ORIGINAL ARTICLE

A prospective, randomised study of a novel transforming methacrylate dressing compared with a silver-containing sodium carboxymethylcellulose dressing on partial-thickness skin graft donor sites in burn patients

Ojan Assadian1, Brett Arnoldo2, Gary Purdue2, Agnes Burris2, Edda Skrinjar3, Nikolaus Duschek3 & David J Leaper4

1 Department for Hospital Hygiene, Medical University of Vienna, Vienna General Hospital, Vienna, Austria
2 Department of Surgery, The University of Texas Southwestern Medical Center, Dallas, TX USA
3 Department for Vascular and Endovascular Surgery, Wilhelminen-Hospital, Vienna, Austria
4 Department of Surgery, University of Newcastle upon Tyne, Newcastle upon Tyne, UK

Key words
Altrazeal; Burns; Carboxymethylcellulose dressing; Dressing change; Pain; Silver dressings; Split-thickness skin graft donor sites; Transforming methacrylate dressing

Correspondence to
Prof. O Assadian, MD, DTMH
Department for Hospital Hygiene
Medical University of Vienna
Vienna General Hospital
Waehringer Guertel 18-20
1090 Vienna, Austria
E-mail: ojan.assadian@meduniwien.ac.at


Abstract

This prospective, randomised study compares a new transforming methacrylate dressing (TMD) with a silver-containing carboxymethylcellulose dressing (CMC-Ag) after application to split-thickness skin graft (STSG) donor sites. This was an unblinded, non-inferiority, between-patient, comparison study that involved patients admitted to a single-centre burn unit who required two skin graft donor sites. Each patient’s donor sites were covered immediately after surgery: one donor site with TMD and the other with CMC-Ag. The donor sites were evaluated until healing or until 24 days post-application, whichever came first. Study endpoints were time to healing, daily pain scores, number of dressing changes, patient comfort and physicians’ and patients’ willingness to use the dressings in the future. Nineteen patients had both the dressings applied. No statistically significant difference was noted in time to healing between the two dressings (14.2 days using TMD compared with 13.2 days using CMC-Ag). When pain scores were compared, TMD resulted in statistically significantly less pain at three different time periods (2–5 days, 6–10 days and 11–15 days; P < 0.001 at all time periods). Patients also reported greater comfort with TMD (P < 0.001). Users rated TMD as being less easy to use because of the time and technique required for application. Reductions in pain and increased patient comfort with the use of the TMD dressing, compared with CMC-Ag, were seen as clinical benefits as these are the major issues in donor site management.

Introduction

Acute wounds, such as burns and crush injuries, chronic wounds, such as venous leg ulcers, and wounds associated with necrotising tissue infection often require excision and split-thickness skin grafting (STSG). STSG donor sites can be expected to heal, with appropriate wound care, within 10–20 days (1,2) using the TIME principles (3). These donor site wounds require a moist, clean wound environment, free of cellular debris and need to be protected from external mechanical and infectious agents (2,4). A variety of dressings

Key Messages
- this prospective, randomised unblinded, non-inferiority, between-patient comparison study involving patients
are available to accommodate these requirements including moist, non-resorbable gauzes and sponges; hydrophilic and hydrogel dressings; occlusive hydrocolloid wound dressings and other interactive wound and burn dressings (classified in national and international formularies), as well as those incorporating topical antimicrobials (including polyhexamethylene biguanide, povidone-iodine and chlorhexidine), silver sulphadiazine, silver emulsions and silver barrier dressings and silicone dressings. One of the most widely used dressings, available for STSG donor sites and partial-thickness burns, is a sodium carboxymethylcellulose sheet, which can be applied to the wound bed (5,6). Aqualcel Ag with Hydrofiber® (ConvaTec, Princeton, NJ) is one of the currently used dressings (7).

Transforming methacrylate wound dressing (TMD; Altrazeal, Uluru Inc., Addison, TX) is a novel dressing composed of biologically inert polymer particles of poly(2-hydroxyethyl methacrylate) and poly(2-hydroxypropyl methacrylate). These hydrophilic polymers contain a covalent cation to split-thickness skin graft (STSG) donor sites. Split-thickness grafts were harvested using a dermatome (Zimmer® Air, Warsaw, IN) at a nominal setting ·012 inches. The grafts were then meshed at a 2:1 or 4:1 ratio. After the burn tissue was excised, the meshed skin grafts were secured to the excised wound beds using a surgical stapling device.

Before application of TMD to the donor site, the surgeon was instructed to clean the skin area with an appropriate wound cleanser to ensure that no oil-based products such as mineral oil, lotion or ointments were present. TMD was applied to the entire moist wound surface in a thin layer, with any excess on the surrounding intact skin being brushed off. The amount of dressing applied was dependent on graft size. Similarly, before application of a CMC-Ag dressing,
the surgeon was instructed to clean the graft donor site area and apply the dressing with a half- to one-inch overlap onto the skin surrounding the wound. As both dressings are incompatible with oil-based products such as petrolatum, identical wound cleansing procedure was required not only for comparison reasons but also to follow the manufacturers’ directions. A secondary protective gauze dressing was applied over both dressings.

Both comparator dressings were designed to cover and protect the STSG donor area until healing without dressing change unless there was evidence of leakage, bleeding, infection or pain. Meticulous wound care and adequate analgesia were provided for the duration of the study. Patients were monitored daily as part of standard procedures whilst they were in the in-patient setting. If and when patients moved to an outpatient setting, they were monitored on alternate days at the study centre. At each visit, the investigator determined whether each skin graft donor site had healed, using the institution’s standard care guidelines (i.e. >95% epithelialisation).

Subjects were questioned about pain using a 0–10 Linear Analog Scale Assessment (LASA) scale (9), with ‘0’ being no pain and ‘10’ being the worst imaginable pain. Similarly, patients’ and investigators’ satisfaction was surveyed using a 1–10 LASA scale. Additionally, adverse events were monitored daily as part of standard procedures whilst they were in the in-patient setting. If and when patients moved to an outpatient setting, they were monitored on alternate days at the study centre. At each visit, the investigator determined whether each skin graft donor site had healed, using the institution’s standard care guidelines (i.e. >95% epithelialisation).

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Results

Twenty patients (15 male and 5 female) were enrolled into the study and had the study dressings applied in accordance with the protocol; one patient was withdrawn from the study immediately after enrolment because of excessive bleeding at the donor sites on the day of surgery. Nineteen patients completed the study as planned, but seven discontinued prematurely: following an adverse event (n = 1), patient’s request (n = 1), protocol violation/non-compliance (n = 2) and lost to follow-up (n = 3).

Patients’ demographics and donor site characteristics

The ages of the 19 study patients ranged from 5 to 76 years, with a median of 36-0 and a mean of 36-6 (SD±16-7) years. Four were female (21%) and 15 were male (79%). Eleven patients (58%) were Caucasians, 4 (21%) African Americans, 3 (16%) Hispanic and 1 (5%) Asian. The mean (±SD) donor site size was 264 cm² (±281.9) for TMD sites and 229 cm² (±157.3) for CMC-Ag sites (Table 1). All grafts from individual patients were harvested at the same nominal thickness.

Table 1 Summary of donor site characteristics

<table>
<thead>
<tr>
<th>Location</th>
<th>TMD</th>
<th>CMC-Ag</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Size (cm²)</td>
<td>Mean (±SD)</td>
<td>264 (±281.9)</td>
</tr>
<tr>
<td>Median (Min–Max)</td>
<td>154 (36, 1008)</td>
<td>197 (64, 759)</td>
</tr>
<tr>
<td>Thigh</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Lower leg</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

TMD, transforming methacrylate dressing; CMC-Ag, silver-containing carboxymethylcellulose dressing.

Efficacy results

When time to healing was compared between the two dressings in the 19 patients treated, no statistically significant difference was found (Table 2). With a time to healing of 14-2 days for the TMD-treated sites and 13-2 days for the CMC-Ag-treated sites, the 1-day difference with the shorter healing time for the CMC-Ag dressing was not statistically significant (P = 0.16). The small sample size did not allow for conclusion of non-inferiority of the TMD (95% confidence interval: −0.5 to 2.8 days).

Pain scores at all time periods showed statistically significant differences between the two dressings, with TMD being associated with lower pain scores than CMC-Ag (Table 3). Between day 2 and day 5, the average pain score recorded was 3-7 following use of the CMC-Ag dressing compared with 1-6 after use of the TMD (P < 0.0001). Similarly, for days 6–10, the average pain score was 2-6 after use of the CMC-Ag dressing compared with 0-7 after use of the TMD (P < 0.0001; Table 3).

Dressing in skin graft donor sites

When inquired about comfort of the dressing at the edges, study subjects found TMD to be more comfortable than CMC-Ag (mean score of 8-6 compared with 5-9, respectively; P < 0.001). Similarly, they experienced less pain when the
TMD dressing came indirectly into contact with clothes or bedding compared with the CMC-Ag dressing (mean pain score of 2.1 versus 5.1; \( P < 0.001 \)). Table 4 summarises responses to the three subject satisfaction survey questions at the final visit.

There was no significant difference between the two dressings with regard to how well they remained in place after application as both dressings performed well (median score of 9.5 for TMD compared with 8.6 for CMC-Ag).

When asked about ease of use during application of the dressings, the surgeons found CMC-Ag to be easier to use and less time-consuming than TMD (average score of 10.0 versus 2.2; \( P < 0.001 \)), and therefore anticipated using CMC-Ag in the future rather than TMD (average score of 10.0 for CMC-Ag versus 1.1 for TMD; \( P < 0.001 \)) principally owing to the application time in the operation theatre environment.

Discussion

This study of a novel TMD compared with a CMC-Ag established that a new dressing is feasible for management of STSG donor sites.

TMD is indicated for use in surgical wounds, exuding superficial acute wounds (such as STSG donor sites and second degree burns) as well as chronic slow-healing wounds including leg ulcers, pressure ulcers and diabetic ulcers. Clinical experience using TMD in the treatment of diabetic foot-related necrotising fasciitis has been published, reporting a decrease in pain after application of the TMD dressing (8). This was attributed by the authors to be related to a decrease in inflammation, the cooling effect of the dressing and the complete wound sealing associated with the application of TMD. Indeed, immediate pain control after application of dressing is one of the most frequently observed clinical features of the TMD dressing. However, while beneficial, the exact mechanism is unknown and further research on this observation is required.

Aquadrel Ag with Hydrofiber (CMC-Ag) is one of the most widely used dressings for the management of STSG (7). In addition, it is one of the most widely studied and published wound dressings. Between 2006 and 2013, six randomised controlled clinical trials (RCTs) have been conducted and published with this hydrofiber dressing containing ionic silver (11–16), with half of these RCTs having been undertaken in patients with partial-thickness burns. Caruso et al. (11) conducted a prospective, randomised study comparing CMC-Ag with silver sulphadiazine in the management of partial-thickness burns covering 5–40% total body surface area (TBSA). While silver sulphadiazine was associated with greater flexibility and ease of movement, the hydrofiber dressing was associated with less pain and anxiety during dressing changes. Similar observations were reported by Muangman et al. (14) after conducting a prospective randomised study in patients with partial-thickness burns less than 15% TBSA. Both time-to-wound closure and pain scores were significantly shorter in the CMC-Ag group during the first week of application compared with the silver sulphadiazine group. In this study, the average pain scores decreased at days 1, 3 and 7 from 4.1 ± 2.1 to 2.1 ± 1.8, and 0.9 ± 1.4, respectively. The pain reduction reported in this previous trial is similar to the results of this study. Although the LASA pain score assessments were not conducted at the same time periods, a similar trend was observable: during days 2–5, the average pain score was 3.7 ± 0.3, during days 6–10 it decreased to 2.6 ± 0.3 and finally during days 11–15 an average pain score of 1.9 ± 0.4 was recorded. The reproducibility of clinical results for the CMC-Ag dressing supports the validity of the data of this study, as the results of the CMC-Ag group reported herein correspond well with published data in burn patients (11–13).

Our study has some limitations. First, this was a small study undertaken in one specialist area. Because of the strict inclusion and exclusion criteria, it was difficult to recruit more patients. However, aside of the fact that patients served as both, intervention and control arm, this additionally resulted

TMD in split-thickness donor sites

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>TMD</th>
<th>CMC-Ag</th>
<th>Difference (TMD – CMC-Ag)</th>
<th>( P )-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>( N )</td>
<td>17</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Means estimate (SE)</td>
<td>14.2 (0.8)</td>
<td>13.2 (0.7)</td>
<td>1.0 (0.8)</td>
<td>( 0.16 )</td>
</tr>
<tr>
<td>Minimum</td>
<td>10</td>
<td>9</td>
<td>–1</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>23</td>
<td>20</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>12.5, 15.9</td>
<td>11.5, 14.6</td>
<td>–0.5, 2.8</td>
<td></td>
</tr>
</tbody>
</table>

*Matched-pairs \( t \)-test with healing times imputed for four patients with censored times, as follows: for patients with healing not observed, the time to healing was assumed to be less than or equal to 24 days and was estimated using each treatment’s conditional survival curve after the observed censored day. If last follow-up without healing was 4 days (subject 08) then days to healing was estimated to be 12.6 days for TMD, 11.2 days for CMC-Ag. If 9 days (subject 04) then 12.5 days was used for TMD, 12.6 days for CMC-Ag, and for 14 days (subjects 01 and 14) from healing was used for TMD, 14.6 days for CMC-Ag.

### Table 3

<table>
<thead>
<tr>
<th>Days</th>
<th>TMD</th>
<th>CMC-Ag</th>
<th>Difference (TMD – CMC-Ag)</th>
<th>( P )-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–5</td>
<td>Least square means estimate (SE)</td>
<td>1.6 (0.3)</td>
<td>3.7 (0.3)</td>
<td>–2.1 (0.4)</td>
</tr>
<tr>
<td>6–10</td>
<td>Least square means estimate (SE)</td>
<td>0.7 (0.3)</td>
<td>2.6 (0.3)</td>
<td>–1.9 (0.4)</td>
</tr>
<tr>
<td>11–15</td>
<td>Least square means estimate (SE)</td>
<td>0.2 (0.4)</td>
<td>1.9 (0.4)</td>
<td>–1.7 (0.4)</td>
</tr>
</tbody>
</table>

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Table 4  Mean subjects’ response to satisfaction survey

<table>
<thead>
<tr>
<th>Final visit</th>
<th>TMD</th>
<th>CMC-Ag</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects with responses</td>
<td>17</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Q1—On a scale of 0–10, with 0 being not at all and 10 being very secure, did the dressing remain in place after application?</td>
<td>Mean (SD)</td>
<td>9·5 (0·9)</td>
<td>8·6 (1·9)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Min–Max</td>
<td>7, 10</td>
<td>5, 10</td>
</tr>
<tr>
<td>Q2—On a scale of 0–10, with 0 being very uncomfortable and 10 being very comfortable, did you find the edges of the dressing to be comfortable?</td>
<td>Mean (SD)</td>
<td>8·6 (2·3)</td>
<td>5·9 (1·9)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Min–Max</td>
<td>2, 10</td>
<td>2, 8</td>
</tr>
<tr>
<td>Q3—On a scale of 0–10, with 0 being no pain and 10 being the worse pain you have ever experienced, did you notice significant pain when the dressing came into contact with your clothing or bedding?</td>
<td>Mean (SD)</td>
<td>2·1 (2·5)</td>
<td>5·1 (2·2)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Min–Max</td>
<td>0, 10</td>
<td>2, 9</td>
</tr>
</tbody>
</table>

TMD, transforming methacrylate dressing; CMC-Ag, silver-containing carboxymethylcellulose dressing; SD, standard deviation.

*P-value from matched-pair t-test.

in a very comparable patient population. Therefore, underlying conditions did not have the ability to affect or skew the outcome. Second, our findings should be interpreted with caution, as it is difficult to transfer findings in healing of donor sites to other types of chronic wounds. However, the use of donor sites as a wound healing model provides a reproducible wound but makes healing end-point comparisons difficult for comparative treatments because donor sites are acute wounds, and of partial thickness, and are expected to heal quickly. The result of equivalent healing time points was, therefore, not unexpected. However, a major complaint made by patients who have a STSG donor site is pain with the need for comfort management, so a dressing that reduces pain and increases patient comfort is an important finding. An important extension of this study would be to determine if similar pain and comfort findings were applicable to other painful acute or chronic wounds. Milne and Serendipity (17) have reported that in a group of seven patients with venous leg ulcers, all patients reported improvements in pain levels within 15 minutes of TMD application, with a corresponding reduction in the use of oral pain medication.

One deviation from the protocol was that timely follow-up proved to be difficult after subjects were released from the hospital and asked to return for regular clinical check-ups. A number of patients did not have twice-weekly follow-up, which also reduced the precision with which the time to healing could be determined in this study. However, both donor site groups were equally affected by these protocol deviations.

Conclusion

This study has demonstrated that the new TMD can be used for the management of STSG donor sites. Compared with a conventional dressing, application of the novel dressing requires skill and is more demanding. Although no difference was noted in the time to healing between the two dressings, patients reported less pain and greater comfort with TMD ($P < 0·001$).

Acknowledgements

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