Evidence-based and clinical views on acute wound healing and scar formation
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Randomized clinical trial of donor-site wound dressings after split-skin grafting

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Chapter 6

Abstract

Background
The aim was to study which dressing material was best for healing donor-site wounds (DSWs) after split-skin grafting as there is wide variation in existing methods, ranging from classical gauze dressings to modern silicone dressings.

Methods
This 14-centre, six-armed randomized clinical trial (stratified by centre) compared six wound dressing materials in adult patients with DSWs larger than 10 cm$^2$. Primary outcomes were time to complete re-epithelialization and pain scores measured on a Visual Analogue Scale (VAS) over 4 weeks. Secondary outcomes included itching (VAS, over 4 weeks), adverse events and scarring after 12 weeks rated using the Patient and Observer Scar Assessment Scale (POSAS).

Results
Between October 2009 and December 2011, 289 patients were randomized (of whom 288 were analysed) to either alginate (45), film (49), gauze (50), hydrocolloid (49), hydrofibre (47) or silicone (48) dressings. Time to complete re-epithelialization using hydrocolloid dressings was 7 days shorter than when any other dressing was used (median 16 versus 23 days; P < 0·001). Overall pain scores were low, and slightly lower with use of film dressings (P = 0·038). The infection rate among patients treated with gauze was twice as high as in those who had other dressings (18 versus 7·6 per cent; relative risk 2·38, 95 per cent confidence interval 1·14 to 4·99). Patients who had a film dressing were least satisfied with overall scar quality.

Conclusion
This trial showed that use of hydrocolloid dressings led to the speediest healing of DSWs. Gauze dressing should be discontinued as they caused more infections. Registration number: NTR1849 (http://www.trialregister.nl).
Introduction

Split-skin grafting is frequently used by surgeons to close skin defects following trauma, ulcers or deep burns.\textsuperscript{1,2} The split-skin harvest technique involves excision of the epidermis and part of the dermis, leaving a donor-site wound (DSW). Although such wounds are created under controlled, sterile conditions, they can be a considerable burden to patients during and after the healing process. They cause itching, pain, infection and cosmetic inconvenience.\textsuperscript{3–5}

Local treatment of DSWs should aim to create an environment that allows rapid and uneventful re-epithelialization, with a minimum of pain, discomfort and hospital stay.\textsuperscript{3,6,7} Based on available evidence, several dressings are suitable for this purpose, ranging from classical gauzes to modern silicone dressings, alginate, films and hydrofibers.\textsuperscript{8–11} However, treatment regimens vary considerably among centres and surgical specialists.\textsuperscript{5,6,8–13}

Available aggregate evidence comprises four systematic reviews based mainly on small trials, from which it is hard to determine the optimal local treatment for DSWs.\textsuperscript{1,6,7,14} Films and hydrocolloids seem most effective in terms of pain relief and patient comfort.\textsuperscript{1,6,15} All the systematic reviews concluded that more convincing evidence is needed.

Apart from the promising evidence regarding hydrocolloids, national surveys have reported on the preferred use in clinical practice of alginate, films, hydrofibres, silicone dressings and gauzes.\textsuperscript{8–11} Hence, these six dressing types were chosen for the comparison in the present trial. This study was conducted to determine which dressing material was best for DSWs after split-skin grafting, in terms of wound healing, pain, complications, itching, costs and scarring.

Methods

A stratified, parallel-group, multicentre randomized clinical trial was designed to compare alginate, films, gauzes, hydrocolloids, hydrofibres and silicone dressings in patients undergoing split-skin grafting (the Recognizing Effective Materials By Randomizing and Assessing New Donorsite Treatments (REMBRANDT) trial). This trial was stratified by centre, with a balanced allocation ratio for each treatment arm using a biased coin\textsuperscript{16}, and was registered as NTR1849 (http://www.trialregister.nl).
14 recruiting centres included Dutch university hospitals and general hospitals, as well as one of the national burn centres.

The institutional review board of each contributing centre approved the study protocol, which has been published in detail elsewhere. Contrary to this protocol, the group ‘paraffin gauzes’ was renamed ‘gauzes’, because Adaptic® (Systagenix, Gatwick, UK) was used in all but three patients (in whom Jelonet® (Smith and Nephew Healthcare, Hull, UK) was applied). Furthermore, the present methods section highlights only the most important issues according to the revised Consolidated Standards of Reporting Trials (CONSORT) statement.

Participants and data collection

Eligible patients (aged 18 years or older) had a single DSW after split-skin harvest for any indication with a surface area larger than 10 cm$^2$. In patients with multiple DSWs, the allocated dressing was used on all wounds, but a single wound was chosen as the target site. Patients having treatment known to impair wound healing (such as chemotherapy, corticosteroids or local irradiation) and those who could not provide written informed consent were excluded.

Contributing centres provided baseline and peri-operative characteristics, and outcome data for all included patients through the trial website. One trial coordinator stored the data, which were checked for correctness independently by another coordinator.

Dressing materials and nursing time involved in caring for the DSWs were recorded on case record forms by each contributing centre. Patients also noted materials and nursing time in patient diaries during follow-up to facilitate precise registration of these data, particularly in the outpatient setting. Despite repeated efforts, a large number of data were still missing. Given these unreliable data, it was decided not to report on the cost outcome.

Treatment and interventions

The methods of harvesting, local haemostasis and desired thickness of the graft were at the surgeons’ discretion. After skin harvest and haemostasis, the patient was randomized. Randomization was done by an appointed officer in each contributing centre who was not responsible for patient recruitment, or by contacting the trial coordinators. A computer programme (ALEA version 2.2; NKI-AVL, Amsterdam, The Netherlands), hosted by an independent clinical research unit, was used to generate the random allocation sequence for the following dressing groups: an alginate (Kaltostat®, ConvaTec, Skillman, New Jersey, USA; Algisite®, Smith and Nephew; or Melgisorb®, Mölnlycke Health Care,
Gothenburg, Sweden); a semipermeable film (Tegaderm®, 3M, St Paul, Minnesota, USA; or Opsite®, Smith and Nephew); a gauze dressing (Adaptic® or Jelonet®); a hydrocolloid (DuoDERM E® ; ConvaTec); a hydrofibre (Aquacel® ; ConvaTec) and a silicone dressing (Mepitel® ; Mölnlycke Health Care).

The brand names indicate the products actually used in this trial. In three dressing groups the centres were allowed to choose from more than one dressing type to accommodate their local practice. Carers applied and changed the allocated dressings according to the instruction protocol provided before the start of the trial by the different manufacturers of the dressings used. The frequency of dressing changes varied from never (alginate and hydrofibre) to weekly (film and hydrocolloid) or every 10 – 14 days (gauze and silicone). During follow-up carers applied the same dressing type until wound healing was complete.

To ensure equal treatment in all groups, only cotton gauzes and bandages were allowed as secondary dressings. When a DSW infection was suspected, carers were allowed to add an iodine-containing product to a fresh primary dressing. In case of a *Pseudomonas* infection, acetic acid was applied. Additional cleansing or protection during dressing changes was allowed in all treatment groups.

Blinding of patients and care providers was obviously not possible. However, to avoid performance bias, patients were instructed only about how to use their wound dressing and wound care, without expressing any expectations regarding the effectiveness of the dressings in the trial.

### Outcomes

Primary endpoints were: time to complete wound healing (defined as full re-epithelialization of the donor site without any remaining scabs) and pain measured on a 10-cm Visual Analogue Scale (VAS). Complete wound healing was planned to be assessed by an independent investigator who was not aware of the treatment given. However, for practical reasons, occasionally patients or carers were asked to assess wound healing themselves, which was found to be reliable. Additionally, patients were asked to write down the day of complete wound healing in their personal diary as an additional check. All patients were followed until 12 weeks after complete wound healing.

Secondary outcomes included: adverse events (clinical signs of DSW infection, hypergranulation or allergic reactions), itching (10-cm VAS), and scarring, assessed 12 weeks after complete healing of the DSW by the carers (observers) and patients, using the Patient and Observer Scar Assessment Scale (POSAS).

The range of scar assessment
scores varies between 6, indicating normal skin, and 60, indicating the worst possible result. Pain and itching were assessed and recorded in diaries by the patients once a day, approximately at noon, during the first 2 weeks of follow-up and twice a week thereafter for a total of 4 weeks.

**Statistical analysis**

With a 5 per cent significance level and a power of 90 per cent, a sample size of 43 patients per group, that is a minimum total of 258 patients if no dropouts occurred, was needed to detect either a 25 per cent quicker wound healing time or a two-point difference on a ten-point VAS in one dressing group compared with the other five groups combined.

The intention-to-treat principle was applied. To analyse differences in wound healing time and possible effects of the stratification factors on time to an event, the Kaplan – Meier method and Mantel – Cox log rank test were employed. The $\chi^2$ test was used to examine differences in number of local adverse events, and a general linear mixed model to analyse the differences in pain and itching over time. This model assumes a continuous outcome variable (VAS), which is linearly related to a set of explanatory variables (dressing material used). After the residuals had been checked for normality and model fitting performed, the auto-regressive of order one (AR-1) model was applied. The AR-1 model is one of a group of linear prediction formulas; it allows the co-variable structure for the random-effects model to be specified. For dichotomous outcome parameters the risk ratio (RR) was calculated with 95 per cent confidence interval (c.i.) and number needed to treat or number needed to harm (NNH). Differences in scar assessment scores were analysed using the Mann – Whitney U test as they were non-normally distributed.

In addition to the protocol, a Bonferroni correction for both primary endpoints (wound healing and pain) resulted in an adjusted $P$ value for significance of 0.025.$^{21}$ SPSS® software (PASW statistics version 18.0; IBM, Armonk, New York, USA) was used for coding and analysis.

**Results**

From October 2009 to December 2011, 358 patients were screened for inclusion, of whom 289 were eligible to be randomized (Fig.1). Baseline demographic and perioperative characteristics were similar among the dressing groups (Table 1), except for the use of haemostasis, which was applied in fewer patients (20 per cent) in the film dressing group. The majority of skin grafts (57.4 per cent) were used to treat a surgical or traumatic wound and were mostly taken from the thigh (270, 93.4 per cent), with a mean (standard deviation (s.d.)) of 0.32(0.15) mm and grafted area of 78.4(109.2) cm$^2$. Participating
centres mainly used Kaltostat® in the alginate group and Adaptic® in the gauze group, whereas Tegaderm® and Opsite® were applied equally often in the semipermeable film group.

**Participant flow**

Follow-up was completed in April 2012. During the trial ten patients dropped out; thus follow-up was complete for 279 patients (96.5 per cent). Crossover to another dressing group occurred in 37 (12.8 per cent) of the 289 patients. Crossover varied from three times in the hydrocolloid group to ten times in the hydrofibre group, owing to unfamiliarity with the product (14), preference of the patient (12), infection (6), leakage (3) or logistical reasons (2) (Table 2). The effects of these dropouts and crossovers were avoided by means of the intention-to-treat analysis. The response rate of the patient diaries returned was over 75 per cent, equally divided between the six groups.

**Primary outcomes: complete wound healing and pain**

Time to complete re-epithelialization was 7 days (30 per cent) shorter when hydrocolloid dressings were used (median 16 days) than with any other dressing (median 23 days) \((P < 0.001)\) (Fig. 2). Wound healing remained significantly quicker with, or without the
Table 1 Baseline patient characteristics and perioperative data by treatment allocation group

<table>
<thead>
<tr>
<th>Dressing type</th>
<th>Alginate (n = 45)</th>
<th>Film (n = 49)</th>
<th>Gauze (n = 50)</th>
<th>Hydrocolloid (n = 49)</th>
<th>Hydrofibre (n = 47)</th>
<th>Silicone (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>60 (18)</td>
<td>61 (18)</td>
<td>62 (18)</td>
<td>61 (17)</td>
<td>60 (16)</td>
<td>62 (17)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (24)</td>
<td>10 (20)</td>
<td>11 (22)</td>
<td>13 (27)</td>
<td>8 (17)</td>
<td>11 (23)</td>
</tr>
<tr>
<td>Smoker</td>
<td>11 (24)</td>
<td>15 (31)</td>
<td>10 (20)</td>
<td>13 (27)</td>
<td>12 (26)</td>
<td>13 (27)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>6 (13)</td>
<td>7 (14)</td>
<td>5 (10)</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>&gt; 5 per cent in 1 month</td>
<td>4 (9)</td>
<td>5 (10)</td>
<td>5 (10)</td>
<td>3 (6)</td>
<td>2 (4)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>&gt; 10 per cent in past 6 months</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>17 (38)</td>
<td>15 (31)</td>
<td>13 (26)</td>
<td>16 (33)</td>
<td>13 (28)</td>
<td>18 (38)</td>
</tr>
<tr>
<td>&lt; 18.5</td>
<td>24 (40)</td>
<td>23 (43)</td>
<td>22 (44)</td>
<td>17 (35)</td>
<td>16 (34)</td>
<td>15 (31)</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>10 (22)</td>
<td>13 (27)</td>
<td>14 (28)</td>
<td>14 (29)</td>
<td>16 (34)</td>
<td>12 (25)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (22)</td>
<td>8 (16)</td>
<td>10 (20)</td>
<td>13 (27)</td>
<td>6 (13)</td>
<td>12 (25)</td>
</tr>
<tr>
<td>Burn wound</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>3 (6)</td>
<td>1 (2)</td>
<td>3 (6)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Surgical/traumatic wound</td>
<td>29 (64)</td>
<td>28 (57)</td>
<td>27 (54)</td>
<td>30 (61)</td>
<td>27 (57)</td>
<td>25 (52)</td>
</tr>
<tr>
<td>Tumour excision</td>
<td>5 (11)</td>
<td>10 (20)</td>
<td>8 (16)</td>
<td>4 (8)</td>
<td>10 (21)</td>
<td>9 (19)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Indication for SSG</td>
<td>27 (60)</td>
<td>30 (61)</td>
<td>20 (40)</td>
<td>25 (51)</td>
<td>28 (60)</td>
<td>28 (58)</td>
</tr>
<tr>
<td>Chronic wound</td>
<td>29 (64)</td>
<td>28 (57)</td>
<td>27 (54)</td>
<td>30 (61)</td>
<td>27 (57)</td>
<td>25 (52)</td>
</tr>
<tr>
<td>Burn wound</td>
<td>5 (11)</td>
<td>10 (20)</td>
<td>8 (16)</td>
<td>4 (8)</td>
<td>10 (21)</td>
<td>9 (19)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Dermatome</td>
<td>44 (98)</td>
<td>44 (98)</td>
<td>46 (92)</td>
<td>47 (96)</td>
<td>44 (94)</td>
<td>45 (94)</td>
</tr>
<tr>
<td>Hand knife and other</td>
<td>1 (2)</td>
<td>5 (10)</td>
<td>3 (6)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Electric</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Pneumatic</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>50.0</td>
<td>49.0</td>
<td>50.0</td>
<td>49.0</td>
<td>37.5</td>
<td>40.0</td>
</tr>
<tr>
<td>Location of DSW</td>
<td>18 (40)</td>
<td>10 (20)</td>
<td>23 (46)</td>
<td>26 (53)</td>
<td>14 (30)</td>
<td>23 (48)</td>
</tr>
<tr>
<td>Thigh</td>
<td>10–240</td>
<td>10–600</td>
<td>10–450</td>
<td>10–800</td>
<td>10–750</td>
<td>10–760</td>
</tr>
<tr>
<td>Thickness of graft (mm)†</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Other</td>
<td>0.1–0.6</td>
<td>0.1–0.6</td>
<td>0.1–0.8</td>
<td>0.1–0.7</td>
<td>0.1–0.6</td>
<td>0.1–0.7</td>
</tr>
<tr>
<td>Haemostasis</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages unless indicated otherwise; values are *mean(s.d.) and †median (range). DSW, donor-site wound; ASA, American Society of Anesthesiologists; SSG, split-skin grafting.
Bonferroni correction ($P < 0.025$). Median and mean times to complete re-epithelialization for each dressing group are shown in Table 3. Healing times with, and without adjustment for stratification during follow-up showed a significant association between quicker wound healing and hydrocolloid dressings: hazard ratio 2.33 (95 per cent c.i. 1.65 to 3.30) and 1.85 (1.35 to 2.53) respectively.

Overall, pain scores (10-cm VAS), as calculated from 3360 recordings, were low (median 0.4, interquartile range (i.q.r.) 0–1.4). However, they were lower in the semipermeable film group than in the other dressing groups combined ($P = 0.038$, type II test of fixed...
effects); the difference did not reach significance when the Bonferroni correction was applied.

**Secondary outcomes: adverse events, itching and scarring**

The infection rate with gauze dressings was 18 per cent, which was only slightly higher than when films or hydrofibres were used, but substantially higher than with silicones or hydrocolloids. The infection rate with gauze dressings was twice as high as the mean of the infection rates of the other five dressing groups combined (18 versus 7.6 per cent; RR 2.38, 95 per cent c.i. 1.14 to 4.99; NNH = 10; P = 0.022, \( \chi^2 \) test) (Table 3). Allergic reactions were never reported and hypergranulation occurred rarely (Table 3).

Itching scores (10-cm VAS) were calculated from 3579 recordings and were lower (median 0.2, i.q.r. 0–0.8) than pain scores. No significant differences were found among the dressing types.

POSAS data were collected from 137 patients from five contributing centres. Results and summary scores are shown in Table 4. Patients who had semipermeable films were significantly less satisfied with their scars (P = 0.018, Mann–Whitney U test), especially

### Table 3 Primary and secondary outcomes by treatment allocation group

<table>
<thead>
<tr>
<th>Dressing type</th>
<th>Alginate (n = 45)</th>
<th>Film (n = 49)</th>
<th>Gauze (n = 50)</th>
<th>Hydrocolloid (n = 49)</th>
<th>Hydrofibre (n = 47)</th>
<th>Silicone (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to wound healing (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (i.q.r.)</td>
<td>22 (19–29)</td>
<td>23 (14–36)</td>
<td>22 (18–33)</td>
<td>16 (12–21)†</td>
<td>22 (15–27)</td>
<td>26 (18–33)</td>
</tr>
<tr>
<td>95 per cent confidence interval</td>
<td>(19.2, 24.8)</td>
<td>(19.2, 26.8)</td>
<td>(19.4, 24.6)</td>
<td>(13.5, 18.5)</td>
<td>(18.7, 25.3)</td>
<td>(22.7, 29.3)</td>
</tr>
<tr>
<td>Mean (s.d.)</td>
<td>27.1(14.4)</td>
<td>32.9(6.2)</td>
<td>27.9(17.1)</td>
<td>19.4(11.5)</td>
<td>26.0(18.2)</td>
<td>29.2(22.5)</td>
</tr>
<tr>
<td>Pain score (0–10 on VAS)*</td>
<td>0.4 (0.0–1.9)</td>
<td>0.3 (0–1.0)†</td>
<td>0.3 (0–1.5)</td>
<td>0.2 (0–1.1)</td>
<td>0.8 (0–1.5)</td>
<td>0.4 (0.1–1.1)</td>
</tr>
<tr>
<td>Itching score (0–10 on VAS)*</td>
<td>0.2 (0–0.9)</td>
<td>0.3 (0–0.9)</td>
<td>0.2 (0–0.6)</td>
<td>0.2 (0–0.8)</td>
<td>0.3 (0–1.0)</td>
<td>0.2 (0–1.0)</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical infection</td>
<td>0 (0)</td>
<td>8 (16)</td>
<td>9 (18)§</td>
<td>1 (2)</td>
<td>7 (15)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypergranulation</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages unless indicated otherwise; *values are median (interquartile range). VAS, Visual AnalogueScale. †P < 0.001 versus any other dressing (log rank test); ‡P = 0.038 versus any other dressing (type II test of fixed effects); §P = 0.022 versus any other dressing (\( \chi^2 \) test).
Study results Rembrandt-trial

regarding the item ‘wound relief’ (P = 0.046, Mann–Whitney U test). There were no differences in scar assessment by the observers among the dressing types.

**Discussion**

This trial compared six commonly used wound dressing materials to cover donor sites after split-skin harvesting. Use of hydrocolloid dressings led to a 7-day shorter healing time than the other materials. The use of gauze tended to result in a higher risk of infection than other dressing types.

This quicker wound healing with hydrocolloid dressings might be explained by differential wound angiogenesis associated with different degrees of occlusion.\(^{22}\) Dressings promoting a moist wound environment, such as hydrocolloids, have been shown to improve re-epithelialization, increase collagen synthesis and ultimately improve healing rates.\(^{1,23–25}\) The shorter healing time of donor sites using dressings that promote moist wound healing had already been suggested by previous aggregated evidence.\(^{1,6,7,14}\)

This trial now offers evidence for the effectiveness of a specific dressing type within this group of materials. Other occlusive or semi-occlusive dressings, such as foam dressings, might have similar healing effects, but these dressings were not included in the present trial based on evidence from previous literature and a national inventory showing lower eligibility.\(^{8,14}\) The (moist) wound environment may also be influenced by the types of secondary wound dressing applied. In this trial the protocol prescribed the uniform use

<table>
<thead>
<tr>
<th>Dressing type</th>
<th>Alginate</th>
<th>Film</th>
<th>Gauze</th>
<th>Hydrocolloid</th>
<th>Hydrofibre</th>
<th>Silicone</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POSAS score*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observer</td>
<td>11 (8–14)</td>
<td>11 (10–15)</td>
<td>12 (8–14)</td>
<td>10 (8–14)</td>
<td>11 (9–15)</td>
<td>11 (8–13)</td>
</tr>
<tr>
<td>Patient</td>
<td>10 (7–13)</td>
<td>14 (11–15)</td>
<td>11 (8–14)</td>
<td>10 (8–12)</td>
<td>10 (7–15)</td>
<td>11 (9–14)</td>
</tr>
<tr>
<td>Overall scar rating*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observer</td>
<td>3 (2–4)</td>
<td>3 (2–4)</td>
<td>3 (2–4)</td>
<td>2 (2–3)</td>
<td>2 (1–3)</td>
<td>2 (2–4)</td>
</tr>
<tr>
<td>Patient</td>
<td>2 (2–5)</td>
<td>4 (1–4)</td>
<td>2 (2–5)</td>
<td>3 (2–5)</td>
<td>3 (2–5)</td>
<td>2.5 (1–4)</td>
</tr>
<tr>
<td>Patient satisfaction with dressing†</td>
<td>7.7 (4–10)</td>
<td>7.5 (1–10)</td>
<td>8.0 (5–10)</td>
<td>7.6 (1–10)</td>
<td>7.3 (4–10)</td>
<td>7.7 (2–10)</td>
</tr>
</tbody>
</table>

Values are *median (interquartile range) and †mean (range). Patient and Observer Scar Assessment Scale (POSAS): for observer and patient a score of 6 indicates normal skin, and 60 indicates the worst possible result. Overall scar rating: for observer and patient a score of 1 indicates normal skin, and 10 indicates the worst possible result. Patient satisfaction with dressing: a score of 1 indicates very dissatisfied and 10 indicates very satisfied.
of gauze-based secondary dressings. Hence, the effects of other secondary dressings (such as semipermeable film) used in clinical practice could not be studied.\(^8\)

The time to complete healing in the hydrocolloid group exceeded the healing times reported in other studies, which varied from 10 to 12 days.\(^5,12,13,26,27\) This is probably due to the strict definition of complete epithelialization, which stated that complete wound healing was not reached until any remaining scabs had fallen off. This is in contrast with a range of definitions from other studies, including epithelial coverage, absence of exudate, scar appearance and proportion of the wound healed.\(^7\) Although the definition used here, and consequently the healing time observed, may differ from that in other studies, it was chosen as an objective, valid, uniform, easily assessable and patient-relevant outcome.\(^19\)

Overall pain scores were low (mean pain scores varied between 0.2 and 3.0). Regardless of any statistically significance difference, this is unlikely to be of clinical relevance.

The high risk of infection in patients treated with gauze dressings was also found for fine mesh gauze dressings with scarlet red, which had a 9.6 per cent infection rate.\(^28\) Patients from all dressing groups in the present trial received systemic antibiotics at a similar rate (21 – 35 per cent), mostly prescribed for indications other than the DSW. Despite the relatively high rate of antibiotic prescription, gauze dressings were accompanied by a significantly higher DSW infection rate, which prolonged healing. However, aggregated results of gauze dressings for DSWs and postoperative wounds did not find an increased risk of infection.\(^1,6,7,14,29\)

Haemostasis was applied in fewer patients in the film and hydrofibre groups than in other dressing groups; however, the surgeon’s decision that haemostasis was not needed was not influenced by the dressing, as the allocation was decided by randomization after haemostasis had been achieved. In the gauze, hydrocolloid and silicone groups, haemostasis was applied in about half of the patients, but time to wound healing differed considerably among these groups, indicating that the need for haemostasis did not have a substantial effect on wound healing.\(^30\)

Some possible limitations of this trial include: variation in thickness of the skin graft, method of harvesting, and the surgeons’ preferences regarding haemostasis and treatment of infection. This was intentional, to allow a pragmatic trial that would mimic daily clinical practice. Furthermore, as in many surgical trials, blinded outcome assessment was not always possible because different dressings leave different imprints on the DSW. However, subjective assessment of wound healing has been shown to be a
reliable and valid method for assessment of epithelialization. Furthermore, a strict definition of complete wound healing was used.

The cosmetic appearance of the scars was assessed after 3 months, even though active remodelling and maturation of scars takes at least 12 months. Nevertheless, the POSAS score is a reliable and valid instrument for identifying changes in scar characteristics. As described in the study protocol, differences in scar development related to the dressing materials investigated. The assumption was that differences seen at 3 months would diminish with time, as shown in other studies.

Finally, it was not possible to report accurately on costs, which play a substantial part in the choice of wound treatment. Unit and total costs of hydrocolloid dressings are high. However, investigators frequently report on unit costs but tend to neglect dressing change frequency, nursing times or rapid healing time, and secondary gains such as early mobilization. In this trial it was difficult to record and report the costs of such factors accurately. However, the costs of local wound treatment should be put in perspective. The relatively high costs per dressing unit are at least in part compensated by a low dressing change frequency (once in up to 7 days), which causes little pain. Besides, patient preferences or priority for rapid healing may downplay the costs of a dressing material, for example in patients with extensive burns or severe co-morbidity. In such scenarios hydrocolloid dressings, which do not need changing frequently, seem preferable to achieve more rapid wound healing.

Comprehensive inclusion criteria (all adults requiring a split-skin graft) was one of the strengths of this trial and allowed application to a broad patient population with DSWs. In addition, the results reflect local practice in 14 national centres, which improves the generalizability. Much effort was put into minimizing the risk of bias due to incomplete outcome data, which resulted in a low dropout rate (3.5 per cent).

Use of a hydrocolloid dressing for DSWs reduced healing time by 7 days compared with other commonly used dressing materials. The results of this study should decrease the current diversity in treatment choices for DSWs as treatment options are now more evidence-based. Several practical considerations should be mentioned about the use of hydrocolloid dressings. Before their application, the skin should be clean; fatty disinfectants should be avoided for better adherence. With large wounds, leakage can be a problem owing to interaction of wound exudate with the dressing. A moist interface between the dressing and the wound, however, reduces postoperative discomfort and minimizes tissue damage during dressing changes.
Collaborators

Other members of the REMBRANDT study group who collaborated in this study: S. J. M. Jongen (Martini Hospital, Groningen, The Netherlands); K. E. A. van der Bogt and J. van Vooren (Leiden University Medical Centre, Leiden, The Netherlands); J. F. A. van der Werff (Haaglanden Kliniek/Nederlands Centrum Plastische Chirurgie, The Hague, The Netherlands); A. K. J. Ahmed and J. van de Geijn (Kennemer Gasthuis, Haarlem, The Netherlands); A. H. Schuurman (University Medical Centre Utrecht, Utrecht, The Netherlands); M. Goedhart and A. van Delft (VU University Medical Centre, Amsterdam, The Netherlands); D. Nio, D. Hoek and W. Vermeul (Sparne Hospital, Hoofddorp, The Netherlands); N. Koedam (Tergooi Hospital, Hilversum, The Netherlands); P. Heres (Waterland Hospital, Purmerend, The Netherlands); L. Levert-Brand and T. de Groot (Langeland Hospital, Zoetermeer, The Netherlands); E. Harink and M. Waindrich (Isala Klinieken, Zwolle, The Netherlands); J. W. T. Verheijden-Melssen (Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands); and K. Groenhuijzen (Gelre Ziekenhuizen, Zutphen, The Netherlands).

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