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The Superiority of Amniotic Membrane in the Treatment of Aplasia Cutis Congenita

Weijie He[1], Ma Ke[2], Yunpu He[3], Zhan Ouyang[3], Jing Su[4✉*] and lujun yang[5✉]

[1]Plastic Surgery, Second Affiliated Hospital, Shantou University Medical College, Shantou, M.D., Ph.D., China

[2]Department of Plastic & Cosmetic Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning, M.D., Ph.D., China

[3]Plastic Surgery, Second Affiliated Hospital, Shantou University Medical College, Shantou, M.D., MA., China

[*4✉]Nursing Faculty, Shantou University Medical College, Shantou, R.N., M.N., Ph.D., China

[5✉]Plastic Surgery, Second Affiliated Hospital, Shantou University Medical College, Shantou, M.D., Ph.D., China

[*]Corresponding author:

Jing Su, R.N., M.N., Ph.D.,
Nursing Faculty, Shantou University Medical College, Second Affiliated Hospital of Shantou University Medical College Dongxia North Road (Zhu-Xia block), Shantou, 515041 Guangdong Province, China, Tel: +86 (0)754 8891 5666;
E-mail: jsu@stu.edu.cn

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Aplasia cutis congenital; Amniotic membrane; Scarring

1. Abstract

1.1. Introduction: Aplasia cutis congenital (ACC) is a heterogeneous group of disorders that share a common feature of focal skin loss. In most cases, this is limited to the scalp, also involve other parts of the body. (ACC) is a heterogeneous group of disorders whose common characteristic is focal absence of skin. In the majority of instances this is limited to the scalp, although other areas of the body may also be involved. It is characterized by a lack of skin and adjacent tissues, and it can extend into underlying tissues, such as muscle tissue and bone, that can be underdeveloped or even absent. ACC can be life-threatening in severe cases. Both conservative and surgical approaches carry risks, and the timing of surgery remains controversial. Most literatures do not have detailed information on the treatment of this disease due to its rarity. Although ACC tends to be superficial and relatively small, it can also be large and poorly organized, increasing the risk of bleeding, infection, and death. Nonsurgical versus surgical intervention in this condition is controversial. Conservative care of two neonatal patients admitted to our hospital was taken by performing amniotic therapy and further gradual development was observed. This therapy was provided in order to investigate the superiority and long-term efficacy of cryopreservation of amniotic membrane (AM) in the treatment of skin defects in congenital cutaneous

agenesis (ACC).

1.2. Methods: Two neonatal cases with congenital cutaneous hy- poplasia diagnosed in 2019 and 2021 in the undergraduate depart-ment were used in this study. Clinical data were obtained from daily records during the diagnosis and treatment of children, and photographs was obtained by the plastic surgery team. Amniotic membranes were obtained from term cesarean section in healthy term pregnancy and cryopreserved in liquid nitrogen after pro- cessing it in a sterile laminar flow hood. The structure of AMs was histologically studied, and the viability of epithelial cells was detected after cryopreservation. The cryopreserved AMs were ap-plied to the skin defect of the lower extremity of children with ACC, and the changes were made in time if necessary until the wound healed.

1.3. Results: This study included 1 conservatively treated case: located on the left upper arm and left anterior chest and left back. Another case of amniotic membrane treatment was located in bothlower extremities, all of which were female. Defect sizes ranged from approximately 40 and 60 cm 2 (50 cm 2 on average). All pa-tients voluntarily received active treatment, one conservative tra- ditional dressing treatment, the other adding amniotic membrane covering dressing treatment, to keep the skin clean and dry. Both treated patients survived and thrived.

1.4. Conclusion: The limb skin defect of ACC infants treated with cryopreserved amniotic membrane was gradually epithelialized after application of AM, and healed after 1 month. Follow-up results at 6 months after treatment showed good skin texture and color without hypertrophic scarring. The children treated with conservative traditional treatment healed within 50 days. The follow-up results of 6 months after treatment showed that the skin texture and color were poor, and there was obvious hypertrophic scar formation, which affected the movement of the upper limbs. AMs has the characteristics of improving wound healing and inhibiting scar formation in the treatment of ACC skin defects. This article highlights the role of the amniotic membrane in the management of patients with extensive congenital cutaneous hypoplasia, and also proposes a practical, treatment-oriented classification that can help physicians estimate disease severity and prognosis, and provide treatment guidelines.

2. Preface

ACC is a rare congenital disorder characterized by the presence of the epidermis in one or several areas. Sometimes congenital defect involves the subcutaneous tissue, usually on the crown of the head or the lower extremities which is limited at birth. Patient's skin and subcutaneous tissue defects were removed since the base is rough and red granuloma, which is thick-walled and large. Its top can quickly fall off, exposing pink discoloration and sore surfaces can heal very slowly [1] was first described as a limb lesion by Cordon in 1767 [2]. In 1826, Campbell reported the first case of congenital agenesis of the skin on the scalp [3]. ACC is rare with a reported incidence of 0.5-1 in 10,000 births [4-5]. However, the actual incidence is likely to be much greater, as mild cases of congenital cutaneous hypoplasia may be largely ignored.

Although the ACC can be located anywhere on the body, studies have shown that 84% of defects are located on the scalp [6]. It most often presents as a solitary lesion, mainly located at the midline apex. The lesions are non-inflammatory, well-defined, and vary in size. Defects rarely appear as ulcers, with rounded stars or elongated forms. At birth, the ACC is usually covered by a thin, fragile, transparent membrane. Histological examination revealed the absence of normal skin structures such as hair follicles, sebaceous glands, and sweat glands, and a lack of collagen fibers, in addition to the lack of collagen fibers in the dermis [7]. Mortality in ACC patients is estimated to be 20 to 55 percent due to associated congenital defects, meningitis, or sagittal sinus hemorrhage due to surgical intervention or dry eschar separation and erosion [8]. The exact pathogenesis is unknown, although several theories have been proposed including neural tube defect, vascular compromise from placental insufficiency, intra-uterine infections, genetic mutations [5]. Congenital non-scalp skin hypoplasia lesions primarily involving the trunk and/or extremities; usually large, bilateral, and symmetrical; often with epidermolysis bullosa. Due to the risks of conservative and surgical management, the type of treatment and timing of surgery for ACC remain controversial. Conservative treatment exposes the patient to congenital cutaneous. Hypoplasia, bed drying and necrosis and related disorders. In contrast, surgical intervention results in the risk of anesthesia, major bleeding, scalp flap necrosis, loss of skin graft, infection, and donor site morbidity [9]. In this study, we present our experiences and considerations in the treatment of neonatal pre-ACC. We proposed a practical, treatment-oriented approach.

3. Methods

After application and approval to the hospital ethics committee, a retrospective survey of the hospital files was conducted for more than half a year. Samples of human infants born at this Medical Center during 2019 and 2021, The infant was born at term, healthy, from healthy parents without consanguinity. The mother had not been diagnosed with infections during pregnancy; also, no drug intake and no traumatic events have been re-corded during pregnancy or at birth. Their medical records were collected through their demographic information, and data were collected from (1) Main files of the medical center (including details of children diagnosed with congenital skin hypoplasia), (2) files of the Obstetrics and Gynecology Department (3) Photos of the patients were taken by the plastic surgery team at the initial diagnosis and follow-up.

3.1. Patient Profile

AM patient: The neonate was transferred from the Neonatal Intensive Care Unit (NICU) to the orthopaedic surgery clinic due to skin defects of the lower extremities, diagnosed with congenital skin hypoplasia, neonatal pneumonia, neonatal anemia, and suspected sepsis, and received appropriate treatment. Physical examination revealed skin defects on both lower extremities, extending from the knee joint to the anterior tibia, ankle joint, and dorsum of the foot (Figures 2a, 2B).

3.2. Treatment

1. Dressing should be changed according to the principle of aseptic technique. The skin around the defect was disinfected first, and then the secretions on the defected skin were wiped. Cotton balls contaminated with secretions should not come into contact with other parts and must be placed in a special container.

2. When the secretions are long, saline gauze can be used, plus multiple layers of dry gauze. When the defected is small and deep, the Vaseline gauze should be delivered to the bottom of the wound, but not blocked. The defect surface with a lot of secretions can be washed repeatedly or fixed with gauze tape outside the wound, and the outer layer of growth factor was used for creating a smear in an undergraduate laboratory routine.

3. New granulation tissue has a certain ability to resist infection, so it is generally not necessary to use local antibiotics. However, some bacterial infections can erode wound tissue, and antibiotics need to be applied. For example, 0.1% phenoxyethanol can be used for Pseudomonas aeruginosa infection.

4. Pay attention to the growth of granulation tissue. If the granulation tissue grows well, it is fresh pink or red, the particles are uniform, the secretion is small, and it is easy to bleed when touched. If it is found that the defect surface is pale and edematous, dark in color with moss, granulation atrophy or excessive growth, etc., the reasons must be analyzed, which may be residual secretions, insufficient local blood supply, etc., and appropriate measures should be taken to improve wound repair.

5. Amniotic membrane users removed cryopreserved AMs from liquid nitrogen and washed 3 times with normal saline at room temperature. The wound was washed with saline, and then the wound surface was covered with the matrix side. Squeeze the air out of the middle by pressing lightly on the film. The dressing is then secured with several layers of gauze and bandages. AMs were replaced weekly, also when the membrane dries and falls off, or when it is found to dissolve.

3.3. Postoperative Care

The child does not need special care, but needs to be admitted to the hospital for observation and treatment, and pay close attention to the stability of the child's vital signs. After the patient's vital signs are stable for one month, they can choose to receive a later dressing change nursing treatment in the outpatient clinic. Analgesics and prophylactic antibiotics were prescribed for 5 days during the hospital stay, and follow-up observation was conducted. A conventional gauze dressing was placed on the defect surface, and the presence of exudation or bleeding was closely observed. Although the duration of care depends on the healing of the defect, a minimum of 25-30 days in the hospital, close observation and follow-up should be 60 and 180 days.

3.4. Deformity Assessment

To assess improvement in deformity and scarring after treatment, we used a modified version of the Vancouver Scar Scale (mVSS) (Table 1). A trained physician evaluated patients' pre-treatment photographs and postoperative photographs and medical records taken at least 6 months after treatment. The nonparametric Wilcoxon test was used to analyze the differences in mVSS scores before and after surgery. All statistical analyses were performed using SPSS version 23.0 (IBM Corporation, Armonk, NY, USA). Statistical significance The P value was 0.001, and the difference was statistically significant.

3.5. Degree of Satisfaction

The patients were followed up for at least 6 months after the operation, and the family members' satisfaction was assessed through the question of the patient's family members' evaluation of the recovery of the defect site. We asked the following four questions, with a score of 5 being the highest satisfaction: (Q1) Are you satisfied with the scarring after treatment of the defect site? (1-5); (Q2) Are you satisfied with the contour of the defect site after treatment? (1-5); (Q3) Are you satisfied with the skin perception after the defect site treatment? (1-5); (Q4) Are you satisfied with the overall results of the treatment? (1-5); Although TRAD patients still have obvious scars and local deformities after treatment, their families still accept the treatment results. And AM patients have higher satisfaction.

Table 1: Modified Vancouver Scar Scale

Scar characteristics	score
TRAD Vascularity	
Normal	0
Pink	1
Red	2
Purple	3
Pigmentation	
Normal	0
Hypopigmentation	1
Hyperpigmentation	2
Pliability	
Normal	0
Supple	1
Yielding	2
Firm	3
Ropes	4
Contracture	5
Height (mm)	
Flat	0
<2	1
2–5	2
>5	3
Depression (cm2)	
Flat	0
<4	1
4–9	2
>9	3
Total score AM	9
Total score TRAD	16

AM: amniotic membrane; TRAD: tradition

4. Results

Two patients were treated, both neonates. Although the TRAD patient had contour depression and obvious scar contracture, the family members expressed acceptance and satisfaction with the treatment results. In the AM1 patient, the skin texture and color were good after recovery, and there was no hypertrophic scarring. Family members are more satisfied. The average defect area in both patients was 50cm^2. No anesthesia and no sedation were received during the treatment, while the TRAD patients were treated in an incubator for 20 days due to complicated respiratory diseases, and were discharged after treatment. The treatment duration was 45 days, and the mean follow-up time was 6 months. Satisfactory contours were achieved in all cases of treatment. Both

patients recovered and were discharged without major complications. The results of the two patients after treatment are satisfied at the end. Although AM is better, for ACC and TRAD, they can be discharged smoothly and grow up healthily after treatment, which is the family's greatest wish. , the corresponding work is already in progress. Postoperative satisfaction scores of patients were 9 and 16, respectively (Table 1). Scar contracture is more obvious in patients with TRAD. Compared with pure AM patient profile, there was a statistically significant difference in preoperative expectancy and postoperative recovery score between the two groups, using the Wilcoxon signed-rank test with a p value of 0.001. The mean scores on postoperative satisfaction surveys were 9 and 16 points, with AM patients scoring more than 4 points per question and TRAD patients averaging 3 points. These results indicated that patients were generally very satisfied (Table 2).

Table 2: Postoperative Aesthetic Satisfaction Scores

Patient No	Satisfaction score				Total
	Q1	Q2	Q3	Q4	
AM	5	5	4	5	19
TRAD	2	3	3	4	12

AM: amniotic membrane; TRAD: tradition

5. Discussion

There is no precedent for the clinical amniotic membrane treatment of congenital skin dysplasia (ACC) in our hospital, and there are not many related papers to refer to, there is great controversy concerning treatment of ACC and there has been a great scientific interest due to the extremely high mortality figures that range from 20 to 55%. [10-15] Though not with a high motality as scalp types, the skin defects of lower limbs are at a risk of infection, bleeding and may result in disabling joint scarring or disfiguring skin scar. The critical aim for newborns with ACC is to restore the skin coverage and the scar treatment is left for teenager hood [16, 17]. For the management of the skin defects, there is no any agreement yet. Conventional wound dressing changes with petrolatum and antibiotic ointment are mostly recommended [18]. As suggested, it may need to change dressing twice a day, which is labor-costly and quite suffering for the newborn. Upon reviewing the articles concerning the human amniotic membrane in treating variety of wounds, and considering our own experience in AM application, we assumed to use the cryopreserved AM to treat the limb skin defects of this ACC patient.

The compactly aligned epithelial cells may also compose a barrier to protect the wounds from getting dry when applied on a wound surface. The freezing medium for the cryopreservation of AMs is free of DMSO and animal components and had been used for preserving cells in liquid nitrogen. The epithelial cells of cryopreserved AMs retained viability and the structures of epithelial layer and the stromal compartment were histologically maintained. As applied onto the donor site of split skin grafts, the cryopreserved AMs attached well on the wounds and the surrounding skin of the limb skin defects of the ACC patient (Figure 2-2.A.B.C) the AMs were replaced only when the AMs dried and sloughed off or got dissolved, which resulted in fewer dressing changes and almost no suffering. The AMs on the wounds kept the wound from getting dry, while without maceration. Upon the AM application, the redness and swelling subsided in a few days, and epithelialization was complete in one month. No infection was noticed. Not only the anti-inflammation and anti-infection features of AMs benefited wound healing, the anti-fibrotic effects may also have contributed to the long term outcome [19.20]. The long-term follow up did not show hypertrophic scarring. The healed wounds of lower limbs presented a quite soft, elastic skin texture, with little depigmentation, with no scar contracture and no limitation of movement of joints. Cryopreservation is a simple way to store AM with retained cell viability and normal histological structure, and the cryopreserved AMs are readily available [21.22]. In treating the large skin defects of lower limbs of ACC patients, the cryopreserved AM presented good features as easy application, pain relief, anti-inflammation and promoted epithelialization [23.24.25]. The anti-fibrosis and suppression of scar formation of the AM on wounds was remarkably manifested in the long-term follow up. The patients were followed up for at least 6 months after the operation, and the family members' satisfaction was assessed through the question of the patient's family members' evaluation of the recovery of the defect site. We asked the following four questions, with a score of 5 being the highest satisfaction: (Q1) Are you satisfied with the scarring after treatment of the defect site? (1-5); (Q2) Are you satisfied with the contour of the defect site after treatment? (1-5); (Q3) Are you satisfied with the skin perception after the defect site treatment? (1-5); (Q4) Are you satisfied with the overall outcome of the treatment (1-5), (Figure 1-2).

Figure 1: Traditional treatment cases in 2019

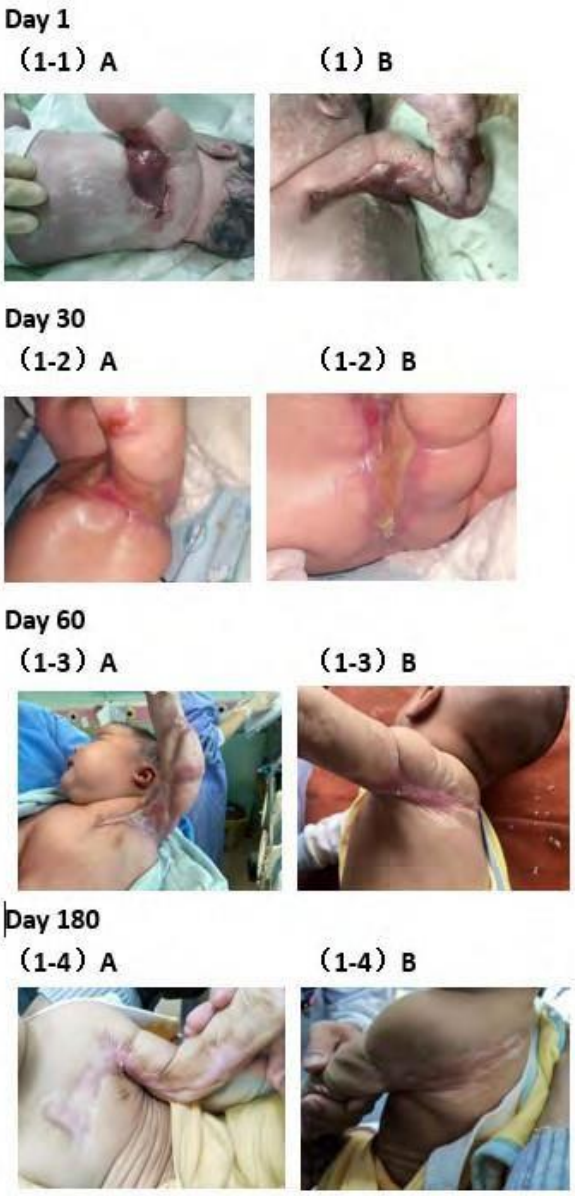
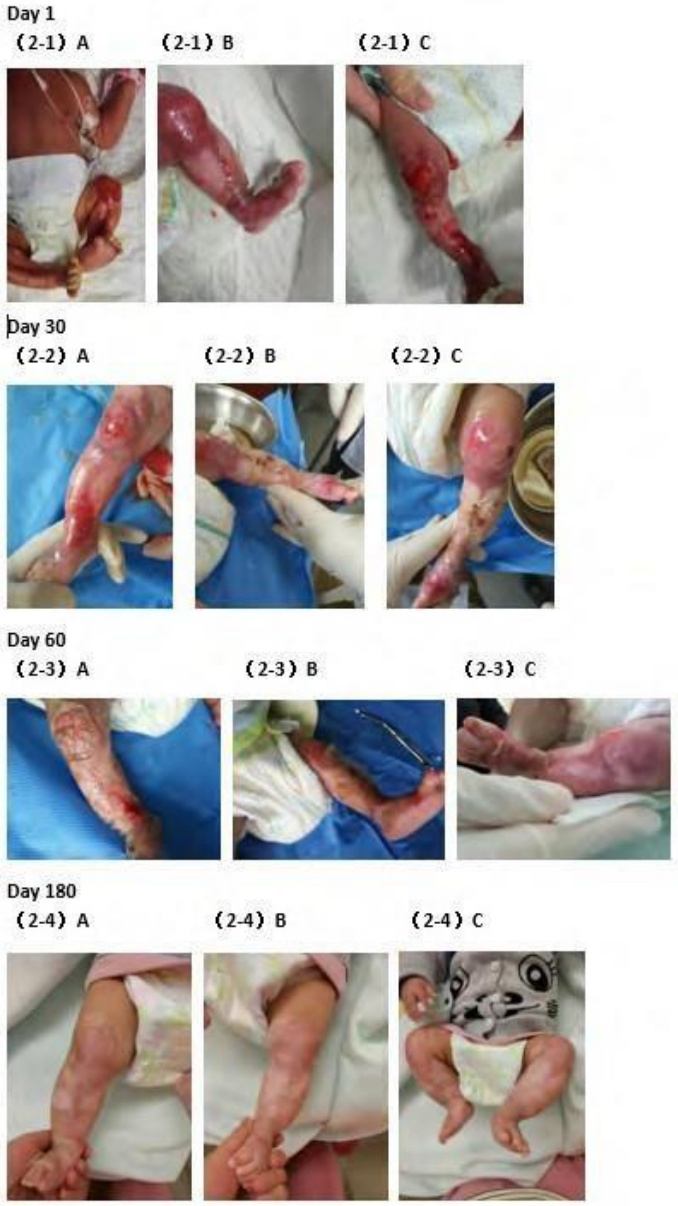


Figure 2: Amniotic membrane treatment cases in 2021



6. Conflict of Interest

No potential conflict of interest relevant to this article was reported.

7. Ethical Approval

The study was approved by the Institutional Review Board of Second Affiliated Hospital of Shantou University Medical College SUMC Second Affiliated Hospital and performed in accordance with the principles of the Declaration of Helsinki. Written informed consents were obtained.

8. Patient Consent

The patients provided written informed consent for the publication and the use of their images.

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