The treatment of donor sites with cultured epithelial grafts

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SUMMARY. In a significant number of elderly patients, the healing of split skin donor sites can be delayed. The cultured allogenic epithelial graft (CAG) has been reported to heal leg ulcers. The mechanism of action may be to improve the healing environment and thus stimulate the host skin cells.

A clinical trial was undertaken to compare the healing rate of the donor sites of elderly patients using CAGs and two commercially available dressings. Compared to Jelonet®, CAGs (p = 0.008) and OpSite® (p = 0.013) significantly reduced the number of patients with delayed healing. There was no significant difference between CAGs and the occlusive dressing, OpSite.

When applied to partial thickness burns (Madden et al., 1986) sheets of cultured epithelial cells have been reported to cause rapid re-epithelialisation. CAGs have been shown to exert a similar effect on leg ulcers (Leigh et al., 1987; Clancy et al., 1988). It was postulated that the epithelial cells may produce factors which stimulate proliferation of the skin cells. Recent evidence suggests that the grafted allogenic cells are not incorporated into the healed wound but are replaced by the patient's autologous cells as they are stimulated to grow by the CAG (Brain et al., 1989; Burt et al., 1989).

In a significant number of elderly patients the donor sites have been shown to be significantly slower to heal than a comparable group of patients under 60 years old (Fatah and Ward, 1984). This clinical trial was undertaken to determine whether the application of CAGs would accelerate the healing of split skin donor sites in a group of patients over sixty.

Patients and methods

Twenty-one patients were selected for the trial. They were over 60 years old, with isolated donor sites and with no other clinical condition which might affect healing. Three patients were subsequently excluded during the study period. The reasons for grafting in the remaining 18 patients are given in Table 1. The predominant donor site was the thigh (16 patients) but in two patients the upper arm was used.

CAGs were established from juvenile donors, previously screened for HIV and hepatitis B infection, using methods described by O'Connor et al. (1984). The CAGs were supported on a woven rayon dressing (N-A dressing, Johnson and Johnson) to enable transfer. In all but two of the patients the donor sites were dressed in three different ways: one-third was covered with the CAG, one-third with Vaseline-impregnated gauze (Jelonet, Smith and Nephew) and one-third with a bio-occlusive moisture-permeable polyurethane dressing (OpSite, Smith and Nephew) (James and Watson, 1975). The remaining two patients had only CAGs and Jelonet on their donor sites. In all cases the grafts were cut by hand, using a Watson or similar knife to remove a medium partial thickness skin graft, and every effort was made to maintain a uniform depth. The dressings were arranged to cover the donor area completely. No set order was maintained; however, a statistically random assignment was not used. The entire area was then covered with dry gauze and a crepe bandage.

The donor sites were examined after 7 days, and every 2 days thereafter the extent of healing was assessed subjectively. After removal of the superficial dressings, if the Jelonet was adherent but dry then the area was considered to be clinically healed. To minimise the trauma to the new epidermis, Jelonet was only removed after a considerable period of soaking. This procedure was not necessary with the other two dressings. Bacteriological swabs were taken if there was clinical evidence of infection. Assessment continued after initial healing to determine the stability of the healed donor sites.

Results

Of the 21 patients included in the trial, three were subsequently excluded—two had incomplete follow-
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up and one patient died. All were female, with an average age of 77.4 years (range 60-99 years).

Eight out of 18 areas dressed with Jelonet showed protracted healing times. In contrast, when CAG and OpSite were used, only two areas out of 18 and two areas out of 16 respectively showed delayed healing. These instances of delayed healing occurred in the same two patients whose wounds also failed to respond to treatment with Jelonet. In one patient the donor site healed after 87 days for zones treated with CAG and OpSite and 136 days in the case of Jelonet, whereas in the second patient all areas required 154 days. Thus, in these two cases it appears that neither CAG nor OpSite had any influence upon wound healing (Tables 2 and 3).

Table 2 Healing of donor sites in all patients, excluding two that took an exceptionally long time to heal

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Type of dressing</th>
<th>Range (days)</th>
<th>Average healing time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>Jelonet</td>
<td>7-44</td>
<td>19.4</td>
</tr>
<tr>
<td>16</td>
<td>CAG</td>
<td>7-20</td>
<td>11.0</td>
</tr>
<tr>
<td>14</td>
<td>OpSite</td>
<td>6-20</td>
<td>10.5</td>
</tr>
</tbody>
</table>

Table 3 Healing of different parts of the two donor sites excluded from Table 2

<table>
<thead>
<tr>
<th>Dressing</th>
<th>Healing time donor site 1 (days)</th>
<th>Healing time donor site 2 (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jelonet</td>
<td>136</td>
<td>154</td>
</tr>
<tr>
<td>CAG</td>
<td>87</td>
<td>154</td>
</tr>
<tr>
<td>OpSite</td>
<td>87</td>
<td>154</td>
</tr>
</tbody>
</table>

Excluding the two patients considered above, the average time of healing for donor site areas dressed with Jelonet was 19.4 days as compared with values of 11 and 16.5 for areas covered with CAG (p = 0.008) and OpSite (p = 0.013). Statistical analysis was by paired t-test and is significant at the 1% and 5% levels respectively. No significant difference was found between CAG and OpSite.

In addition to the two patients whose donor site areas showed delayed healing when dressed with either CAG, OpSite or Jelonet, six patients' wounds showed healing of donor site areas dressed with OpSite and CAG within the expected 21 days and delayed healing where dressed with Jelonet; the areas dressed with Jelonet in these six patients healed on days 23, 24, 25, 29, 39 and 44.

Evaluation of the appearance of the healed donor site and its stability after initial healing revealed some differences. The CAG-treated area often had a keratinous crust over it (assumed to be the remains of the CAG). The crust peeled away easily to reveal a well-consolidated epidermis similar in appearance to the area treated with Jelonet. In contrast the OpSite-treated area appeared smooth and shiny and the healed epidermis less consolidated.

Subsequent to initial healing, breakdown of the donor site occurred in four cases. In three patients breakdown was localised to the OpSite-treated area and occurred on days 15, 17 and 19 after initial healing. No apparent infection was observed in two cases although a bacteriological swab did reveal colonisation with Staphylococcus aureus in the third case. In the fourth patient breakdown occurred on day 15 and originated in the CAG-treated area which became red and blistered. There was no evidence of infection but histology revealed an inflammatory response with lymphocyte infiltration indicating tissue rejection (Aubock et al., 1988).

Discussion

We have studied the effect of CAGs on the healing of split skin donor sites in a sample of patients over the age of 60 years. All the patients in this study were female.

Donor sites are normally expected to heal within 21 days (Sawhney et al., 1969). However, in the elderly a significant number of patients show delayed healing (Fatah and Ward, 1984). To be an effective treatment, any dressing must significantly reduce this morbidity.

A comparison with the conventional donor site dressing shows that CAGs significantly reduce the overall healing time by reducing the number of patients exhibiting delayed healing. However, two patients showed delayed healing after treatment with both CAG and OpSite; no underlying clinical cause for such a prolonged period without healing was established.

Recent evidence indicates that the donor cells are not incorporated into the healed areas (Brain et al., 1989; Burt et al., 1989); CAG can therefore be regarded as a biological dressing. The application of growth factors to donor sites has been shown to promote rapid re-epithelialisation (Brown et al., 1989).

It is postulated that cultured cells may produce physiologically active factors which may stimulate the remaining autologous cells to proliferate. However, in this study we did not establish this as the mode of action of the CAG.

Healing may be promoted by creating a moist environment and preventing infection and further mechanical trauma (Davis, 1984). OpSite provides such an environment. The reduced healing time achieved with OpSite compared with Jelonet was similar to that shown with CAG, suggesting that an improved physical environment may play a major role in the improved healing promoted by CAGs.

The average day of healing and the number of patients showing delayed healing with CAG and OpSite are similar; no significant difference was shown.

The quality of healing achieved with each dressing is to some extent indicated by the incidence of subsequent breakdown. Once healing had been achieved with a Jelonet dressing it appeared stable. OpSite resulted in a new epidermis with a smooth, shiny and less consolidated appearance, which appeared to be due to lack of early adequate keratinisation. Where breakdown occurred in the OpSite-treated area, infection was noted in one of the three cases but whether the infection led to the breakdown or followed
an incidence of mechanical trauma could not be determined. In the absence of any evidence of infection in the remaining two cases, mechanical trauma could be a possible cause of breakdown. However, recent in vitro studies indicate the presence of cytotoxic substances which can leach out of the OpSite dressing (Thomas et al., 1988). Cell damage due to these agents may possibly provide an alternative explanation to this observation.

Conclusion

This study shows that CAGs provide a better wound environment than do conventional dressings for wound healing and therefore reduces the morbidity of delayed healing of donor sites in the elderly. The healing times with CAG and the occlusive dressing are similar and not statistically significant. The incidence of breakdown was less than with OpSite where, in the short term, the healed skin appeared less resistant to mechanical trauma. The possibility of previous sensitisation of the patient to the allograft tissue must be considered in donor selection.

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References


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