AnnalsofClinicalandMedical Case Reports

Case Series ISSN2639-8109Volume10

TheSuperiorityofAmnioticMembraneintheTreatmentofAplasiaCutisCongenita

WeijieHe[1],MaKe[2],YunpuHe[3],ZhanOuyang[3],JingSu[4]*andlujunyang[5]

[1]PlasticSurgery,SecondAffiliatedHospital,ShantouUniversityMedicalCollege,Shantou,M.D.,Ph.D.,China

[2]DepartmentofPlastic&CosmeticSurgery,TheFirstAffiliatedHospitalofGuangxi MedicalUniversity,Nanning, M.D.,Ph.D., China

[3]PlasticSurgery,SecondAffiliatedHospital,ShantouUniversityMedicalCollege,Shantou,M.D.,MA.,China

*[4]NursingFaculty,ShantouUniversityMedicalCollege,Shantou,R.N.,M.N.,Ph.D.,China

[5]PlasticSurgery,SecondAffiliatedHospital,ShantouUniversityMedicalCollege,Shantou,M.D.,Ph.D.,China

***Correspondingauthor:**

JingSu,R.N.,M.N.,Ph.D.,
Nursing Faculty, Shantou University Medical College,SecondAffiliatedHospitalofShantou University MedicalCollegeDongxiaNorthRoad (Zhu-Xia block), Shantou, 515041 Guangdong Province, China, Tel: +86 (0)754 8891 5666;
E-mail:jsu@stu.edu.cn

Received:26Oct2022
Accepted:05Nov2022
Published:11Nov2022
JShortName:ACMCR

Citation:

Jing Su, The Superiority of Amniotic Membrane in the Treatment of Aplasia Cutis Congenita. Ann Clin Med Case Rep. 2022; V10(5): 1-6

Keywords:

Aplasiacutiscongenital;Amnioticmembrane;Scarring

1. Abstract

Introduction: Aplasia cutis congenital (ACC) is a heterogeneousgroupofdisordersthatshareacommon featureoffocalskin 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 ma- jorityof instances thisislimited tothe 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 tis- sues, such asmuscle tissue and bone, that can be underdeveloped or even absent.ACC can belife-threateningin severecases.Both conservative and surgical approaches carry risks, and the timing of surgeryremains controversial. Most literatures donot have de- tailed information on thetreatmentofthisdiseaseduetoitsrarity. Although ACC tends to be superficial and relativelysmall, it can also be large and poorly organized, increasing the risk of bleeding,infection,anddeath.Nonsurgicalversussurgicalinterventio n in this condition is controversial. Conservative care of two neo- natalpatientsadmittedtoourhospitalwastakenbyperforming

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)inthetreatmentofskindefectsincongenitalcutaneous

agenesis(ACC).

Methods: Two neonatal cases with congenital cutaneoushy-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 wereap-pliedtotheskin defect ofthelower extremity of children with ACC, and the changes were made in time if necessary until the wound healed.

Results: This study included 1 conservatively treated case: located on the left upper arm and left anterior chest and leftback. Another caseofamnioticmembranetreatment waslocated 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 voluntarilyreceived active treatment,one conservative tra- ditional dressing treatment, the other adding amniotic membrane covering dressing treatment, to keep theskin clean and dry. Both treated patients survived and thrived.

Conclusion: ThelimbskindefectofACCinfantstreatedwith cryopreservedamnioticmembranewasgraduallyepithelialized af- terapplicationofAM,andhealedafter1month.Follow-upresults at 6 months after treatment showed good skin texture and color without hypertrophic scarring. Thechildren treated with conserv- ative traditional treatment healed within 50 days. The follow-up results of 6 months after treatment showed that the skin texture andcolor werepoor, andtherewasobvioushypertrophicscar for- mation,whichaffectedthemovementoftheupperlimbs.AMshas thecharacteristicsofimprovingwoundhealingandinhibiting scar formation in thetreatment ofACC skin defects. Thisarticlehigh- lights the role of the amniotic membrane in the management of patients with extensive congenital cutaneous hypoplasia, and also proposesapractical,treatment-orientedclassificationthatcanhelp physicians estimate disease severity and prognosis, and provide treatment guidelines.

2. Preface

ACCisararecongenitaldisorder characterized bythepresence of theepidermisinoneorseveralareas.Sometimescongenitaldefect involvesthesubcutaneoustissue, usuallyon thecrown ofthehead orthelowerextremitieswhichislimitedatbirth.Patient'sskinand subcutaneous tissue defects were removed since the base isrough and red granuloma, which is thick-walled and large. Its top can quicklyfall off, exposingpinkdiscoloration andsoresurfacescan healveryslowly[1]wasfirstdescribed asalimblesion byCordon in1767[2].In1826,Campbellreportedthefirstcaseofcongenital 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 in- cidence 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,stud-ies have shownthat 84% of defects are located onthe scalp [6].It most often presents as a solitary lesion, mainly located at the midlineapex.Thelesionsarenon-inflammatory,well-defined,and varyin size. Defects rarelyappear as ulcers,withrounded stars or elongated forms. At birth, the ACC is usually covered by a thin, fragile, transparentmembrane. Histological examination revealed the absence of normal skin structures such as hair follicles, seba- ceous glands, and sweat glands, and a lack of collagen fibers, in additiontothelackofcollagenfibersinthedermis[7].Mortalityin ACC patientsisestimatedtobe20 to55 percent duetoassociated congenitaldefects, meningitis, or sagittalsinushemorrhagedueto surgicalinterventionordryeschar separationanderosion[8].The exact pathogenesis is unknown, although several theories have been proposed includingneuraltubedefect, vascular compromise from placental insufficiency, intra-uterine infections, genetic mu- tations[5].Congenitalnon-scalpskinhypoplasialesionsprimarily involvingthetrunkand/or extremities;usuallylarge,bilateral,and symmetrical; oftenwith epidermolysis bullosa. Due to the risksof conservative and surgical management, the type of treatment

andtimingofsurgeryforACCremaincontroversial. Conservative treatmentexposesthepatienttocongenitalcutaneous.Hypoplasia, beddryingandnecrosisandrelateddisorders. Incontrast, surgical interventionresultsintheriskofanesthesia,major bleeding,scalp flapnecrosis,lossofskingraft,infection,anddonorsitemorbidity [9]. In this study, we present our experiences andconsiderations in the treatment of neonatal pre-ACC. We proposed a practical, treatment-oriented approach.

3. Methods

After application andapproval tothehospital 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 Centerduring2019and2021,Theinfantwasbornatterm,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 preg- nancy or at birth. Their medical records were collected through their demographic information, and data were collected from (1) Mainfilesofthemedicalcenter(includingdetailsofchildrendiag- nosed with congenital skin hypoplasia), (2) files of the Obstetrics andGynecologyDepartment (3)Photosofthepatientsweretaken bythe plastic surgeryteam at the initial diagnosis and follow-up.

PatientProfile

AMpatient:TheneonatewastransferredfromtheNeonatalInten- siveCareUnit(NICU)totheorthopaedicsurgeryclinicduetoskin 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).

Treatment

1. Dressingshouldbechangedaccordingtotheprincipleofaseptic 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 multiplelayersofdrygauze.When thedefectedissmallanddeep, theVaselinegauzeshouldbedeliveredtothebottomofthewound, butnotblocked. Thedefect surfacewith alot ofsecretionscan be washedrepeatedlyorfixedwithgauzetapeoutsidethewound,and theouterlayerofgrowthfactor wasusedfor creatingasmearinan 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. Payattention tothegrowth ofgranulation tissue. Ifthegranulationtissuegrows well, it isfresh pinkorred, theparticlesareuniform, the secretion is small, and it is easyto bleed when touched. Ifit is foundthatthedefect surfaceispaleand edematous, darkin colorwithmoss,granulationatrophyorexcessivegrowth,etc.,the reasonsmustbeanalyzed,whichmayberesidualsecretions,insufficientlocalbloodsupply,etc.,andappropriatemeasuresshouldbe 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 thensecuredwithseverallayersofgauzeandbandages.AMswere replaced weekly, also when the membrane dries and falls off, or when it is found to dissolve.

PostoperativeCare

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 vitalsignsarestableforonemonth,theycanchoosetoreceive a later dressing change nursing treatment in the outpatient clinic. Analgesicsandprophylacticantibioticswereprescribed for5days duringthehospitalstay,andfollow-upobservationwasconducted. A conventional gauze dressing was placed on the defect surface, and the presence of exudation or bleeding was closely observed. Althoughthedurationofcaredependsonthehealingofthedefect, a minimum of 25-30 days in the hospital, close observation and follow-up should be 60 and 180 days.

DeformityAssessment

To assess improvement in deformityand scarringafter treatment, we used a modified version ofthe 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.

DegreeofSatisfaction

Thepatientswerefollowed upfor atleast6monthsafter theoperation, and the familymembers' satisfaction was assessed through the question of the patient's family members' evaluation of the recoveryofthedefectsite.Weaskedthefollowingfour questions, withascoreof5beingthehighestsatisfaction:(Q1)Areyousatisfiedwith thescaringaftertreatmentofthedefect site?(1-5);(Q2) Are you satisfied with the contour of the defect site after treat- ment? (1-5); (Q3)Areyou satisfied with the skin perceptionafter the defect site treatment? (1-5); (Q4) Are you satisfied with the overall results of the treatment? (1-5); Although TRAD patients stillhaveobviousscarsandlocal deformitiesafter treatment,their families still accept the treatment results. And AM patients have higher satisfaction.

Table1: ModifiedVancouverScar Scale

Scarcharacteristics	score
TRADVascularity	
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
TotalscoreAM	9
TotalscoreTRAD	16

AM:amnioticmembrane;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 afterrecovery, andthere wasnohypertrophicscarring. 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.Theresultsofthetwopatientsaftertreatmentaresatisfied at the end. Although AMisbetter, for ACCandTRAD, theycan be discharged smoothlyandgrowup healthilyafter treatment,which isthefamily'sgreatestwish.,thecorrespondingworkisalreadyin progress. Postoperative satisfaction scores of patients were 9 and 16,respectively(Table1). Scar contractureismoreobviousin patients with TRAD. Compared with pure AM patient profile, there was a statisticallysignificant 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 andTRADpatientsaveraging3points.Theseresultsindicatedthat patients were generally very satisfied (Table 2).

Table2: PostoperativeAestheticSatisfactionScores

PatientNo	Satisfaction score				Total
	Q1	Q2	Q3	Q4	
AM	5	5	4	5	19
TRAD	2	3	3	4	12

AM:amnioticmembrane;TRAD:tradition

5. Discussion

There is no precedent for the clinical amniotic membrane treatmentofcongenitalskindysplasia(ACC)in ourhospital,andthere are not many related papers to refer to, there is great controversy concerningtreatment ofACC andtherehasbeen agreatscientific interestduetotheextremelyhigh mortalityfiguresthatrangefrom 20to55%.[10-15]Thoughnotwith ahighmotalityasscalptypes, the skin defects of lower limbs are at a risk of infection, bleeding and mayresult in disabling joint scarring or disfiguring skin scar. Thecriticalaim fornewbornswithACCistorestoretheskin coverageandthescartreatmentisleft for teenagerhood[16, 17]. For the management of the skindefects, there is no any agreement yet. Conventional wound dressing changes with petrolatum and antibiotic ointment are mostly recommended [18]. As suggested, it mayneed 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 assumedto use the cryopreserved AMto treat the limb skin defectsofthisACCpatient.

Thecompactlyalignedepithelial cellsmayalsocomposea barrier to protect the wounds from getting drywhen applied on a wound surface. The freezing mediumforthe cryopreservationof AMsis free of DMSO and animal components and had been used for preservingcellsinliquidnitrogen. Theepithelial cells ofcryopreserved AMsretainedviabilityandthestructures ofepitheliallayer and the stromal compartment were histologically maintained. As applied onto the donor site of split skin grafts, the cryopreserved AMsattached well on thewoundsand thesurrounding skinofthe limbskin defects of the ACC patient (Figure 2-2.A.B.C) theAMs 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 gettingdry, whilewithoutmaceration. Upon theAMapplication, the redness and swellingsubsided in a fewdays, andepithelialization was complete in one month. No infection was noticed. Not only theanti-inflammationandanti-infectionfeaturesofAMsbenefited woundhealing, theanti-fibroticeffects mayalsohave contributed tothelongtermoutcome[19.20].Thelong-term followup didnot 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.CryopreservationisasimplewaytostoreAMwithretained cell viability and normal histological structure, and the cryopreservedAMsarereadilyavailable[21.22]. In treatingthelargeskin defects of lower limbs of ACC patients, the cryopreserved AM presented good features as easy application, pain relief, anti-inflammationandpromotedepithelialization [23.24.25].Theanti-fibrosisandsuppressionofscarformationoftheAMonwoundswas remarkably manifested in the long-term follow up. The patients werefollowedupfor atleast6monthsafter theoperation, andthe family members' satisfaction was assessedthrough the question ofthe patient's familymembers' evaluation oftherecoveryofthe defectsite.Weaskedthefollowingfour questions,withascoreof 5 being the highest satisfaction: (Q1) Are you satisfied with the scarringafter treatmentofthedefect site?(1-5);(Q2)Areyousatisfied with the contour of the defect site after treatment? (1-5); (Q3)Areyousatisfiedwiththeskinperceptionafterthedefectsite treatment? (1-5); (Q4) Are you satisfied with the overall outcome of the treatment (1-5), (Figure 1-2).

Figure1: Traditionaltreatmentcasesin2019

Figure2: Amnioticmembranetreatmentcasesin2021

6. ConflictofInterest

No potential conflict of interest relevant tothisarticlewasreport-ed.

7. EthicalApproval

ThestudywasapprovedbytheInstitutionalReviewBoardofSec- ond 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

Thepatientsprovidedwritteninformedconsentforthepublication and the use of their images.

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