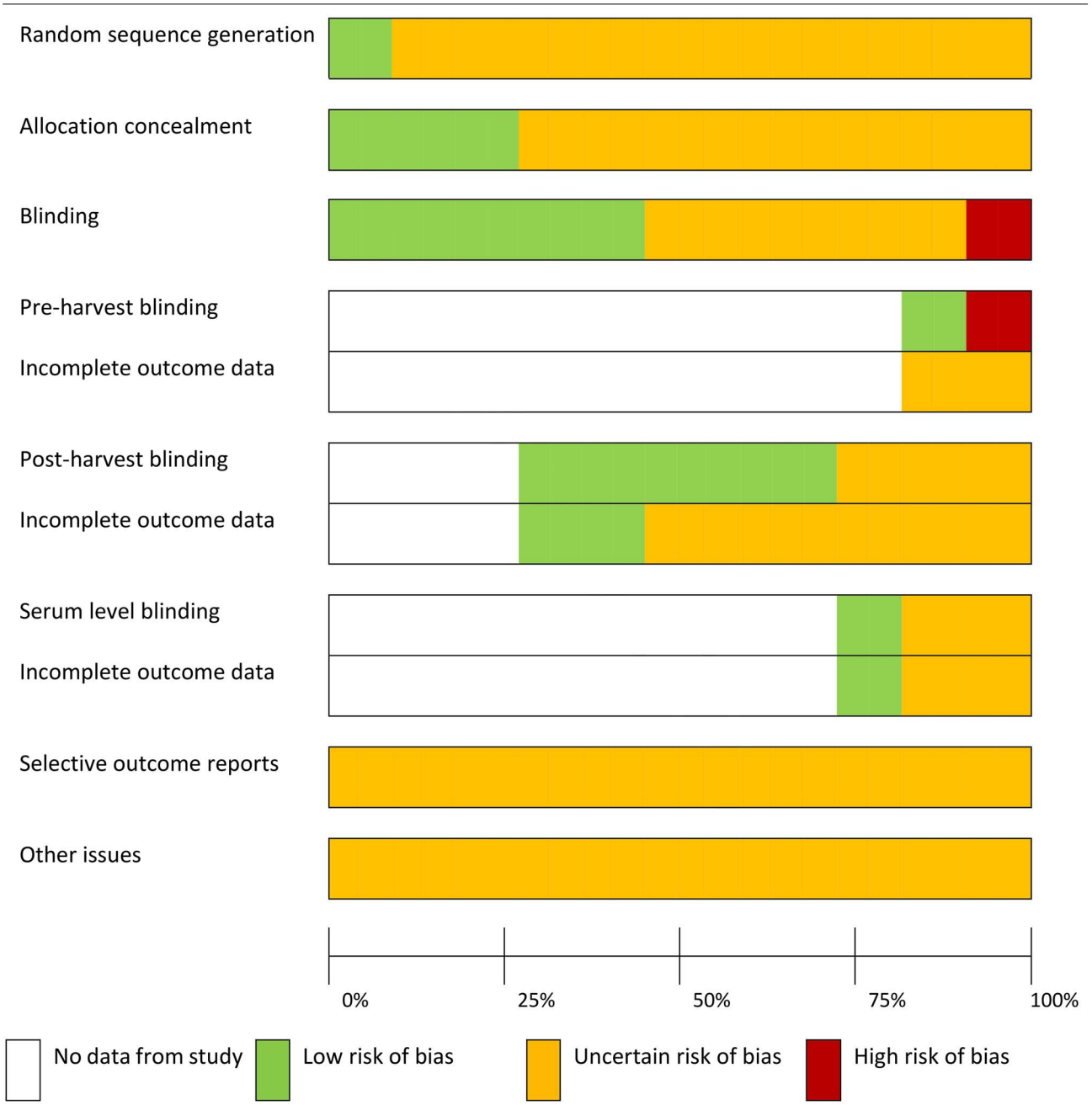
**Pain during STSG harvest** Two studies investigated pre-harvest EMLA and its analgesic effect at the time of STSG [36, 37]. Läteenmäki *et al.* [36] compared two different doses of EMLA (30 and 60 g) in 78 patients. Pain scores were 'none' in 54 patients, 'slight' in 16 and 'moderate' or 'severe' in 6 (3 in each group). There were no significant differences between the two groups of patients. Goodacre *et al.* compared EMLA with infiltrated 0.5% lidocaine with adrenaline 1:200,000 [37]. Mean visual analogue scale (VAS) pain scores (100-point scale) at STSG harvest were 8 and 11 in the EMLA and local infiltration groups respectively, with no significant differences between the two groups.

**Table 1.** Risk of bias assessment of included studies, with reported outcomes

| | Sequence generation | Allocation concealment | Blinding | Blinding (Pre) | Incomplete outcome data (Pre) | Blinding (Post) | Incomplete outcome data (Post) | Blinding (Serum) | Incomplete outcome data (Serum) | Selective outcome reports | Other issues |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Bupivacaine studies** | | | | | | | | | | | |
| 2014 Raza *et al.*[32] | + | + | + | | | + | + | | | + | + |
| 2002 Jenwitheesuk *et al.*[33] | + | + | + | | | + | + | | | + | + |
| 1999 Jellish *et al.*[34] | + | + | + | | | ++ | + | + | + | + | + |
| 1998 Alvi *et al.*[30] | + | + | + | | | | | + | + | + | + |
| 1993 Butler *et al.*[25] | + | + | ++ | | | + | + | | | + | + |
| 1990 Morris & Lamb [35] | + | + | + | | | ++ | + | | | + | + |
| **Lidocaine studies (also Butler *et al* above)** | | | | | | | | | | | |
| 2014 Desai *et al.*[40] | ++ | ++ | ++ | | | | | ++ | ++ | + | + |
| **EMLA studies** | | | | | | | | | | | |
| 1988 Lähteenmäki *et al.*[36] | + | ++ | ++ | ++ | + | | | | | + | + |
| 1988 Goodacre [37] | + | + | -- | -- | + | | | | | + | + |
| **Morphine studies** | | | | | | | | | | | |
| 2016 Fransén *et al.*[38] | + | ++ | ++ | | | ++ | ++ | | | + | + |
| 2014 Zaslansky *et al.*[39] | + | + | ++ | | | ++ | + | | | + | + |

*EMLA* eutectic mixture of local anaesthetics

**Table 2.** Summary risk of bias for reported outcomes from included publications




**Post-STSG harvest analgesia** Two studies investigated the use of morphine gel at various strengths against placebo [38, 39]. Neither study demonstrated significantly improved pain scores when compared to placebo.

Five studies used topical bupivacaine at various doses (0.25, 0.5%) with or without adrenaline [25, 32–35]. For the most part, the studies used an intravenous preparation of bupivacaine, though one study used bupivacaine gel. Saline (0.9%) was the most common comparator, although 2% lidocaine and ketoprofen gel were also comparators.

Three studies (105 patients) showed a significant benefit of bupivacaine over inert control (0.9% saline, or same dressing without bupivacaine), as measured by pain scores or the requirement for rescue analgesia [25, 32, 33]. Jellish *et al.* [34] reported best results with 2% lidocaine immediately post-operatively and at 6, 8 and 24 h. In that study the lidocaine group had the smallest DSW area [8% total body surface area (TBSA)] compared with the saline control arm (10% TBSA) or the bupivacaine arm (12% TBSA). Morris and Lamb [35] studied 40 patients in their 4-arm trial. The majority of

**Table 3.** Studies investigating the analgesic effects of topical local anaesthesia on donor site wounds following split-thickness skin grafts

| Study | Method | Results |
|---|---|---|
| **Bupivacaine or lidocaine** | | |
| Raza *et al.* [32] | RCT with 75 patients in each arm.<br>12 mL/100 $cm^2$ 0.25% bupivacaine *vs* 12 mL/100 $cm^2$ 0.9% NaCl; repeated at 12 hour intervals.<br>VAS pain scale every 6 h. Rescue analgesia if VAS > 4. | 5/75 Patients given rescue analgesia in bupivacaine arm *vs* 72/75 in NaCl arm ($p < 0.001$). |
| Jenwitheesuk *et al.* [33] | RCT with 20 patients in each arm.<br>0.5% Bupivacaine 6 mL/100 $cm^2$ *vs* saline 6 mL/100 $cm^2$ to STSG DSW every 12 h via wound catheter.<br>NRS (0–10) at 24, 48, 72, 96 and 120 h. | Significant improvement in pain scores days 1–4 ($p = 0.001$) and day 5 ($p = 0.05$).<br>Bupivacaine / Saline<br>Day 1: 1.4 / 4.8<br>Day 2: 0.8 / 3.5<br>Day 3: 1 / 3<br>Day 4: 0.7 / 3<br>Day 5: 1.2 / 2.2 |
| Butler *et al.* [25] | RCT of 45 patients.<br>Dry Kaltostat vs. Kaltostat/20 mL saline vs. Kaltostat/20 mL 0.5% bupivacaine. | Pain scores 3–4 on linear analogue scale for no local anaesthetic groups, compared with scores of ~1 for bupivacaine group ($p < 0.04$). No difference in pain scores across the three groups at 72 h (pain scores ~1). |
| Jellish *et al.* [34] | Double-blind RCT of 60 patients.<br>0.9% NaCl *vs* 0.5% bupivacaine *vs* 2% lidocaine. Each solution also contained 1:200,000 epinephrine.<br>Pain scores post-operatively. Morphine given if pain scores >5. | Pain scores significantly lower in lidocaine group than other two groups immediately post-operatively, and at 6, 8 and 24 h post-discharge from post-anaesthetic care unit.<br>Lidocaine group smaller graft area (8%TBSA *vs* 10% in NaCl and 12% in bupivacaine arms). |
| Morris and Lamb [35] | Randomized 4-arm trial.<br>9 patients bupivacaine (0.25% plus adrenaline 1:400000) and Scarlet red, 9 epinephrine and Scarlet red, 11 bupivacaine/adrenaline and Opsite, 11 Opsite only. | Majority of patients in each arm reported no pain (30/40).<br>Use of bupivacaine on donor sites did not reduce pain. |
| **EMLA** | | |
| Lähteenmäki *et al.* [36] | Randomized, double-blind multicentre trial of 78 patients.<br>Eutetic mixture of lidocaine and prilocaine: 30 g/200 $cm^2$ (40 patients) or 60 g/200 $cm^2$ (38 patients) prior to STSG harvest (115–300 min dwell time on skin). STSG harvested awake. | 30 g / 60 g<br>No pain: 29 / 25<br>Slight pain: 7 / 9<br>Moderate pain: 2 / 1<br>Severe pain: 1 / 2 |
| Goodacre *et al.* [37] | 80 patients randomized to EMLA topically or 0.5% lidocaine with 1:200,000 adrenaline infiltration before awake STSG harvest.<br>VAS 0–100 and verbal rating scales of pain during harvesting. | Mean VAS scores 8 (EMLA) *vs* 11 (lidocaine). Not significant.<br>No significant differences in verbal rating scale pain scores (none, slight, moderate, severe). |
| **Morphine** | | |
| Fransén *et al.* [38] | Randomized paired double-blind placebo controlled trial.<br>13 patients with thigh DSW.<br>2 mL placebo gel *vs* 2 mL morphine hydrochloride 1 mg/mL<br>Pain assessed 3x daily for 5 days using VAS (0–10) | No significant differences between the two arms. Mean (SD) VAS 1.5 (2.2) for morphine group and 2.0 (2.5) for placebo. |
| Zaslansky *et al.* [39] | Single-centre prospective double-blind placebo controlled multi-arm trial. 44 patients.<br>STSG under GA, 2 mL of gel per 100$cm^2$ DSW area<br>• Placebo<br>• 0.25 mg/100 $cm^2$ morphine<br>• 0.75 mg/100 $cm^2$ morphine<br>• 1.25 mg/100 $cm^2$ morphine<br>Pain scores at 2, 3, 4, 6, 8, 24 h using 0–10 NRS | No significant differences in pain scores across the four groups of patients. |

*DSW* Donor site wound, *EMLA* eutectic mixture of local anaesthetics, *NRS* numeric rating scale, *RCT* randomized controlled trial, *STSG* split-thickness skin graft, *TBSA* total body surface area, *VAS* visual analogue scale

**Table 4.** Studies investigating systemic toxicity of topical local anaesthesia/analgesia on donor site wounds following split-thickness skin grafts

| Study | Method | Findings |
|---|---|---|
| Desai *et al.* [40] | Single-centre, randomized, double-blind, parallel pilot RCT. 28 Patients.<br>13 patients—4% lidocaine (Xylocaine™) as lidocaine hydrochloride aqueous solution.<br>15 patients—3% lidocaine base emulsion formulation (NOPAYNE™).<br>Serum samples pre- and post-dressing. | Plasma concentrations in 3% emulsion group (NOPAYNE™)—all below 0.1 $\mu$g/mL.<br>2 Patients in 4% lidocaine group had levels of 0.6 $\mu$g/mL and 0.3 $\mu$g/mL. All others <0.1 $\mu$g/mL.<br>No relationship between dose and plasma concentration for NOPAYNE group, but linear correlation for 4% lidocaine group. |
| Jellish *et al.* [34] | RCT with 60 patients, 20 in each arm.<br>2% Lidocaine, 0.5% bupivacaine, 0.9% NaCl topical post-harvest (all with 1:200,000 adrenaline). No volumes stated.<br>Serum samples at 5, 15, 30, 60, 90, 120, 180, 240 and 360 min. | Plasma levels noted at 5 min. Peak levels 30–60 min after the initial application of the local anaesthetic.<br>Concentrations declined thereafter, with measurable levels still present at 6 h.<br>All levels <2 ng/mL. |
| Alvi *et al.* [30] | 12 patients, 6 in each arm. Results for 5 patients in each arm.<br>Bupivacaine gel (2.5 mg/mL) and ketoprofen gel (1.6 mg/mL) post-harvest. No volumes stated. Donor site up to 200 $cm^2$.<br>Serum samples at 10, 20, 30, 60, 120, 240 and 480 min. | Plasma levels first measurable at 10–30 min for both agents, depending on patient.<br>Peak levels at 120 min for both agents.<br>Highest plasma bupivacaine 0.1 $\mu$g/mL (toxic level 4 $\mu$g/mL).<br>Highest plasma ketoprofen level 0.27 $\mu$g/mL (toxic level 1128 $\mu$g/mL). |

*RCT* randomized controlled trial

patients (30/40) reported no pain. The bupivacaine group did not have lower pain scores.

### Secondary outcome—serum levels

Three studies assayed serum levels of topical agents (Table 4). Their results are outlined below.

Alvi *et al*. studied the absorption of bupivacaine gel (2.5 mg/mL) in 5 patients [30]. Peak bloodstream bupivacaine levels were seen at 120 min (mean 0.07 $\mu$g/mL, range 0.03–0.10). The next sampling point was 240 min, with lower levels recorded at this timepoint in most patients. Jellish *et al*.'s study also showed safe levels in plasma of both bupivacaine and lidocaine, with higher levels in the lidocaine group. These levels peaked at 30–60 min post-application and were still recordable in serum 6 h later [34]. Measured serum levels of lidocaine were also well below toxic levels in the study by Desai *et al*. [40].

**Infection or other wound complications** Within the LA studies the majority of authors did not report on wound complications such as infection or delayed healing [25, 30, 32, 40], or reported no difference in complication rates [33–35]. EMLA and morphine studies showed no significant differences in other outcomes measured [36–39].

## Discussion

### Local anaesthetic/analgesic agents to the donor site wound

Based on the limited, small population and heterogenous RCTs included in the systematic review, bupivacaine and lidocaine appear more effective than placebo for post-harvest pain [25, 32–35, 40]. Topical morphine is no better than placebo [38, 39]. EMLA was not significantly better than lidocaine infiltration pre-harvest for analgesia at time of harvest [37].

In the included studies several application methods were used (direct application followed by dressing, LA-soaked definitive dressing, LA-soaked dressing subsequently removed, LA instillation via catheter into the dressing). Awake catheter instillation into the wound was associated with increases in pain scores [32, 33]. Furthermore, these studies did not show an increased length of action and so there are no data to recommend this method over simple LA application at time of dressing. Given the safe serum profile of LA application, there is no need to remove and replace an LA-soaked temporary dressing. LA can safely and effectively be incorporated into the definitive dressing at the time of STSG harvest.

**Pre-harvest EMLA** One small study shows that EMLA does not perform better than lidocaine infiltration, in terms of pain relief. EMLA cannot be applied post-harvest due to the risk of methaemoglobinaemia from absorption through a de-epithelialized surface [41]. There are also data demonstrating that EMLA application leads to increases in skin thickness of up to 0.004 inches, well within the typical tolerances used when determining STSG thickness [42]. If this method is to be used, then adjustments may have to be made to dermatome settings to compensate. There are some data suggesting that thinner STSGs lead to decreased donor site scarring at 3 and 6 months [43]. There are no studies exploring the effects on

re-epithelialization or scarring at either the donor or graft site where pre-harvest EMLA is used, so no conclusions can be drawn.

**Lidocaine *vs* bupivacaine** Lidocaine performed better than bupivacaine in the only study comparing two different active agents [34]. This study however had small numbers for each group and was underpowered. All other studies compared against an inert control, differing doses of the same agent or against subcutaneous infiltration. It is difficult to explain the observed sustained effect of lidocaine over bupivacaine given their known durations of action, but the initial faster effect may be explained by the faster average onset of action of lidocaine. The analgesic effect for either agent also appears to be sustained far longer than their expected duration of action.

Based on our findings, use of topical lidocaine or bupivacaine alleviates pain effectively but there are inadequate data currently to determine the better agent.

**Topical *vs* infiltrated LA** Only one study, by Goodacre *et al*. [37], compared topical (EMLA) vs. infiltrated LA (0.5% lidocaine with 1:200,000 adrenaline). There was no significant difference in outcomes between the two groups in this study.

### Risk of systemic toxicity from topical LA

All of the studies cited above, using bupivacaine (0.5% intravenous preparation or 2.5 mg/mL gel) or lidocaine (4 or 2% intravenous preparation, 3% emulsion) showed peak plasma levels well below toxic levels for either anaesthetized or awake patients. Data regarding actual volumes of LA used are lacking in some of the above studies. In the absence of more accurate absorption curves, and even taking into account the lower absorption when comparing topical to intravenous, it seems reasonable therefore to limit topical LA to the presumed safe intravenous dose.

The addition of adrenaline may slow and flatten absorption curves through its vasoactive effects at the wound bed. This is commonly a desired effect to limit DSW bleeding under dressings. However, there are no data directly comparing solutions with and without adrenaline in this review.

S(−)-Enantiomers (ropivacaine, levobupivacaine) may be even safer at higher doses, but there are no data available in this setting from which to draw a conclusion.

### Study limitations and implications for practice, policy and future research

This systematic review highlights the lack of high-quality data comparisons to definitively determine the optimal topical LA or method of application for the management of donor graft site. With the exception of one study, there was rather uncertain to high risk of bias in the included studies, often due to lack of a clear description of the methodology [40]. Study heterogeneity rendered meta-analysis unfeasible. There were no dedicated paediatric RCTs and all studies included only adult patients.

## Conclusions

Application of topical LA to the donor site post-harvest is a simple method with proven efficacy compared to placebo. Good quality studies on this topic are limited, with inadequate data/comparisons to determine the best type of LA or method of application. Morphine gel application performs no better than placebo and should not be used for this purpose. Current data support the use of lidocaine or bupivacaine as a topical LA for application to donor site wounds post-harvest or EMLA pre-harvest. No other topical agents have been shown to be effective in RCTs. Serum levels at the doses used in studies fall well short of toxic levels. It seems reasonable at present to limit topical LA doses to the equivalent maximum established safe intravenous dose, as there are no studies exploring safe maximums for topical application. There are no RCT data available for other agents, particularly S(−)-isomers such as ropivacaine or levobupivacaine, which may remain safe at higher doses. For small to medium-sized grafts, where the surface area permits safe volumes of LA, topical LA provides effective and safe analgesia. This systematic literature review highlights the importance of further research into a simple yet effective method for pain management in donor site wounds.

## Abbreviations

DSW: Donor site wound; EMLA: eutectic mixture of local anaesthetics; LA: Local anaesthetic; NRS: Numeric rating scale; RCT: Randomized controlled trial; ROS: Reactive oxygen species; STSG: Split-thickness skin graft; TBSA: Total body surface area; VAS: Visual analogue scale.

## Supplementary material

Supplementary material is available at *BURNST Journal* online.

## Conflict of interest

None declared.

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