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Research Article

Application of Amniotic Tissue Matrix to Surgically Excised Hidradenitis Suppurativa Wounds: A Retrospective Review

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ABSTRACT

Background: Hidradenitis suppurativa is a painful and disfiguring disease, which requires surgical management in severe cases. Improvements in management are necessary to decrease disease morbidity and improve outcomes.

Aim: To determine the efficacy of applying amniotic tissue matrix to surgically-excised hidradenitis suppurativa wounds.

Materials & Methods: A 5-year retrospective chart review of patients who underwent surgical treatment of perineal, perianal, and inguinal hidradenitis suppurativa at the University of Miami Hospital was completed. The study group consisted of 5 patients who had amniotic tissue matrix applied to their surgical wounds postoperatively. The control group, 18 patients, did not receive the amniotic tissue matrix application.

Results: The average disease surface area in the study group was larger at $1278 \pm 723 \text{ cm}^2$ compared to $700 \pm 555 \text{ cm}^2$ for the control group. Duration of intensive care unit admission in the study group was shorter at 4.2 ± 4.3 days compared to 6.7 ± 8.8 days for the control group. Duration of inpatient admission was longer in the study group, 28.2 ± 12.4 days, compared to 24.6 ± 11.9 days for the control group. Postoperative hypergranulation tissue occurred more frequently in the control group (52.6%) than in the study group (20%).

Conclusion: While further evaluation in a larger cohort of patients is necessary, application of amniotic tissue matrix to surgically-excised hidradenitis wounds appears to offer an adjunctive improvement to the treatment of hidradenitis.

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Introduction

Hidradenitis suppurativa (HS) is an inflammatory disease of the apocrine gland containing soft tissues of the body [1]. Frequently affected sites include the axilla, perineum, gluteal, inguinal, and perianal region [2, 3]. Hidradenitis prevalence in the United States has been estimated between 0.09% and 0.20%; however, worldwide prevalence has been estimated as high as 4% [4-6]. Patients with hidradenitis commonly experience debilitating pain and disfiguring chronic wounds with purulent drainage that significantly affect their quality of lives [7]. Advanced disease is common, particularly since the identification of a diagnosis typically

takes 7 years in patients [8]. The Hurley grading system is used to classify the severity of hidradenitis and guiding treatment [1]. Mild HS described as the presence of abscesses in the absence of scarring would be considered Hurley stage I. Moderate HS presents with limited scarring and/or sinus tracts and is defined as Hurley stage II. Severe HS with extensive scarring and sinus tracts is classified as Hurley stage III [9]. Lower stage disease may be successfully treated with topical and oral antibiotics such as clindamycin or minocycline; however, relapse is common when treatment is discontinued [10]. HS is poorly understood in terms of pathophysiology; it is challenging to treat and usually involves a multidisciplinary approach, including lifestyle modification

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(like smoking cessation and weight loss), medical management, and surgical management [9].

Administration of biologic agents, including infliximab and adalimumab, have been shown to improve symptoms in patients suffering from moderate and severe hidradenitis [11, 12]. There are 11 drugs in phase 2 and phase 3 clinical research trials, but adalimumab remains the only biologic approved by the US FDA at this time [9]. Moreover, failure to respond, limited or transient responses are not uncommon [12, 13]. Additionally, these medications may be associated with dangerous side effects, including serious infections, demyelinating disorders, drug-induced lupus, and increased risk of neoplasms [9, 13, 14]. The increasing use of these potentially toxic agents in hidradenitis underscores the severity of the disease and notorious difficulty in treatment. While medical management may provide relief from hidradenitis, these treatments are not curative. Remission is possible; however, symptoms commonly recur when treatment is discontinued. Given the serious side effect profile and the high rate of recurrence, long-term medical management is not ideal. The only potentially curative treatment for hidradenitis is wide surgical resection of affected tissues.

Depending upon the disease severity, resection may entail extensive surgery with protracted recovery. Resection may result in large open wounds and significant pain. Postoperatively, pain control, lengthy inpatient admissions, and physical therapy are frequently required [15, 16]. In addition to the psychological and physical costs to the patient, treatment is also associated with a large financial burden to the patient and health care system [17, 18]. Therefore, it is essential to explore alternative treatments, both medical and surgical, to improve the care of patients with hidradenitis. At our institution, we have begun applying amniotic tissue matrix to hidradenitis wounds directly following excision. In this report, we present our results using this adjunctive treatment following excision of perineal, perianal, and inguinal hidradenitis.

Materials and Methods

A retrospective review of patients undergoing surgical treatment of hidradenitis between May 2012 and May 2017 was conducted. Patients were identified by ICD9 and ICD10 search using diagnosis codes 705.83 and L73.2 and from a prospectively maintained list of cases performed by the senior author. Patients who had amniotic tissue matrix applied to their surgically excised hidradenitis wounds were included within the study group. For comparison, a control group consisted of patients undergoing surgical excision of hidradenitis who did not have the application of amniotic tissue matrix. Patients were included if they underwent surgical treatment of hidradenitis located in the perineal, perianal, and inguinal hidradenitis. Patients undergoing simultaneous treatment for hidradenitis at other sites were included as well. However, patients undergoing isolated treatment of disease at other sites were excluded. Patients undergoing surgery for recurrent disease after previous resection and those treated with alternative tissue matrix products applied to the surgically excised hidradenitis wound were also excluded.

Demographic information including date of birth, date of surgery, comorbidities, current smoking status at the time of surgery, location of hidradenitis, surgical procedures performed, use of amniotic tissue

matrix and site of application, duration of intensive care unit (ICU), and total hospital admission days were recorded. The surface area of the disease was recorded, which was reported in the operative report. If this information was not explicitly reported, the surface area was estimated based upon the surface area reconstructed by tissue rearrangement, skin grafting, and amniotic tissue matrix application. Duration of postoperative follow-up and complications were recorded as well.

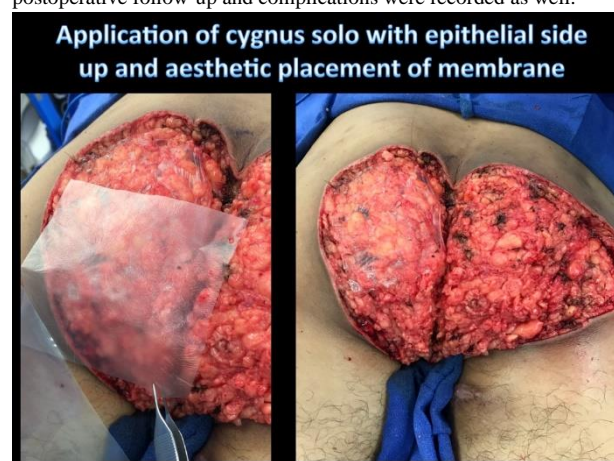


Figure 1: Placement of Cygnus amniotic wound matrix to the surgically excised hidradenitis wounds in a 32-year-old patient with Hurley's grade III hidradenitis.



Figure 2: The same patient is shown 1 week after excision with the placement of the Cygnus amniotic wound matrix.

For patients in the experimental group, Cygnus (Vivex Biomedical, Miami, Florida) amniotic tissue matrix was applied to surgically excised hidradenitis wounds to expedite the wound healing process and potentially decrease pain and the duration of inpatient and ICU admission hospital stay. Upon excision, Cygnus amniotic tissue matrix is placed onto the surgically excised wound (Figure 1), covered with xeroform, abdominal pads, or a black VAC sponge, and taped to the skin. This dressing is left in place for 5-7 days postoperatively to allow for the integration of multiple growth factors (i.e., hepatocyte growth factor, fibroblast growth factor, etc.) within the amniotic tissue matrix into the wound bed. This is the time when the wounds are usually reconstructed with local tissue and skin grafts. However, the outer dressing may be removed earlier if it becomes soiled by drainage or feces, particularly in cases of perianal and perineal wounds. Upon removal of the dressing, the wound is evaluated to assess for a clean granulating wound bed to

determine the timing for reconstruction (Figures 2 & 3). The dressing is then replaced with a non-adherent gauze and abdominal pads, changed daily until reconstruction is performed. In contrast, the comparative controls underwent normal saline wet-to-dry dressing changes twice daily in the postoperative period. This is not only painful for the patients due to the mechanical debridement, but it also increases the nursing labour required to perform the dressing change. These wounds were similarly assessed to determine the timing for reconstruction, which was commonly performed at approximately one week.



Figure 3: The patient is shown preoperatively, 1 week, and 6 weeks after undergoing wide excision and split-thickness skin grafting of the surgical wound.

The duration of total postoperative admission hospital days and the duration of postoperative ICU admission hospital days were compared between the study and comparative groups. Additionally, the surface area of the disease was similarly compared between the two groups. A

student's t-test was performed to assess if there was a statistically significant difference between the two groups.

Results

Five patients who underwent surgical excision of hidradenitis with the placement of Cygnus amniotic tissue matrix to the surgical wounds were identified and included as the study population. The average age of patients at the time of initial surgery was 45.7 years (range 33-76 years). The average disease surface area was 1278 cm² (range 310-2000 cm²). The average duration of total admission after the initial excision procedure was 28.2 days (range 16-49 days), and the average duration of ICU admission was 4.2 days (range 0-10 days). Eighteen patients who underwent surgical excision of hidradenitis without placement of amniotic tissue matrix onto the surgical wounds were identified and included for comparison. The average age at the time of initial surgery for patients in the comparative group was 40.9 years (range of 20-70 years). The average surface area of disease was 700 cm² (range of 200-2100 cm²). The average duration of total admission after the initial excision procedure was 24.6 days (range 4-50 days), and the average duration of ICU admission was 6.7 days (range 0-24 days).

Demographics for the study and comparison groups included age, history of comorbid medical conditions [arrhythmias, coronary artery disease (CAD), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), hypertension, diabetes mellitus (DM), end-stage renal disease (ESRD)] and smoking status (Table 1). The sites of excised disease for the study and comparison groups are presented in (Table 2). The estimated disease surface area and duration of total inpatient admission days, ICU admission days, and follow-up days are presented in (Table 3). Postoperative complications are shown in (Table 4).

Table 1: Demographics.

	Study Group	Comparative Group
Average Age \pm Standard of deviation	45.7 \pm 20.8	40.9 \pm 11.9
History of Tobacco use	2/5, 40%	3/18, 16.7%
Active Tobacco use	0/5, 0%	3/18, 16.7%
Comorbid medical conditions	2/5, 40%	7/18, 38.9%
- Arrhythmia	0/5, 0%	2/18, 11.1%
- CAD	0/5, 0%	1/18, 5.6%
- CHF	1/5, 20%	2/18, 11.1%
- COPD	0/5, 0%	1/18, 5.6%
- DM	1/5, 20%	3/18, 16.7%
- ESRD	1/5, 20%	0/18, 0%
- Hypertension	2/5, 40%	4/18, 22.2%

Table 2: Sites of excised disease.

	Study Group	Comparative Group
Gluteal	3/5, 60%	9/18, 50%
Perineal/inguinal/genital	5/5, 100%	18/18, 100%
Perianal	1/5, 20%	4/18, 22.2%
Lower abdomen/suprapubic	1/5, 20%	5/18, 27.8%
Axillary	2/5, 40%	8/18, 44.4%
Thigh	3/5, 60%	1/18, 5.6%
Sacral	0/5, 0%	2/18, 11.1%

Table 3: Disease surface area, length of admission & follow up.

	Study Group	Comparative Group	P-value
Estimated disease surface area \pm standard of deviation	1278 \pm 723	700 \pm 555	.0988
Total duration of admission \pm standard of deviation	28.2 \pm 12.4	24.6 \pm 11.9	.5591
ICU admission \pm standard of deviation	4.2 \pm 4.3	6.7 \pm 8.8	.0549
Duration of follow-up \pm standard of deviation	65.4 \pm 30.1	199.5 \pm 187.6	.0700

Table 4: Postoperative complications.

	Study Group	Comparative Group
Hypergranulation tissue	1/5, 20%	10/18, 55.6%
Hematoma	0/5, 0%	1/18, 5.6%
Wound infection	0/5, 0%	2/18, 11.1%
Penile lymphedema	0/5, 0%	1/18, 5.6%
Hypertrophic scarring	0/5, 0%	1/18, 5.6%
Vulvar introital stenosis	0/5, 0%	1/18, 5.6%

Discussion

With advancements in wound care, new approaches for the treatment of wounds continue to be developed. Biologic tissue products, such as amniotic tissue matrix, are an important advancement in the care of complex wounds due to their ability to provide vital growth factors to the wound environment. In this retrospective review, we have shown a decrease in the duration of postoperative ICU hospital days in patients with extensive Hurley stage III hidradenitis on their genitalia, perineum, buttocks, and inguinal crease with the application of Cygnus tissue matrix to the wound during the first stage of treatment. We have compared these larger wounds to our own smaller controls to decrease their pain, limit dressing changes until reconstruction which are both time-consuming, painful, and costly, in addition to expediting their healing process.

The average duration of postoperative ICU admission in the study group was over one third less than the comparative group. The duration of postoperative ICU admission in patients undergoing Cygnus amniotic tissue matrix application to the surgical excision wounds was 4.2 ± 4.3 days and 6.7 ± 8.8 days in the comparative group. However, there was a wide range in duration of postoperative ICU admission; 0-10 days for the study group and 0-24 days for the comparative group. Because the extent of the disease varies greatly between hidradenitis patients, significant variability of the postoperative course is not unexpected. To demonstrate statistical significance in a disease with such variability would require a dramatically and potentially prohibitively larger population size. Nevertheless, our results provide evidence to suggest that the application of Cygnus amniotic tissue matrix has decreased postoperative admission to the ICU. In select patients, the extent of disease may be amenable to outpatient surgical management. Consequently, it is important to consider the extent of disease when comparing postoperative admission after surgical excision of hidradenitis. To improve the comparison between the study and comparison groups, we have estimated disease surface area based upon the recorded surface areas of resected disease and subsequent reconstruction. Despite shorter ICU admission in the study group, the average surface area of disease was much larger at $1278 \pm 723 \text{ cm}^2$ versus $700 \pm 555 \text{ cm}^2$ for the comparative group.

Patients in the study group spent on average 28.2 ± 12.4 days admitted to the hospital, while patients in the comparative group were admitted for 24.6 ± 12.0 days. However, it is again important to note that the average surface area of disease was much larger for patients in the study group. More severe disease entails both a larger resection and more extensive reconstruction. This would be expected to necessitate a longer recovery period and postoperative admission. While the average surface area of disease in the study group was over 50% larger, the duration of postoperative admission was less than 15% longer. This may indicate a benefit upon the duration of postoperative inpatient admission with the application of Cygnus to surgically excised hidradenitis wounds. The exact pathogenesis of hidradenitis remains unresolved. Follicular occlusion and rupture with resultant inflammation have been suggested as a potential etiology. An autoimmune process has also been proposed to have a role in the pathogenesis of hidradenitis. Various cytokines have been observed to be elevated in the cutaneous tissues of patients with hidradenitis, including IL-1 β , IL-10, IL-17, TNF- α [19, 20]. Disease improvement with biologic agents, including adalimumab and infliximab, both of which target TNF- α further supports the role of cytokines in the pathogenesis [11, 12].

Our study is the first report to present the results of the application of amniotic tissue matrix in the treatment of hidradenitis. These products have shown success in treating various wounds, including corneal wounds, diabetic foot ulcers, and burn wounds [21-23]. *In vitro* analysis has shown amniotic membrane contains a variety of growth factors and cytokines [24-26]. The mechanism through which these products promote wound healing is believed to be through local delivery of these cytokines and growth factors [24-26]. While surgical resection removes grossly involved tissue, nearby healthy appearing tissue has been shown to display elevated levels of inflammatory cytokines [19, 20]. Application of amniotic membrane tissue may consequently benefit surgically excised hidradenitis wounds by altering the levels of local cytokines and improving wound healing. Given the success of systemic biologic agents, topical application of agents capable of altering local cytokines and growth factors is a novel approach in treating hidradenitis. As the pathogenesis of hidradenitis continues to be elucidated, additional pathways for modulating disease both systemically and locally may be identified.

In our review, patients in the study population had decreased rates of postoperative hypergranulation tissue. 1 of 5 patients in the study group developed hypergranulation tissue treated with silver nitrate compared with 10 of 18 patients in the comparative group. This may reflect improved wound healing with the application of Cygnus amniotic tissue matrix. Other complications within our comparative group included two wound infections and one instance of each: hematoma, vaginal introital stenosis, hypertrophic scarring, and penile lymphedema. No additional complications were noted in the study group. A shorter postoperative ICU admission in the study group may be multifactorial. Performing twice daily wound care in patients with extensive wounds results in significant nursing needs. Furthermore, narcotics and sedatives are often necessary during dressing changes in these particular anatomic regions, which lengthens ICU admission. Because Cygnus tissue matrix is left in place for up to 1 week before changing the dressing, postoperative wound care needs and the pain associated with frequent dressing changes decreased. Furthermore, inflammatory cytokines have been shown to have a role in inflammatory pain [27]. Altering local cytokine levels may potentially offer a pathway to decrease pain associated with hidradenitis wounds in addition to the covering of transected nerve endings with the amniotic membrane helping decrease the patient's pain.

Our study is limited by the retrospective methodology and the availability of data within the medical records. The study is also limited by the population size, with only five patients in the study group. Application of Cygnus amniotic tissue matrix to surgically excised hidradenitis wounds was implemented during the past year, which resulted in limited sample size and shorter duration of follow-up. Additionally, our study is limited by the varying extent of disease among the included patients. To provide a means of accounting for this factor, we estimated the extent of the disease by the surface area of reconstruction. Patients in the study group had an average disease surface area over 50% larger than the comparative group, but postoperative admissions were less than 15% longer. While further evaluation within a larger cohort of patients is necessary, the application of amniotic tissue matrix to surgically excised hidradenitis wounds appears to offer an adjunctive means of improving surgical treatment of hidradenitis.

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