Knowledge development and research utilization in evidence-based wound care
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Which dressing do donor site wounds need? The results of a randomized controlled trial (Rembrandt Trial)

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Dirk T Ubbink;
On behalf of the Rembrandt study group.

Submitted
ABSTRACT

Objective: To study which dressing material for donor site wounds (DSWs) after split-skin grafting is best for a quick and uneventful wound healing.

Background: Large variation exists in the local treatment of DSWs, ranging from classic gauze dressings to modern silicone dressings.

Methods: A 14-center, six-armed randomized clinical trial (stratified per center) was conducted comparing six wound dressing materials in adult patients with DSWs larger than 10cm² for any indication. Primary outcomes were complete re-epithelization and pain using a Visual Analogue Scale (VAS; 4 weeks). Secondary outcomes included itching (VAS; 4 weeks), adverse events and scarring after 12 weeks using the Patient Observer Scar Assessment Scale (POSAS).

Results: Between October 2009 and December 2011, 289 patients were randomized (of whom 288 were analyzed) to either alginate (n = 45), film (n = 49), gauze (n = 50), hydrocolloid (n = 47), hydrofiber (n = 47) or silicone (n = 48). Time to complete re-epithelization using hydrocolloid dressings (median 16 days) was seven days shorter than using any other dressing (median 23 days) (P-value < 0.001, log-rank test). Overall pain scores were low and slightly lower using film dressings (P-value = 0.038, type-III test of fixed effects). Infection rate among patients treated with gauzes was twice as high as in those receiving other dressings (18% vs. 9%, risk ratio 2.39, 95% confidence interval 1.14 to 5.01). Patients receiving films were least satisfied about overall scar quality.

Conclusion: This trial shows that hydrocolloid dressings lead to the shortest healing time of DSWs among the dressings investigated, while gauzes should be avoided due to increased risk of infection.
BACKGROUND

Split-skin grafting (SSG) is frequently used by general, trauma and plastic surgeons to close skin defects like traumatic injuries, chronic ulcers, abdominal wall defects or deep burns\(^1\);\(^2\). This split-skin harvest technique involves excision of the epidermis and part of the dermis and leaves a so-called 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 in terms of itching, pain, infection and cosmetic inconvenience\(^3\);\(^5\).

Surgeons largely agree that local treatment of DSWs should aim at creating an environment that allows rapid and uneventful re-epithelialization with a minimum of pain, discomfort and length of hospital stay\(^3\);\(^6\);\(^7\). Based on available evidence, several dressings seem suitable for this purpose, ranging from classic gauzes to modern silicone dressings, alginates, films and hydrofibers\(^8\);\(^11\). However, treatment regimes vary considerably among centers, disciplines and individual surgical specialists\(^5\);\(^6\);\(^12\);\(^13\).

Available aggregate evidence comprises four systematic reviews based on mainly small trials, from which it is hard to distil the optimum local treatment for DSWs\(^1\);\(^6\);\(^7\);\(^14\). Films and hydrocolloids seem most effective in terms of pain relief and patient comfort\(^1\);\(^6\);\(^15\). All SRs conclude that more convincing evidence is needed.

This study was conducted to detect which dressing material for DSWs after SSG stands out in terms of wound healing, pain, complications, itching, costs and scarring.

METHODS

Trial design and study setting

A stratified, parallel group, multicenter randomized clinical trial (RCT) was designed comparing alginates, films, gauzes, hydrocolloids, hydrofibers or silicone dressings in patients undergoing SSG (the Rembrandt Trial; Recognizing Effective Materials By Randomizing & Assessing New Donorsite Treatments). This trial was registered as NTR1849 (www.trialregister.nl). The 14 recruiting centers included Dutch university centers and general hospitals as well as one of the national burn centers.

The institutional review boards of each contributing center approved the study protocol, which has been published in detail elsewhere\(^16\). Contrary to this protocol, the group “paraffin gauzes” was renamed to “gauzes”, since Adaptic\(^®\) was used in all but three cases (where Jelonet\(^®\) was applied) in this group. Furthermore, the present Methods section only highlights the most important issues according to the revised CONSORT statement\(^17\).
Participants and data collection

Eligible patients should have a DSW with a surface area larger than 10 cm² after SSG for any indication. Patients under treatment known to seriously impair wound healing or those who could not provide written informed consent were excluded. The flow of patient inclusion and follow-up is shown in Figure 1.

Contributing centers provided baseline and peri-operative characteristics and outcome data of all included patients through the trial website (www.rembrandt-trial.nl). One of the trial coordinators stored the data in the trial database, which were checked for correctness independently by another (FEB and AME).

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

**Figure 1.** Flow of participants during the study

Treatment and interventions

The methods of harvesting, local haemostasis and desired thickness of the graft were to the surgeons’ discretion. These variables were recorded for possible sub-group analyses. After the skin harvest and local haemostasis, if any, the patient was randomized using a computer program (ALEA v. 2.2, NKI-AVL, Amsterdam, The Netherlands) by an appointed officer in each center or by calling the trial coordinators.
(FEB and AME) to be treated with a dressing material from one of the following dressing groups:
1. A gauze-based material (Jelonet®, Adaptic®);
2. A hydrocolloid (DuoDERM® E);
3. An alginate (Kaltostat®, Algisite®, Melgisorb®);
4. A semi-permeable film (Tegaderm®, Opsite®);
5. A silicone dressing (Mepitel®);
6. A hydrofiber (Aquacel®).

The brand names indicate the products actually used in this trial. In three dressing groups the centers were allowed to choose from more than one dressing type to accommodate their local practice and to reflect “real life”. Caregivers applied and changed the allotted dressings according to the instruction protocol provided before the start of the trial by the different manufacturers of the dressings used. During the follow-up period caregivers were to apply the same dressing type until complete wound healing.

To ensure equal treatment in all groups, only cotton gauzes and bandages were allowed as secondary dressing. When a DSW infection was suspected, caregivers were allowed to add an iodine-containing product to a fresh primary dressing. In case of a Pseudomonas infection acetic acid was to be 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 only instructed about how to use their wound dressing and care for their wound without expressing any expectations regarding the effectiveness of the dressings in the trial.

Outcomes
Primary endpoints were: days to complete wound healing (defined as full re-epithelialization of the donor site without any remaining scabs) and pain using a 10-cm Visual Analogue Scale (VAS). Wound healing was assessed by patients, caregivers or investigators. Secondary outcomes included adverse events (i.e. clinical signs of DSW infection, hypergranulation, or allergic reactions), itching (VAS), and scarring, assessed 12 weeks after complete healing of the DSW by the caregivers (observers) and the patients, using the Patient Observer Scar Assessment Scale (POSAS)\textsuperscript{18}. The range of the scar assessment 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 two weeks of follow-up and twice a week thereafter until complete wound healing.
Sample Size
With a 5% significance level and a power of 90%, a sample size of 43 patients per group, i.e. a minimum total of 258 patients if no dropouts would occur, was needed to detect either a 25% quicker wound healing time or a 2-point difference on a 10-point VAS scale in one dressing group as compared to the other five groups combined.

Statistical methods
SPSS software (PASW statistics version 18.0, IBM, Armonk, NY, USA) was used for coding and analysis. The intention-to-treat principle was applied to analyze the outcome data. To analyze differences in wound healing time we used the Kaplan-Meier method and the Mantel-Cox log-rank test. Furthermore, a Chi-square test was used to examine differences in number of local adverse events and a general linear mixed model to analyze 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 (i.e. dressing material used). After the residuals were checked for normality and model-fitting was 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 and allows specifying the covariance structure for the random-effects model. For dichotomous outcome parameters the risk ratio (RR) was calculated with 95% Confidence Intervals (CI) and Numbers Needed to Treat or Harm (NNT, NNH). Differences in scar assessment scores were analyzed using the Mann-Whitney U test due to their non-normal distribution.

RESULTS
Participant flow
From October 2009 to December 2011, 358 patients were screened for inclusion, of whom 289 were eligible to be randomized (Figure 1). Follow-up was completed in April 2012.

During the trial ten patients dropped out; thus follow-up was complete for 279 patients (96.5%). Crossover to another dressing group occurred in 37 out of the 289 patients (13%). Crossover varied from thrice in the hydrocolloid group up to ten times in the hydrofiber group, due to unfamiliarity with the product (n = 14), preference of the patient (n = 12), infection (n = 6), leakage (n = 3), or logistic reasons (n = 2). By means of the ITT-analysis we avoided the effects of these drop-outs and crossovers. The response rate of the patient diaries returned was over 75 percent, equally divided over the six groups.
Baseline data

Patients’ baseline demographic and peri-operative characteristics were similar among the dressing groups (Table 1), except for the use of haemostasis, which was applied in

Table 1. Baseline and peri-operative characteristics by treatment allocation

<table>
<thead>
<tr>
<th></th>
<th>Alginate (n=45)</th>
<th>Film (n=49)</th>
<th>Gauze (n=50)</th>
<th>Hydrocolloid (n=49)</th>
<th>Hydrofiber (n=47)</th>
<th>Silicone (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD, years</td>
<td>60 ± 17.8</td>
<td>61 ± 17.9</td>
<td>62 ± 17.7</td>
<td>61 ± 17.1</td>
<td>60 ± 16.1</td>
<td>62 ± 17.2</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>36 (80)</td>
<td>37 (74)</td>
<td>30 (60)</td>
<td>32 (65)</td>
<td>27 (57)</td>
<td>36 (75)</td>
</tr>
<tr>
<td>DM, n (%)</td>
<td>11 (24.4)</td>
<td>10 (20.0)</td>
<td>11 (22.0)</td>
<td>13 (26.5)</td>
<td>8 (17.0)</td>
<td>11 (22.9)</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>11 (24.4)</td>
<td>15 (30.0)</td>
<td>10 (20.0)</td>
<td>13 (26.5)</td>
<td>12 (25.5)</td>
<td>13 (27.1)</td>
</tr>
<tr>
<td>Weight loss, n (%)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>&gt;5% in 1 month</td>
<td>6 (13.3)</td>
<td>7 (14.0)</td>
<td>5 (10.0)</td>
<td>2 (4.1)</td>
<td>2 (4.3)</td>
<td>2 (4.2)</td>
</tr>
<tr>
<td>&gt;10% in last 6 months</td>
<td>4 (8.9)</td>
<td>5 (10.0)</td>
<td>5 (10.0)</td>
<td>3 (6.1)</td>
<td>2 (4.3)</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>BMI, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &lt; 18.5</td>
<td>1 (2.2)</td>
<td>1 (2.0)</td>
<td>2 (4.0)</td>
<td>1 (2.0)</td>
<td>2 (4.3)</td>
<td>4 (8.3)</td>
</tr>
<tr>
<td>BMI &gt; 30</td>
<td>12 (26.7)</td>
<td>14 (28.0)</td>
<td>10 (20.0)</td>
<td>12 (24.5)</td>
<td>15 (31.9)</td>
<td>6 (12.5)</td>
</tr>
<tr>
<td>Antibiotics, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- for DSW</td>
<td>-</td>
<td>2 (4.0)</td>
<td>-</td>
<td>-</td>
<td>1 (2.1)</td>
<td>-</td>
</tr>
<tr>
<td>- not for DSW</td>
<td>11 (24.4)</td>
<td>14 (28.0)</td>
<td>15 (30.0)</td>
<td>17 (34.7)</td>
<td>13 (27.7)</td>
<td>10 (20.8)</td>
</tr>
<tr>
<td>ASA classification, n (%)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>- ASA I</td>
<td>17 (37.8)</td>
<td>15 (30.0)</td>
<td>13 (26.0)</td>
<td>16 (32.7)</td>
<td>13 (27.7)</td>
<td>18 (37.5)</td>
</tr>
<tr>
<td>- ASA II</td>
<td>18 (40.0)</td>
<td>21 (42.0)</td>
<td>22 (44.0)</td>
<td>17 (34.7)</td>
<td>16 (34.0)</td>
<td>15 (31.3)</td>
</tr>
<tr>
<td>- ASA III</td>
<td>10 (22.2)</td>
<td>13 (26.0)</td>
<td>14 (28.0)</td>
<td>14 (28.6)</td>
<td>16 (34.0)</td>
<td>12 (25.0)</td>
</tr>
<tr>
<td>Indication for SSG, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Chronic wound</td>
<td>10 (22.2)</td>
<td>8 (16.0)</td>
<td>10 (20.0)</td>
<td>13 (26.5)</td>
<td>6 (12.8)</td>
<td>12 (25.0)</td>
</tr>
<tr>
<td>- Burn wound</td>
<td>1 (2.2)</td>
<td>2 (4.0)</td>
<td>3 (6.0)</td>
<td>1 (2.0)</td>
<td>3 (6.4)</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>- Surgical/traumatic wound</td>
<td>29 (64.4)</td>
<td>28 (56.0)</td>
<td>27 (54.0)</td>
<td>30 (61.2)</td>
<td>27 (57.4)</td>
<td>25 (52.1)</td>
</tr>
<tr>
<td>- Tumor excision</td>
<td>5 (11.1)</td>
<td>10 (20.0)</td>
<td>8 (16.0)</td>
<td>4 (8.2)</td>
<td>10 (21.3)</td>
<td>9 (18.8)</td>
</tr>
<tr>
<td>- Other</td>
<td>-</td>
<td>1 (2.0)</td>
<td>1 (2.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Location of the DSW, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>- Thigh</td>
<td>44 (97.8)</td>
<td>44 (88.0)</td>
<td>46 (92.0)</td>
<td>47 (95.9)</td>
<td>44 (93.6)</td>
<td>45 (93.8)</td>
</tr>
<tr>
<td>- Other</td>
<td>1 (2.2)</td>
<td>5 (10.0)</td>
<td>3 (6.0)</td>
<td>1 (2.0)</td>
<td>2 (4.2)</td>
<td>2 (4.2)</td>
</tr>
<tr>
<td>Median DSW surface area, cm² (range)</td>
<td>50.0-240</td>
<td>49.0-600</td>
<td>50.0-450</td>
<td>49.0-800</td>
<td>49.0-750</td>
<td>49.0-760</td>
</tr>
<tr>
<td>Median thickness of graft, mm (range)</td>
<td>0.30-0.6</td>
<td>0.30-0.6</td>
<td>0.30-0.6</td>
<td>0.30-0.7</td>
<td>0.30-0.7</td>
<td>0.30-0.7</td>
</tr>
<tr>
<td>Haemostasis, n (%)</td>
<td>18 (40)</td>
<td>10 (20.0)</td>
<td>23 (46)</td>
<td>26 (53.1)</td>
<td>14 (29.8)</td>
<td>23 (47.9)</td>
</tr>
</tbody>
</table>

SD, Standard Deviation; DM, Diabetes Mellitus; BMI, Body Mass Index; DSW, Donor Site Wound; ASA, American Society of Anesthesiologists; SSG, Split-Skin Grafting.
fewer patients (19.6%) in the film dressing group. The majority of grafts (57.4%) was used to treat a surgical or traumatic wound and were mostly taken from the thigh (n = 270, 93.4%), with a mean thickness of 0.32 millimeters (SD 0.15) and a mean grafted area of 78.4 cm² (SD 109.2). Participating centers mainly used Kaltostat® in the alginate group and Adaptic® in the gauze group, while Tegaderm® and Opsite® were applied equally frequent in the semi-permeable film group.

Primary outcomes: Complete wound healing and pain

Time to complete re-epithelization was seven days (i.e. 30%) shorter using hydrocolloid dressings (median 16 days) than using any other dressing (median 23 days) (Figure 2; cumulative wound healing; P-value <0.001, log rank test). Median time to complete re-epithelization for each dressing group is shown in Table 2.

Overall, pain scores (10-cm VAS), as calculated from 3360 recordings, were low (median 0.4, Inter-quartile range [IQR] 0 to 1.4), although these were slightly but significantly lower in the semi-permeable film group (P-value = 0.038, type-III test of fixed effects) than in the other dressing groups combined.

Figure 2. Kaplan-Meier cumulative wound healing curve comparing hydrocolloid dressing to the remaining dressings in donor site wounds. The difference in wound healing time between the two curves is significant (log-rank test P value < 0.001).
Study results Rembrandt Trial

Secondary outcomes: Adverse events, itching and scarring

Infection rate was twice as high in patients treated with gauzes as in those receiving other dressings (18% vs. 9%, RR 2.39, 95% CI 1.14 to 5.01, NNH= 11). Allergic reactions were never reported and hypergranulation occurred rarely, as shown in Table 2.

Itching scores (10-cm VAS) were calculated from 3579 recordings and were lower (median 0.2, IQR 0 to 0.8) than the pain scores. No significant differences were found among the dressing groups.

POSAS data were collected in 137 patients from five contributing centers. Results and summary scores are shown in Table 3. Patients receiving semi-permeable films

Table 2. Primary and secondary outcomes by treatment allocation group

<table>
<thead>
<tr>
<th>Group</th>
<th>Alginate (n=45)</th>
<th>Film (n=49)</th>
<th>Gauze (n=50)</th>
<th>Hydrocolloid (n=49)</th>
<th>Hydrofiber (n=47)</th>
<th>Silicone (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to wound</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>healing, days (IQR)</td>
<td>22.0 (19-29)</td>
<td>23.0 (14-36)</td>
<td>22.0 (18-33)</td>
<td>16.0 (12-21)*</td>
<td>22.0 (15-27)</td>
<td>26.0 (18-33)</td>
</tr>
<tr>
<td>Pain, median (IQR)</td>
<td>0.4 (0.0-1.9)</td>
<td>0.3 (0.0-1.0)*</td>
<td>0.3 (0.0-1.5)</td>
<td>0.2 (0.0-1.1)</td>
<td>0.8 (0.0-1.5)</td>
<td>0.4 (0.1-1.1)</td>
</tr>
<tr>
<td>Itching, median (IQR)</td>
<td>0.2 (0.0-0.9)</td>
<td>0.3 (0.0-0.9)</td>
<td>0.2 (0.0-0.6)</td>
<td>0.2 (0.0-0.8)</td>
<td>0.3 (0.0-1.0)</td>
<td>0.2 (0.1-0.7)</td>
</tr>
<tr>
<td>Adverse events, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Clinical infection</td>
<td>0</td>
<td>8 (16.0)</td>
<td>9 (18.0)*</td>
<td>1 (2.0)</td>
<td>7 (14.9)</td>
<td>2 (4.2)</td>
</tr>
<tr>
<td>- Allergic reaction</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>- Hypergranulation</td>
<td>1 (2.2)</td>
<td>1 (2.0)</td>
<td>0</td>
<td>1 (2.0)</td>
<td>1 (2.1)</td>
<td>2 (4.2)</td>
</tr>
<tr>
<td>- Other</td>
<td>0</td>
<td>2 (4.1)</td>
<td>2 (4.0)</td>
<td>0</td>
<td>0</td>
<td>1 (2.1)</td>
</tr>
</tbody>
</table>

IQR, Inter-quartile range. *P-value < 0.05

Table 3. Patient and observer scar assessment results by treatment allocation groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Alginate</th>
<th>Film</th>
<th>Gauze</th>
<th>Hydrocolloid</th>
<th>Hydrofiber</th>
<th>Silicone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>24</td>
<td>20</td>
<td>22</td>
<td>21</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>POSAS, median (IQR)</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 observer, median (IQR)</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>Overall scar rating patient, median (IQR)</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>Dressing satisfaction patient, mean (range)</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>

POSAS, Patient Observer Scar Assessment Scale; for Observer and Patient a score of 6 indicates normal skin, and 60 indicates the worst possible result. IQR, Inter-quartile range.
were significantly less satisfied with their total score of the scar (P-value = 0.018, Wilcoxon rank sum test), especially regarding the item “wound relief” (P-value = 0.046, Mann-Whitney U test), as compared to those in the other dressing groups. Scar assessment by the observers did not show significant differences among the dressing groups.

DISCUSSION

This trial allowed the comparison of six commonly used wound dressing materials to cover donor sites after split-skin grafting. The evidence obtained shows that hydrocolloid dressings lead to a 7-day, i.e. a 30% shorter healing time than the other materials. The use of gauze dressings was found to increase the risk of infection.

This quicker wound healing when using hydrocolloid dressings might be explained by a differential wound angiogenesis associated with different degrees of occlusion. Dressings promoting a moist wound environment, like hydrocolloids, have been shown to improve re-epithelialization, increase collagen synthesis and ultimately improve healing rates. The shorter healing time of donor sites using dressings that promote moist wound healing was already suggested by previous aggregated evidence. 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 this trial based on evidence from previous literature and a national inventory showing a lower eligibility. The (moist) wound environment may also be influenced by the type of secondary wound dressings applied. In this trial the study protocol prescribed the uniform use of gauze-based secondary dressings. Hence, the effects of other secondary dressings (e.g. semi-permeable film) used in clinical practice could not be studied.

The time to complete healing we found in the hydrocolloid group exceeds the healing times reported in other studies, which varied from 10 to 12 days. This is likely due to our strict definition of complete epithelialization stating that complete wound healing was not reached until any remaining scabs had fallen off. This is in contrast with a range of definitions applied in other studies, including epithelial coverage, absence of exudates, scarring appearance, and proportion of the wound healed. Although our definition and, consequently, our healing time results may differ from other studies, it was chosen as an objective, uniform, easily assessable and patient-relevant outcome. Moreover, this definition had no influence on the differences in complete wound healing as found here.

The high risk of infection in patients treated with gauze dressings was also found for fine mesh gauze dressings with scarlet red, showing a 9.6% infection rate. The
prescription of antibiotics may have influenced the infection rates recorded. In the present trial, patients in all dressing groups received systemic antibiotics in similar percentages from 20-30%, mostly subscribed for other indications than the DSW. This may have underestimated the infection rates found in our study. Still, despite the relatively high percentage of patients receiving antibiotics in this trial, gauze dressings were accompanied by a significantly higher infection rate of the donor sites, which will have prolonged the healing time. On the other hand, aggregated evidence of gauze dressings for donor site wounds and postoperative wounds did not find an increased risk of infection\textsuperscript{1,6,7,14,27}.

Haemostasis was applied in fewer patients in the film and hydrofiber groups than in other dressing groups. However, the surgeon’s decision to perform haemostasis was not influenced by the dressing the patients were allocated to, as this was decided by randomization after the haemostatic intervention. In the gauze, hydrocolloid, and silicone groups, haemostasis was applied in about 50% of the patients, but time to wound healing differed considerably among these groups, indicating haemostasis does not seem to have a substantial effect on wound healing. Available literature also offers little evidence on the relation between haemostasis and wound healing\textsuperscript{28}.

Some possible limitations of this trial are the following. First, we accepted some variation regarding the thickness of the graft, method of harvesting, and the surgeons’ preferences regarding haemostasis and treatment of infection. This was intentional, to allow for a pragmatic trial that would mimic daily clinical practice.

Second, cosmetic appearance of the scars was assessed after three months, even though actively remodeling and maturation of scars takes at least 12 months\textsuperscript{29}. Nevertheless, the POSAS score is a reliable and valid instrument to identify a change of scar characteristics\textsuperscript{18,30}. In our study protocol we were interested in differences in scar development related to the dressing materials investigated. Our assumption was that differences seen at three months would diminish in time, as shown in other studies\textsuperscript{31,32}.

Third, we were unable to accurately report on costs, which play a substantial part in the choice of wound treatment. Unit and total costs of hydrocolloid dressings are reported as costly\textsuperscript{1,33}. However, investigators frequently report on unit costs but do not take into account dressing changes, nursing times, or rapid healing time and secondary wins as early mobilization. We were confronted with the same difficulty to accurately record and report the costs of such factors. However, the costs of local wound treatment should be put in perspective of other factors. The relatively high costs per dressing unit\textsuperscript{1,4,33} are at least in part compensated by a low dressing change frequency of once in up to seven days, which causes little pain. Besides, patient preferences or priority for rapid healing may downplay the costs of a dressing material, e.g. in cases with extensive thermal injuries or severe comorbidity. In such scenarios
hydrocolloid dressings, which do not need frequent dressing changes, seem preferable to achieve a more rapid wound healing.

Comprehensive inclusion criteria (e.g. all adults requiring a split skin graft regardless of the presence of diabetes mellitus) are one of the strengths of this trial and allow application to a broad patient population with donor site wounds that may benefit from a hydrocolloid dressing. Also, these study results reflect local practice of 14 national centers that improve the generalizability and implementation\textsuperscript{34}. Finally, in our trial set-up we put effort in minimizing the risk of bias due to incomplete outcome data, which resulted in a low percentage (3\%) of dropouts.

The results of our study should decrease the current diversity in treatment choices of donor site wounds since treatment options can be made more evidence-based. Several practical considerations should be mentioned using hydrocolloid dressings. Before application of the dressing, the skin should be clean, i.e., fatty disinfectants may be avoided for better adherence. Especially with increasing wound size area, wound leakage can be a problem due to interaction of wound exudate with the dressing\textsuperscript{35;36}. On the other hand, a moist interface between the dressing and the wound could reduce the postoperative discomfort and minimize tissue damage during dressing changes\textsuperscript{23;35}.

In conclusion, this randomized multicenter trial showed that hydrocolloid dressings lead to a seven-day shorter healing time than other commonly used dressing materials for donor sites. This result combined with other patient-relevant outcomes found, like infection rate, pain, and scarring, should contribute to a uniform and evidence-based treatment of donor site wounds.
REFERENCES


