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Effectiveness of a topical local anaesthetic spray as analgesia for dressing changes: A double-blinded randomised pilot trial comparing an emulsion with an aqueous lidocaine formulation☆

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ABSTRACT

Background: Partial thickness skin graft wounds are painful. Topically applied lidocaine has been used for analgesia in several clinical trials. This study compared the effectiveness of two different formulations of topical local anaesthetic for dressing changes of partial thickness skin graft donor sites.

Methods: A double-blind randomised controlled, pilot trial was conducted in 29 patients undergoing split thickness skin graft surgery. Subjects were randomised to either a 3% lidocaine emulsion formulation "Treatment E" (NOPAYNE™) or a 4% aqueous solution "Treatment A" (Xylocaine™). Subjects received one spray per 3 cm^2 of donor site area followed by up to two further spays as required. Endpoints included pain intensity measured by the numerical rating scale (NRS) up to 1 h after dressing change commencement, sting sensation, overall satisfaction and lidocaine plasma concentration.

Results: The 60 min pain scores for E and A were 1.3 ± 0.3 (mean ± SEM) and 1.8 ± 0.4 ($p = 0.98$) respectively. Nearly 90% of patients were very satisfied with their treatment. The mean plasma concentrations of lidocaine for A and E were 0.132 mg/l and 0.040 mg/l respectively ($p = 0.069$).

Conclusion: The topical local anaesthetic formulations achieved low pain scores during dressing changes. The safety profile was potentially improved with the emulsion formulation of lidocaine.

☆ Clinical trial registration number: EC 2008/183.

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1. Introduction

Burns are among the most painful and severe forms of injuries affecting the human body [1]. The pain of repeated therapeutic procedures such as skin debridement and grafting procedures is the biggest challenge-faced by patients during recovery from a burn [2]. Procedural pain is short in duration but very intense [3].

The use of multimodal analgesia is the cornerstone of the management of patients with burns similar to many other acute settings [4]. Besides opioids, paracetamol, NSAIDs and gabapentin/pregabalin among others are used. However, procedural pain with dressing changes often remains quite severe, even when opioids are administered to a maximum safe dose. Other analgesics have therefore been used for burns dressing changes [2].

Local anaesthetics have been used for pain relief in burns as a topical gel or IV infusion and are an obvious choice in regional blockade for wound care procedures. Lidocaine (1 mg/kg) applied topically to wounds has been found to significantly reduce traumatic and postoperative pain and analgesic intake, without apparent adverse effects on healing [5,6]. Lidocaine has potent anti-inflammatory effects, which may also present an advantage for its application at a wound site during dressing changes [1].

However, the use of lidocaine on wounds carries the risk of systemic absorption. High concentrations of lidocaine have the potential for CNS toxicity (e.g. seizures) (>5 mg/l) and CVS toxicity (e.g. arrhythmias) (>9 mg/l) [5]. The maximum recommended single dose of lidocaine is 3 mg/kg up to 200 mg [7]. However, higher doses have been reported in topical application [8]. The plasma concentration of lidocaine will depend upon drug dose, rate of absorption, patient weight and physical status. The plasma concentration also depends on the thickness of skin harvested [9].

Most topical local anaesthetic products are non-sterile and available in an aqueous based gel or cream formulations and contain lidocaine in a salt form. In practice, sterile local anaesthetic products are administered directly from ampoules and vials, which lack accurate dosing.

A sterile emulsion based formulation of lidocaine 3% in the base form (NOPAYNE™) has been designed so that it remains localised at the wound site and, has the potential to reduce the risks of systemic absorption and toxicity. Thus far no study has reported the role of emulsion based topical local anaesthetics as analgesia for dressing changes at a partial thickness skin graft donor site. The aim of this study is to compare aqueous and emulsion topical lidocaine preparations at the time of first donor site dressing change of a post-split thickness skin graft with specific reference to pain control and systemic absorption.

2. Methods

2.1. Clinical trial

The study was a single centre, randomised, double-blind, active-controlled, parallel pilot trial to compare a topical 4% lidocaine as lidocaine hydrochloride aqueous solution ''Treatment A'' (Xylocaine™ as standard) with a 3% lidocaine base emulsion formulation ''Treatment E'' (NOPAYNE™). Subjects were allocated at random to receive either treatment A or E. The study was conducted in the State Adult Burns Unit and Burns Outpatient Dressing Clinic at Royal Perth Hospital (RPH), Western Australia for a period of seven months. The study was registered under, and approved, by the Ethics committee of Royal Perth Hospital (RPH) in April 2009 (Reg. No.: EC 2008/183). The study interventions were administered by registered medical and nursing staff of RPH, working in the Burns Service. The patients were prescribed only oral analgesics for pain management. The Clinical Trials Pharmacy was responsible for the dispensing of trial drugs. Plasma concentrations were measured by a central facility (Chemcentre WA) accredited by the National Association of Testing Authorities (NATA). Subject eligibility was based on the following inclusion and exclusion criteria.

Inclusion criteria: (eligible subjects must satisfy all of these criteria):

- Patients undergoing skin grafting of an area less than 2% of their body surface area.
- Written informed consent.
- Able to self-assess and report their pain level.
- Aged 18–55 years.

Exclusion criteria (eligible subjects must not satisfy any of these criteria):

- Pregnancy.
- Known hypersensitivity to lidocaine.
- Major renal or hepatic dysfunction.
- Participation in other clinical trials.
- History of allergy to sulfides, lidocaine or mepivacaine.

All split grafts were performed using an air driven dermatome. The trial evaluated the first donor site dressing removal only and subsequent dressing removals were managed according to normal clinical practice. Follow up swabs of the donor site for microbiology was only done when clinically indicated.

2.2. Randomisation

The trial participants were randomised by the central Clinical Trials Pharmacy at RPH by a computer generated random number. The randomisation was organised using a blocking strategy to ensure that accumulation of subjects to the two treatment arms occurred at an approximately equal rate (block length was fixed at 10). The allocation sequence was held exclusively by the Clinical Trials Pharmacy which had no clinical involvement in the implementation of the trial treatment.

2.3. Blinding

All clinical staff involved in managing the study participants (nursing staff, medical staff), the study investigator and trial

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coordinator (responsible for data handling and storage), as well as the participants themselves, were blinded to the treatment allocation.

The trial and control sprays were dispensed in identical amber spray bottles labelled identically (''Lidocaine 3% or 4% spray-NOPYANE™ Study'') by the clinical trial pharmacy staff.

Assessments of pain and collection of other trial data including blood pressure and heart rate were performed by nursing staff. The procedure for administering both treatments was identical. The dataset was un-blinded only at the conclusion of the study, when all data had been checked and entered into a database. The statistical analysis was undertaken only once, at the conclusion of the trial.

2.4. Interventions

Venous blood was sampled and the time recorded immediately prior to the application of the spray, to determine baseline lidocaine plasma concentration. Blood pressure and heart rate were also recorded to determine any pre-existing hypotension or bradycardia.

Standard donor site dressings applied at the time of surgery consisted of a primary dressing of calcium alginate and a secondary retention tape dressing with outer reinforcement as necessary. Donor sites from both trial groups were dressed according to this standard. The time at the start of dressing removal was recorded. Any outer dressings such as gauze and bandaging were removed from the donor site area and the primary dressing was moistened with normal saline prior to the application of the spray.

The trial treatment was applied at the commencement of the dressing change. Initially 1 spray was applied per 3 cm^2 of donor site area as the primary dressing was slowly removed. If pain was clearly evident a further 2 sprays were applied while taking care not to exceed the maximum dosage calculated for the patient. The maximum dosage of lidocaine determined for the study was 3 mg/kg, and maximum dosages (numbers of sprays) for a range of patient weights were tabulated as a reference guide for the nurses using the spray to ensure this dose was not exceeded. It was recognised that this level was chosen specifically to minimise the risk of toxic-effects.

On application of the spray the participant was asked if they felt any stinging (Yes or No). Pain scores were measured using the verbal Numerical Rating Scale (NRS). The anchor points of the scale were from 0 (no pain) to 10 (extreme pain). The pain scores were measured at 2 min, 5 min, 10 min, 1 h after commencement of dressing removal and the overall pain score after completion of the dressing. Blood pressure and heart rate were measured before and after completion of redressing. Patient satisfaction was determined using a scale of 1 (very satisfied) to 5 (very unsatisfied). The time taken to remove the dressing was recorded. The donor site was redressed with retention tape according to usual practice. The used spray bottle was returned to the Clinical Trial Pharmacy for weighing, to determine accurate dosing and to perform sterility testing of the spray content. Each spray container was only used once. Sterility testing was carried out according to British Pharmacopoeia Guidelines at the Therapeutic Goods Administration (TGA) accredited facility of PathWest Laboratory of Princess Margret Hospital (PMH). A blood sample to determine lidocaine absorption was taken as close as possible to 1 h after commencement of the dressing removal procedure. The wound was photographed at the time of the second dressing change.

Adverse events were recorded from the time of trial intervention to the healing of the treated donor site. The events were collected from the medical notes of the participants as recorded by nursing and medical staff following observation of an event or of reporting of the events by the participants.

2.5. Formulation and packaging

NOPAYNE™ is a lecithin and soybean oil based oil-in-water miniemulsion containing 3% lidocaine in the base form. The emulsion product was packaged in a Cartridge Pump Spray (CPS) system, purchased from Ing. Enrich Pfeiffer GmbH; Aptar Group; Radolfzell, Germany (Pfeiffer). The CPS system is a multiple use pump spray and specifically designed to maintain the sterility of the contents after each use. The CPS pump spray allows accurate dosing and is a validated delivery system with a consistent spray pattern.

Xylocaine™ (Astra Zeneca) is a 4% lidocaine as lidocaine hydrochloride non-sterile aqueous solution. Xylocaine solution was sterilised by autoclave using standard conditions and repackaged in the CPS system in a laminar flow hood.

2.6. Outcomes

The primary outcomes were pain scores measured at 60 min and sting rate. Secondary outcomes included systemic absorption of lidocaine and patient satisfaction.

2.7. Data collection and statistical analysis

Additional data collected for the study included: the amount of spray used; the subject weight, dressing time, size of skin harvest (donor size) and treatment. Standard descriptive statistics (mean and standard error of mean (SEM) for variables measured on a continuous scale, numbers and percentages for categorical variables) were used to summarise the profile of study participants. Chi-square or *t*-tests (as appropriate) were used to compare the profiles between the two treatment arms of the study. For all statistical tests, a *p*-value ≤ 0.05 was taken to indicate a statistically significant association.

2.8. Analysis of pain score data

A Chi-square statistic was used to compare the presence of pain (pain score > 2) at 60 min between the two treatment groups (primary objective). Pain scores were compared between groups using a Student's *t*-test (based on either the raw scores, or the log-transformed data as appropriate), or a non-parametric Wilcoxon 2-sample test. Where any imbalance in demographic or baseline characteristics appeared between treatment groups, a logistic regression model was used to assess difference in pain (presence or absence) between treatment groups after adjustment for other independent variables.

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2.9. Analysis of lidocaine plasma concentration

Plasma was collected from the blood samples by centrifugation. Plasma samples were protein-precipitated, filtered, and analysed by LC–MS/MS. The plasma concentration of lidocaine was standardised for an adult weight of 70 kg based on linear pharmacokinetics. The total exposure time for an individual patient was calculated from patient dressing time, using following equations. Plasma half-life of 2 h for lidocaine was adopted from the Australian Pharmaceutical Formulary [10,11].

Number	Equation
1	$k = 0.693/t_{1/2}$ *where: k = Elimination rate constant* $t^{1/2}$ = *Half life*
2	$\ln Ct = \ln Co - kt$ *where Ct = after dressing plasma concentration of lidocaine* *Co = pre-plasma concentration of lidocaine* *k = elimination rate constant* *t = total exposure time*

A regression model was used with the lidocaine plasma concentration as dependent variable and combinations of exposure time, amount of sample used and/or the treatment as independent variables. The Wilcoxon 2-sample test was used to compare the lidocaine plasma concentrations between the two treatments groups.

3. Results

3.1. Clinical trial

Participants were enrolled with informed signed consent from the inpatient population of the State Adult Burns Unit. There were 34 participants randomised into the trial and 29 completed all trial treatments and assessments.

The 5 participants who did not complete the trial were excluded before receiving their allocated treatment and were not included in the analysis. Grounds for exclusion were:

- Too young.
- Participation in another trial not known at the time of randomisation.
- Inadvertent and premature removal of target dressing prior to receiving trial treatment.
- Postoperative dressing inappropriate for trial treatment.
- Target area was too large.
- Accidental breakage of used treatment bottle in transit.

Fourteen of the study participants were allocated to receive treatment A and 15 received treatment E. An error occurred in the recording of the drug dosage for one participant (randomised to the treatment group A), who was excluded, so all analyses were based on the remaining 28 subjects.

The size of the donor site skin harvest was not recorded for one participant from the treatment group E and was not included in the regression analyses where wound area was used for the analysis.

Background pain was managed by prophylactic use of regularly administered analgesia including oral paracetamol, oxycodone, tramadol hydrochloride and anti-inflammatory agents. No participant requested the administration of analgesics for procedural pain other than the prescribed trial treatment. A description of participants and their parameters is given in Table 1.

3.2. Pain score

The pain scores measured at any of the specified time intervals during the dressing changes were similar (Table 2). No patient in either treatment arm exceeded a pain score of 4. There appeared to be no significant association between pain at various time points and the treatment. A multivariate logistic regression model was also used to examine if there was any difference in pain scores between groups at 60 min, but no significant associations appeared. The overall pain (Fig. 1) scores were recorded at the end of the dressing change to indicate overall pain experienced during the procedure.

3.3. Sting sensation

There was no significant difference found between the two treatments for occurrence of stinging sensation at the donor

Table 1 – Demographic distribution of participants (Mean ± SEM). *p*-Values are calculated using the Student's *t*-test unless otherwise stated.

Variables	Treatment A ($n = 13$)	Treatment E ($n = 15$)	*p*-Value
Gender (male, female)	(9, 4)	(10, 5)	1.0[a]
Age (year)	37.0 ± 3.7	35.9 ± 3.6	0.84
Dressing time (min)	60.7 ± 3.4	80.1 ± 10.6	0.14[b]
Subject weight (kg)	81.8 ± 6.5	81.6 ± 4.1	0.98
Donor size (cm^2)	73.7 ± 12.4	80.3 ± 23.4	0.52[b]
Pre-dressing heart rate (beats/min)	81.1 ± 4.0	68.4 ± 2.4	0.0088
After-dressing heart rate (beats/min)	79.9 ± 3.6	69.7 ± 2.0	0.0150
Pre-dressing blood pressure (systolic) (mm/Hg)	125.8 ± 4.7	127.1 ± 6.2	0.87
After-dressing blood pressure (systolic) (mm/Hg)	128.6 ± 4.1	123.5 ± 5.1	0.46
Pre-dressing blood pressure (diastolic) (mm/Hg)	78.5 ± 3.5	75.3 ± 3.6	0.55
After-dressing blood pressure (diastolic) (mm/Hg)	79.6 ± 2.9	74.7 ± 3.3	0.28

[a] Fisher's exact test.
[b] Wilcoxon 2-sample test.

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Table 2 – Occurrence of pain at three different time periods during and on completion of the dressing change procedure.

Timing (min)	No of patients with pain total[a] (%)		Mean pain score		*p*-Value
	Treatment E	Treatment A	Treatment E	Treatment A	
2	10/15 (67%)	7/13 (54%)	1.9	1.5	0.49
5–10	9/15 (60%)	6/13 (46%)	2.1	1.5	0.46
60	8/15 (53%)	7/13 (54%)	1.3	1.8	0.98
On completion	7/15 (47%)	7/13 (54%)	1.1	1.6	0.71

p-Values are calculated using the Chi-square statistic.
[a] Pain is classified as "present" if the pain score was 2 or more.

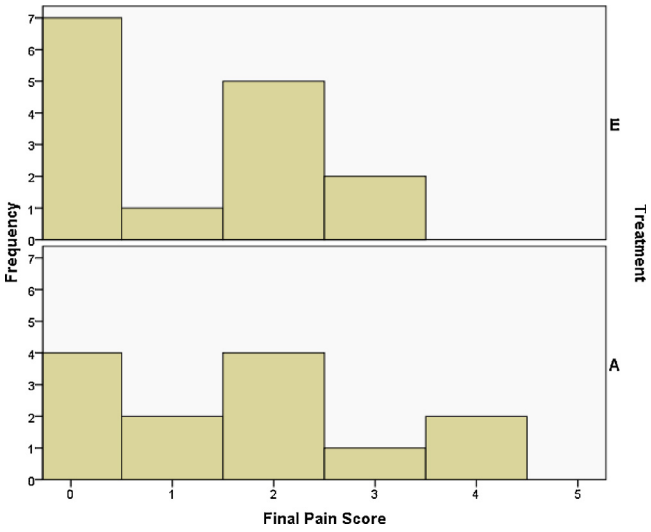

Fig. 1 – Frequency distribution of overall pain score for the two different treatment groups.

site ($p = 0.98$). The percentages of patients reporting no sting were essentially the same for both treatments (46%).

3.4. *Lidocaine plasma concentration*

The lidocaine concentration data for each patient and treatment group are recorded in Fig. 2, separated by treatment group. Subjects in the treatment group E showed significantly lower lidocaine plasma concentrations compared with the treatment group A (Table 4). Linear regression indicated no relationship between dose and plasma concentration for the treatment group E ($p = 0.65$), but a strong positive relationship between these variables for the treatment group A ($p < 0.0001$). The slopes of the regression lines for each treatment are given in Table 3. Exposure time appeared to have no influence on lidocaine plasma concentration ($p = 0.37$).

Exclusion of outliers did not affect the relationship between dose and plasma concentration for group E. However, the slope was slightly reduced after exclusion of outliers in the treatment group A. The detailed data regarding the spray administered and patient plasma concentrations are given in Table 4.

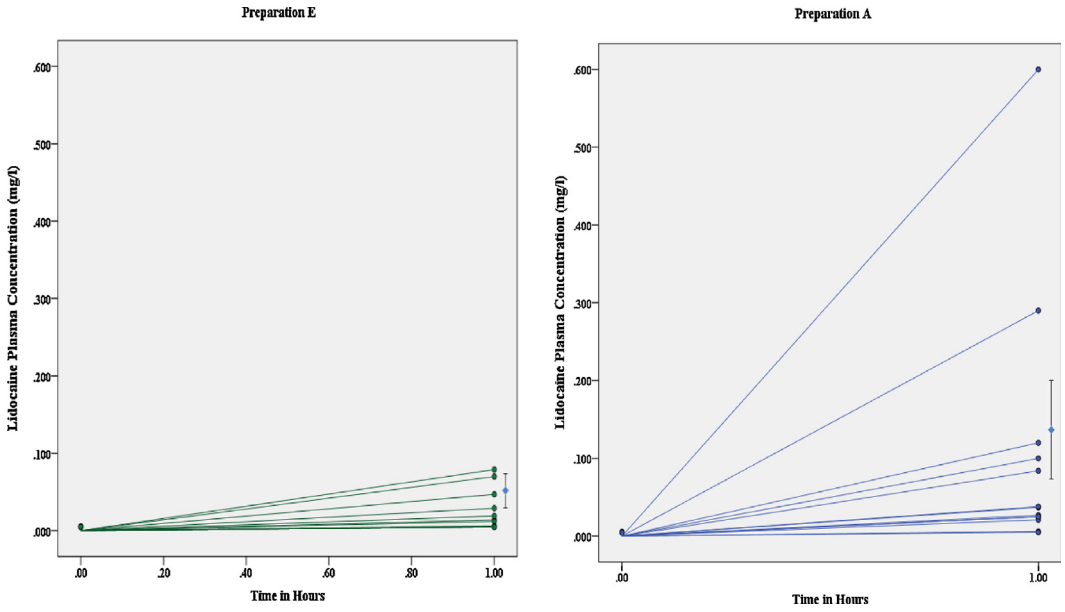

Fig. 2 – Pre- and after-dressing lidocaine plasma concentrations (mg/l) for each participant in the two different treatment groups. The bars are mean ± SEM.

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Table 3 – The regression relationship between dose of drug and lidocaine plasma concentration at 60 min after procedure for each treatment.

Independent variable	Slope	95% confidence interval for slope	*p*-Value
Dose (treatment E)	3.08×10^{-4}	−0.001 to 0.002	0.65
Dose (treatment A)	2.09×10^{-3}	0.0013 to 0.0029	<0.0001

Table 4 – Comparisons of treatments, on the basis of dose of lidocaine received and detected in the serum.

Observations	Treatment A	Treatment E	*p*-Value
Amount of spray used (g)	1.8 ± 0.6	1.6 ± 0.5	0.87
Amount of lidocaine used (mg)	70.3 ± 23.3	49.0 ± 13.7	0.42
No. of sprays used per dressing change	13.1 ± 4.3	12.1 ± 3.4	0.86
Mean pre-dressing lidocaine concentration (mg/l)	Not detected	Not detected	–
Mean after-dressing lidocaine concentration (mg/l)	0.11 ± 0.05	0.036 ± 0.02	0.044[a]
Mean after-dressing lidocaine plasma concentration/70 kg (mg/l)	0.13 ± 0.06	0.04 ± 0.02	0.069[a]

p-Values were calculated using Student's *t*-test unless otherwise marked.
[a] Wilcoxon 2-sample test.

3.5. *Patient satisfaction*

Patients in both treatment groups were very satisfied showing a mean (±SEM) satisfaction score of 1.4(±0.1) (where, 1 represents ''very satisfied'' and 5 is ''very unsatisfied''). The number of patients very satisfied with the level of pain control overall was similar for the treatment E (93%) and treatment A (92%).

3.6. *Adverse events*

A total of seven adverse events were recorded, none of which were serious or persistent or related to study treatment. There were four participants in group A and three in group E (Fisher's Exact Test: $p = 0.67$). One participant was treated for food allergy.

All of the adverse events listed resolved with no residual effects:

- Positive microbiology from donor sites of 3 participants (Staph aureus).
- Left lateral rib pain.
- Failure of skin graft to burn area in 2 participants.
- Two episodes of small amount of blood in stools in one participant.

3.7. *Sterility test*

The product content of all CPS bottles was sterile after use in the trial.

4. Discussion

We conducted a double blind randomised controlled trial comparing the effects of two different formulations containing lidocaine in patients undergoing a painful dressing change. Procedural pain is a most intense burning and stinging pain, which lasts for minutes to hours and is most likely to induce anxiety and stress if undertreated [3]. Topical local anaesthetic agents are widely applicable in plastic surgery and attractive as tools for pain management without the side effects associated with opioids [12].

We found that both treatments were equally effective in managing the procedural pain related to dressing change. The pain scores of all patients were below 5 on the standard rating scale (0–10). All patients were satisfied with the treatment received. Our results showed agreement with those of Jellish et al. who reported that the topical application of lidocaine at a skin harvest site reduced the perception of pain [2].

Sixty minutes after application, pain scores amongst patients receiving treatment A were non-significantly higher than in treatment E. The number of patients receiving treatment E who experienced some pain decreased over the first hour compared with treatment A (Table 2). The effect could be associated with slower release of lidocaine from the emulsion formulation and a longer wound residence time. The higher and variable plasma levels in treatment A also suggested the more rapid absorption of the dissolved lidocaine HCl in aqueous preparation (Fig. 2). The emulsion appeared to provide reduced and consistent systemic absorption compared with the aqueous preparation. This might be due to the emulsion not facilitating rapid release of the insoluble base in the clinical environment. Although the difference in plasma lidocaine concentrations was notable for formulation E compared with formulation A, the wide variation in plasma concentration limits the power (27.4%) to detect this difference.

Reports of toxicity associated with topical use of local anaesthetics have mainly been observed with its application to mucosal membranes leading to rapid absorption. In contrast, we found that lidocaine plasma concentrations were significantly less (25 times for treatment A, more than 70 times for treatment E) than recommended toxic plasma concentration of >5 mg/l [13]. Mills et al. also suggested that topical aerosol application of local anaesthetics improved analgesic effects and possibly reduced toxicity at donor sites [14]. Findings from Bulmer also support that an aqueous gel (dispersed system) containing lidocaine applied to split skin

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donor sites provided an effective analgesia for skin grafting procedures with small systemic absorption [6]. Other studies have also noted that the plasma concentration was well below the toxic threshold after lidocaine gel or aerosol solution application on post-operative wounds or split skin donor sites [6,15,16].

A spray application of lidocaine proved an effective delivery system within a high safety margin and provided analgesia immediately after application. The CPS spray unit combined with an emulsion formulation provided a novel delivery system for open wound and procedural pain management. The CPS spray unit maintained microbial integrity during and after use by creating a microbiological seal directly below the spray orifice. This mechanism along with the tip design avoided a residual drop of product at the dispensing tip and subsequently, microbial contamination after multiple use. This specialised unit allowed a preservative free sterile product to maintain sterility during and after the trial period.

Limiting factors in this study include that some variation may have occurred in the pre-treatment of dressings prior to the administration of either lidocaine formulations. Theoretically the amount of normal saline required to moisten the dressing prior to the application of the lidocaine sprays has the potential to initially dilute especially the aqueous spray. However, this would not influence the initial dose, which was equivalent between the two groups. There are some variations in patient weight and product volume delivered within each group. It would have been difficult in the trial setting to manage a consistent ratio of product delivered per kilogram patient weight.

In summary both topical anaesthetic products provided clinically effective anaesthesia during dressing changes at skin graft donor sites. The new emulsion formulation showed a tendency towards better outcome for pain relief for a longer duration with smaller lidocaine dosage required leading to lower plasma concentrations.

Conflict of interest statement

The project is a part of doctoral thesis by Chiragkumar Desai. Chiragkumar Desai and Charles Fridlender are directors and shareholders of the sponsor company, N S Technologies Pty Ltd. To the best of our knowledge, no other conflict of interest or financial or other exists. A study sponsor was involved in all stages of the project except data collection.

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