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Use of two stage keratinocyte-dermal grafting to treat the separation site in conjoined twins

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We illustrate a case of wound healing achieved by grafting with both cadaver dermis and keratinocytes cultured from the affected patient (autologous cultured keratinocytes). In this difficult case, grafting with stored, meshed skin failed to work, necessitating a novel approach. Whilst a stable skin substitute that can be produced in the laboratory is not yet available, the use of a dermal substrate and cultured keratinocytes as described here provides a useful model.

Case report

AH and KH were born in 1988 at 38 weeks gestation by lower segment Caesarean section and were separated at Great Ormond Street Hospital in April 1992. They were fused from shoulder to pelvis, sharing many internal organs although with separate heart and lungs. Pre-operatively, tissue expanders were inserted intraperitoneally and in the anterior and posterior thoracic areas to provide skin that was meshed and stored for future grafting. In addition, skin biopsies were taken and cultured in the laboratory to provide sheets of keratinocytes.

One twin survived separation, the ensuing wound encompassing the left side of the thoracic and abdominal walls (Figure 1). At the end of the procedure, the rib cage was closed and the area over this was successfully grafted with skin from the deceased twin. Abdominal closure, however, was not possible and the abdominal viscera were contained underneath a proline mesh, which was sutured to the muscles of the abdominal wall. Subsequent grafts of stored skin over the proline mesh failed to take and the abdominal wound dehised.

At this stage, all of the previously stored skin had been used. In an attempt to avoid split skin grafts from other sites, we then applied sheets of cultured keratinocytes to the abdominal wound bed. This was followed 2 weeks later by a two stage grafting technique whereby cadaver de-epidermalized dermis was applied to the wound followed by further cultured keratinocytes.

Over the subsequent 4 months the abdominal wound has continued to heal (Figure 2) with the underlying proline mesh being trimmed away regularly, the last remnants being recently removed.

Discussion

Skin has been successfully grown in the laboratory since 1975[1] and keratinocytes can now be grown into multilayered sheets suitable for grafting. The keratinocyte sheets are attached to gauze dressings by staples or sutures therefore allowing correct orientation, ensuring the basal cells are placed next to the wound bed and allowing easy application. The actual take rate of autologous keratinocytes is difficult to assess as the wound appears poorly epithelialized initially and becomes opaque with time, although in the best hands is probably no higher than 60%[2]. Apart from take, however, keratinocyte grafts may have a wound healing effect by producing a number of keratinocyte derived growth factors, promoting healing from the wound edge[3].

Ultimately, the best grafts are those with a dermal and epidermal component. Take of keratinocyte autografts is enhanced by pretreatment with a dermal element, which promotes attachment, development of the basement membrane and maturation of the graft. In our case, the dermal component was cadaver dermis. This was obtained from Euro Skin Bank, a branch of the Dutch Burns Foundation. Skin harvested from cadavers is preserved in 85% glycerol, where it can be stored for up to 2 years. Before grafting the Euro-skin the epidermis is removed by means of an enzyme 'Dispase' leaving the dermis which is then used for grafting.

Antigenicity of cadaver donor skin preserved in this way is lost, so the skin can be grafted without the need for

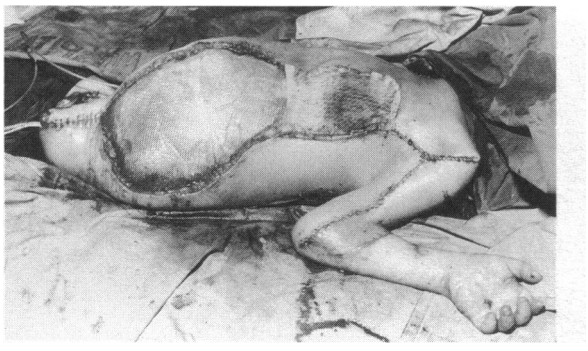

Figure 1. Immediately after separation

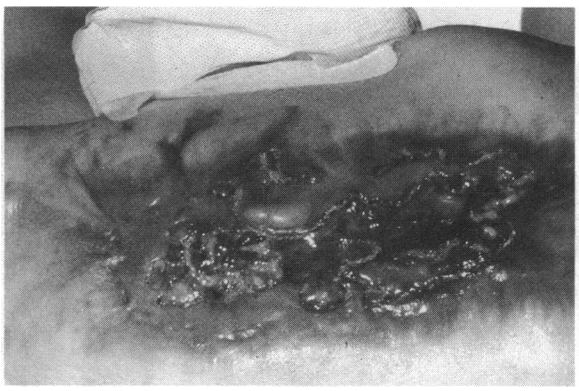

Figure 2. Three months after separation

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immunosuppression. Meshing the dermis allows a larger surface area to be grafted and allows simultaneous grafting with cultured keratinocytes.

Unfortunately, the demand for cadaver skin greatly outstrips supply and there is a need for a connective tissue component (dermal substitute) that can be produced in the laboratory. Various techniques have been tried leading to the formation of a number of composite skin grafts or 'artificial skin substitutes'. Collagen gels contracted by incorporation of fibroblasts have had keratinocytes cultured on the surface to form a composite culture graft[4] and a combination of bovine collagen and shark chondroitin-6-sulphate has been overlaid with sheets of Silastic in an attempt to produce a stable skin substitute[5]. In fact, a number of complex culture systems exist, containing substrates of human, rat or bovine collagen some cross linked with glycoproteins and others containing fibroblasts. Unfortunately, many groups have reported poor handling with these systems[6] and dermo-epidermal separation remains a problem. Certainly, at present, intact whole dermis appears to be the best substrate available.

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Hypoglycaemia and Golytely in distal intestinal obstruction syndrome

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Keywords: distal intestinal obstruction syndrome; cystic fibrosis; Golytely; hypoglycaemia

Distal intestinal obstruction syndrome (DIOS) is a well recognized complication of cystic fibrosis (CF). Osmotic agents such as gastrografin or a balanced intestinal lavage solution, Golytely (Seward Medical, London, UK) are often used in treating this condition with few side effects[1-4]. Cleghorn *et al.*[1] have shown that Golytely produces clinical and radiological improvement in DIOS and that it is well accepted, safe and effective[3].

These reports refer to patients in the adolescent age group or older. There are no reports of its use in younger children. We present an 8½-year-old girl who had a hypoglycaemic convulsion following treatment with Golytely.

Case report

SJ was an 8½-year-old girl with CF who had presented with meconium ileus. She required a partial ileal resection in the neonatal period and by the age of 7 years had developed chronic liver disease. The main clinical problems were weight loss and peripheral oedema with hepatomegaly of 5 cm and her spleen was not enlarged. Investigations showed an elevated AST 125 u/l, a prolonged KPTT (57 s, control 36 s), abnormal prothrombin time (20 s, control 13 s) and low albumin 20 g/l. Liver ultrasound showed changes suggestive of fatty infiltration and an imino diacetic (HIDA) scan showed evidence of chronic gall bladder involvement. Her liver disease progressed, she developed portal hypertension with grade II-III oesophageal varices and ultrasonography suggested cirrhosis. In view of her poor nutrition and weight which was below the 3rd centile, she was commenced on overnight nasogastric feeds with 800 ml of medium chain triglyceride (MCT) peptides which she tolerated very well. During this period, she had recurrent episodes of DIOS characterized by nausea, vomiting and abdominal pain mainly in the right iliac fossa. This was treated initially with lactulose, oral acetylcysteine and cisapride. Her intestinal obstruction recurred and she was therefore treated with Golytely. Between these episodes, her main source of calories was through the overnight feeds.

Golytely solution is prepared by adding lukewarm drinking water to the powder in the ready made bottles. The chemical composition of the solution is sodium 125 mmol/l, potassium 10 mmol/l, sulphate 40 mmol/l, bicarbonate 20 mmol/l, chloride 35 mmol/l, polyethylene glycol (4000) 17.6 mmol/l. Following a period of 1 to 3 h fasting the solution is administered orally or through a nasogastric tube at a rate of 500 to 1000 ml/h. The total volume of infusate required ranges from 1 to 5 l, but the infusion is continued until the discharge per rectum becomes clear of faecal material. In this case the patient became drowsy and had a convulsion when she had received approximately 1.2 l of Golytely over a period of 1 h. She had then been fasted for a total of 2 h. Blood sugar was low (0.8 mmol/l) and she responded to 10% dextrose intravenously becoming fully conscious and with no further seizures. A subsequent 24 h blood glucose profile showed intermittently high insulin levels (range 5 to 65.3 μu/l, normal 0 to 10 μu/l). The insulin/glucose ratio during fasting was, however, normal. Fasting levels of β-3-hydroxy buterate, free fatty acids, growth hormone and lactate were normal. On fasting over 8 h, she had low levels of plasma cortisol, though the synacthen test was normal.

Discussion

Golytely (recently renamed 'Klean-Prep') is a non-absorbable osmolar agent with minimal transmucosal flux of fluid and electrolytes which has become popular in the treatment of DIOS[1,3]. At the Hospital for Sick Children in London, Golytely has been used since 1986 for 22 episodes of DIOS in a total of 12 CF children. Their ages ranged from 8 to 15.5 years and the volume of Golytely infused ranged from 1 to 5 l. Side effects were minimal. Nausea, abdominal discomfort, bloating and occasional vomiting have been reported previously[1,3,4]. A hypoglycaemic convulsion following Golytely has not previously been reported. The

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