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Dehydrated Human Amniotic Membrane for Early Return of Erectile Function After Robotic Radical Prostatectomy: A 10-Year Journey and Lessons Learned

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Abstract

Objective

The first description of dehydrated human amniotic membrane (dHAM) use in robotic urologic surgery was by Razdan et al. in 2014 at the World Congress of Endourology. Since then, it has been utilized as a nerve and anastomotic wrap to enhance early return of erectile function and continence, respectively, during robotic radical prostatectomy (RALP). We describe our ten-year experience with dHAM as a nerve wrap.

Materials and Methods

After obtaining hospital institutional review board (IRB) approval, a retrospective review of a prospectively maintained single center prostate cancer database was performed. All men undergoing RALP with dHAM by a single high-volume surgeon were examined and compared to a cohort of men who underwent RALP alone. Groups were matched demographically, clinically, and biochemically. Potency was defined as the ability to have satisfactory penetrative intercourse > 50% of time and a SHIM score of ≥ 17.

Results

A total of 2,560 men underwent bilateral nerve sparing (ns)RALP with dHAM from 2014 to 2024 (Group 1). These were matched to 1,495 men who underwent nsRALP without dHAM (Group 2). Baseline patient and tumor characteristics are found in Table 1. Mean follow up was 8 years. The mean number of days until first erection was 7 vs. 14 ($p < 0.05$) in Groups 1 and 2. The mean number of days until erection sufficient for penetration was 21 vs. 36 ($p < 0.05$). The percent of potent patients in Group 1 at 3, 6, 12, and 24 months was 75%, 87%, 98%, 98%. The percent of potent patients in Group 2 during the same time frame was 60%, 78%, 90%, 94% ($p < 0.05$). There was no difference in complications or oncological outcomes between the two groups. A subgroup analysis stratifying patients based on age showed lower erectile function recovery in men over the age of 60 in Group 2.

Conclusion

dHAM is a safe adjunct at the time of RALP to hasten return of erectile function as well as improve 12-month and 24-month potency rates without compromising oncological outcomes. Men over the age of 60, especially, show improved 12- and 24-month potency with dHAM.

Introduction

The first description of dehydrated human amniotic membrane (dHAM) use in robotic urologic surgery was by Razdan et al. in 2014 at the World Congress of Endourology. In the original description, the authors used dHAM as a “nerve wrap” around the neurovascular bundles that were dissected out during robotic radical prostatectomy (RALP). In their initial pilot study, the authors showed significant improvement in time to return of erectile function after RALP. Since then, dHAM was more extensively described by Patel et al. in their landmark paper in 2015.[1] In their initial series of 116 men who underwent nerve sparing RALP (nsRALP), 58 had bilateral dHAM nerve wraps placed, while the remaining 58 served as a control. After an average follow up of 4 months, the authors showed a shorter mean time to return of full continence in the dHAM group (1.21 mo vs. 1.83 mo) as well as shorter time to potency recovery (1.34 mo vs. 3.39 mo) (both $p < 0.05$).[1]

These initial studies showed promise, and follow up medium term outcomes were recently reported by Noel et al. A total of 529 patients who underwent nsRALP with dHAM nerve wraps were followed up for a median of 42 months. Median time to potency was 119 days and time to continence was 42 days.[2] This group found longer potency times than in their initial pilot study, which was corroborated across grades of nerve sparing (NS). When comparing full vs. partial NS, median time to potency was 92 days vs. 184 days, and median time to continence 42 days vs. 44 days. When comparing patients older than 55 and younger than or equal to 55 years old, median time to potency was 167 days vs. 80 (35–288) days, and median time to continence 42 days in both groups.[2]

While existing literature reports favorable short-term and medium-term outcomes of dHAM in nsRALP, long-term functional and oncological outcomes are lacking. Our center has been using dHAM (AmnioFix, MIMEDX, Marietta, GA) since 2014, accruing long-term data on patient outcomes in this unique cohort of men. For the first time in the urological literature, we can report long-term functional outcomes in patients who underwent nsRALP with the use of dHAM nerve wrap as well as describe prostate cancer-specific outcomes.

Materials and Methods

After obtaining institutional review board approval (No: LCH 2-092-019), a retrospective analysis of a prospectively maintained single-institution prostate cancer database was conducted. After excluding men with baseline erectile dysfunction (defined as SHIM < 21), we analyzed all patients undergoing bilateral nsRALP with dHAM from October 2014 to October 2024 performed by a single high-volume surgeon. (Group 1) Group 2 comprised patients who underwent nsRALP by the same surgeon prior to dHAM use (before 2014). Exclusion criteria for analysis were men < 18 years of age, salvage RALP, non-nsRALP.

RALP was performed in standard transperitoneal fashion as initially described by Menon et al. and further refined by Reddy et al. with the addition of maximal urethral length preservation technique (MULP).[3, 4] The da Vinci® multiport robotic platform (Intuitive Surgical, Sunnyvale, CA) was used, with the Si system prior to 2019 and Xi thereafter. dHAM (AmnioFix®, MIMEDX) was applied as a bilateral

nerve wrap following neurovascular bundle dissection. The grafts were placed after specimen bagging and prior to anastomosis. (Fig. 1) At the first postoperative visit, all patients were started on a penile rehabilitation program comprising daily tadalafil 5mg with on demand sildenafil 25mg.

Primary outcomes included time to first erection, time to erection sufficient for penetration (potency), SHIM scores at 12 months and 24 months, and continence. Secondary outcomes included perioperative outcomes, complications, and positive surgical margin (PSM) status and biochemical recurrence.

Binary logistic regression was used to examine the relationship between independent variables including Age, BMI, AUA score, PSA, prostate size, pre- and post-operative Gleason score, estimated blood loss, clinical staging, D'Amico risk levels, and dHAM usage on potency in patients undergoing RALP (defined as erection sufficient for sexual intercourse) after the surgery. Student's t-test was used for continuous variables and chi-square testing for categorical comparisons, including potency rates at 3, 6, 12, and 24 months. All statistical analyses were performed using SPSS v.22.0 software (IMB, Chicago, IL, USA).

Results

A total of 2,560 men underwent bilateral nsRALP with dHAM from October 2014 to October 2024 (Group 1). These were matched to 1,495 men who underwent nsRALP without dHAM prior to 2014 (Group 2). Baseline patient and tumor characteristics are found in Table 1. There was no significant difference in patient age, comorbidities, and preoperative tumor factors between both groups. Of note, there was a slightly higher incidence of higher grade prostate cancer on prostate biopsy in Group 1, although not statistically different from Group 2.

Table 1
Preoperative Characteristics and Patient Demographics

Characteristic	Group 1	Group 2	P value
Number	2,560	1,495	
Age (years)	64.3 ± 6.8	62.4 ± 4.9	P = 0.12
BMI	29.6 ± 6.3	28.4 ± 8.7	P = 0.25
Hypertension	45%	43%	P = 0.40
Diabetes Mellitus	24%	28%	P = 0.28
PSA (ng/mL), median (IQR)	7.2 (5.1–9.8)	7.5 (5.8–10.1)	P = 0.10
Prostate volume (mL)	58 ± 1.2	60 ± 2.2	P = 0.36
Biopsy Grade Group 1	16.4%	18.0%	P = 0.089
Biopsy Grade Group 2	41.0%	43.0%	P = 0.10
Biopsy Grade Group 3	25.2%	24.3%	P = 0.32
Biopsy Grade Group 4	12.3%	10.5%	P = 0.070
Biopsy Grade Group 5	5.1%	4.2%	P = 0.15
SHIM Score	23 ± 2.9	22 ± 3.2	P = 0.24
AUASI Score	8.2 ± 3.1	8.0 ± 2.4	P = 0.68
All values reported as mean ± SD unless otherwise stated.			

Mean follow up was 8 years. The mean number of days until first erection was 7 vs. 14 ($p < 0.05$) in Groups 1 and 2. The mean number of days until erection sufficient for penetration was 21 vs. 36 ($p < 0.05$). The percent of potent patients in Group 1 at 3, 6, 12, and 24 months was 75%, 87%, 98%, 98%. The percent of potent patients in Group 2 during the same time frame was 60%, 78%, 90%, 94% ($p < 0.05$). (Fig. 1). Mean SHIM score in Group 1 at 12 months was 20.6 ± 0.8 and in Group 2 was 18.0 ± 1.8 ($p<.05$). Mean SHIM in Group 1 at 24 months was 21.4+/-1.2 and Group 2 was 20.8+/-2.4 ($p = 0.05$). (Table 2). At mean follow up, 10% of patients Group 1 endorsed some degree of erectile dysfunction, whereas 11% of patients in Group 2 did.

Table 2
Functional Outcomes

Outcome	Group 1	Group 2	P value
Time Until Continence (Pad Free)	3.4	4.5	P = 0.18
Time Until First Erection (Days)	7 +/- 1	14 +/- 2	P < 0.05
Time Until Potency (Days)	21 +/-3	36 +/- 3	P < 0.05
SHIM at 12 months	20.6 ± 0.8	18.0 ± 1.8	P = 0.043
SHIM at 24 months	21.4 ± 1.2	20.8 ± 2.4	P = 0.05
All values reported as mean ± SD unless otherwise stated.			

There were no significant differences in biochemical recurrence, margin status, or complication rates between groups (Table 3). PSM rate in Group 1 was 17% and 20% in Group 2 ($p > 0.05$). BCR-free survival was not reached at mean follow up in Group 1 and was 6.3 years in Group 2 ($p > 0.05$). No cases of graft-related infection, inflammation, or immune response were observed. Stratifying Groups 1 and 2 based on age showed significant difference in erectile function recovery in men older than 60 years of age compared to younger. (Supplementary Fig. 1).

Table 3
Perioperative, Oncological, and Complications Outcomes

Outcome	Group 1	Group 2	P Value
Final Pathology			
Gleason Grade Group 1	20%	22%	p = 0.06
Gleason Grade Group 2	34%	35%	p = 0.18
Gleason Grade Group 3	28%	24%	p = 0.66
Gleason Grade Group 4	9%	11%	p = 0.08
Gleason Grade Group 5	9%	8%	p = 0.06
Positive Surgical Margin Rate	17%	20%	P = 0.30
Estimated Blood Loss (mL)	90 ± 20	91 ± 18	P = 0.64
Any Postoperative Complications	21%	23%	p = 0.83
Clavien-Dindo >/=3 Complications	4%	4%	p = 0.70
Biochemical Recurrence Free Survival (years)	NR	6.3 +/- 2.4	p = 0.40
All values reported as mean ± SD unless otherwise stated.			

Discussion

This study represents the longest follow-up to date of dHAM use in RALP, encompassing over 3,000 patients and nearly a decade of data. Our findings demonstrate that dHAM significantly accelerates return of erectile function, with earlier time to first erection and penetrative intercourse, without adverse effects on cancer outcomes. Additionally, use of dHAM results in higher rates of potency at 12 and 24 months post RALP with a lower decrease in SHIM scores at 12 months.

Surgery induced neuropraxia results from the secondary inflammatory response due to dissection, traction, or thermal injury. In radical prostatectomy, this phenomenon occurs regardless of the degree of nerve-sparing.[5, 6] Furthermore, inflammation induces cellular edema, acidosis, blocked nerve conduction, and eventually apoptosis leading to permanent nerve tissue damage and dysfunction.[7, 8] A rabbit model of ulnar nerve neurorrhaphy showed that application of a human amniotic wrap at the time of nerve repair resulted in significantly less perineural adhesion and fibrosis than controls.[9] This was corroborated in the spine literature, with dHAM decreasing epidural fibrosis after transforaminal lumbar interbody lumbar fusion.[10]

Recent experimental studies using dHAM have provided encouraging data regarding the potential to rehabilitate nerves after injury. [13] More specifically, dHAM has been shown to house and release many factors involved in tissue growth, repair, and inflammation such as EGF, TGF-β, FGF, PDGF, and VEGF.[11] dHAM has proven benefits in wound healing through its numerous cytokines and growth factors and has been proposed as a scaffolding for future tissue engineering applications.[12–15] Preclinical and clinical studies of perinatal tissue allografts used in radical prostatectomy have shown promising neurotrophic, anti-fibrotic, and anti-inflammatory properties.[16] These have increased the usage of dHAM and spurred fervent research on the topic.

Ogaya-Pinies et al. showed that application of dHAM as nerve wraps at time of RALP does not increase risk of biochemical recurrence (BCR) after RALP, even in the presence of adverse pathologic features such as positive surgical margin (PSM), extra-prostatic extension of disease (EPE), or high Gleason score (Gleason Grade Group >/= 4).[17] The authors also demonstrated for the first time continuous improvement in return of potency with different grades of nerve sparing (full vs. partial). Of note, the authors showed on subgroup analysis that the time to return of potency was faster in men < 55 years old who received dHAM (2.06 ± 1.94 versus 2.58 ± 2.48 mo. in the control group (p = 0.0056)) compared to men > 55 years old who received dHAM (2.93 ± 2.74 mo. and 3.43 ± 3.05 mo. for the subgroup in the control (p = 0.1476)).[17] These findings are in contradistinction to our long-term outcomes, which showed significant improvement in return to potency across all age categories with the dHAM nerve wrap.

Our group initially published our work with dHAM in 2019, comparing 700 consecutive RALP patients who underwent bilateral nerve sparing with dHAM and 700 without dHAM. We reported that the first noticeable erection sufficient for a satisfactory penetrative intercourse in the intervention group was

significantly earlier ($p < 0.01$; 34.6 ± 3.6 days), whereas the decrease in SHIM score was lower (4.27 ± 0.14 days).[18] Now, ten-year data of over 3,000 men supports our initial study results, showing that dHAM at the time of nsRALP can improve functional outcomes without compromising long-term oncological outcomes. This is particularly beneficial in men older than 60 years of age, as this subgroup had similar erectile functional recovery as younger men without dHAM.

Strengths of this study include its large cohort size and a mean follow-up duration of eight years, which represents the longest reported follow-up to date for patients undergoing nsRALP with dHAM. Additional strengths include the use of a single surgeon and a reproducible study design, which help to minimize variability in surgical technique and nerve wrap application. The primary limitation of the study is its retrospective design; however, the large sample size mitigates some of the inherent biases, including regression to the mean, thereby reducing potential confounding. Another limitation pertains to the long follow up (comparing patient groups pre- and post-2014). Further refinement of surgical technique by the operating surgeon may have potentially contributed to the improved outcomes observed in the contemporary dHAM cohort. However, the magnitude of this difference is likely minimal, given the large size of the historical cohort (> 1,400 patients) and the surgeon's progression beyond the learning curve. Further multicenter, prospective trials are required to validate this single-institution study.

Conclusion

Ten-year data of dHAM as a nerve wrap at the time of nerve sparing RALP show that it is a safe and effective adjunct to hasten return of erectile function as well as improve 12-month and 24-month potency rates without compromising oncological outcomes. Men over the age of 60, especially, show improved 12- and 24-month potency with dHAM.

Declarations

Conflicts of Interest:

The authors have no relevant conflicts of interest to disclose.

Author Contribution

SR (first author) wrote main manuscript and created tables. AF and AA performed statistical analysis and revised manuscript. SR (senior author) was project manager and revised manuscript.

Data Availability

Data is available upon request.

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Figures

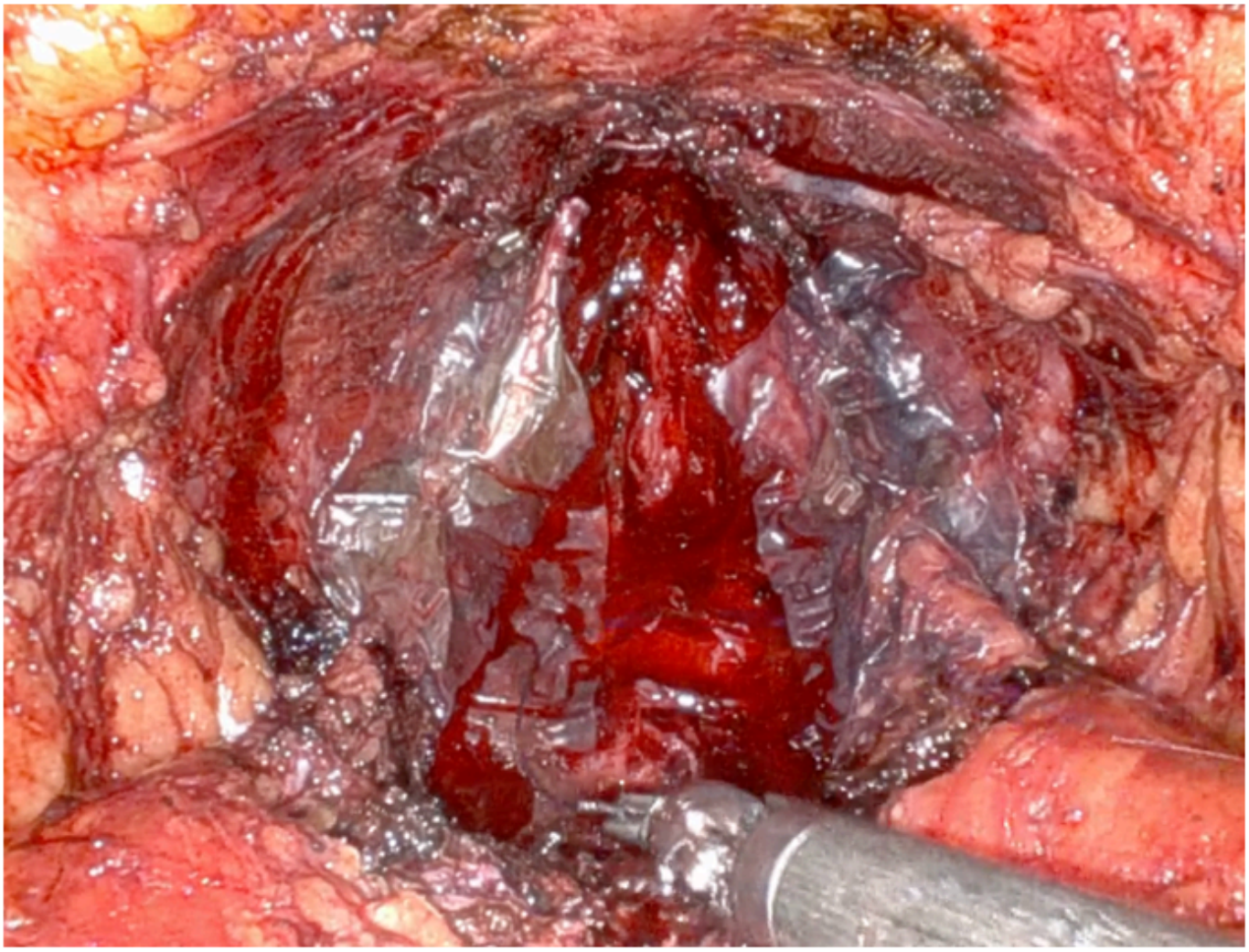

Figure 1

dHAM nerve wraps placed prior to anastomosis

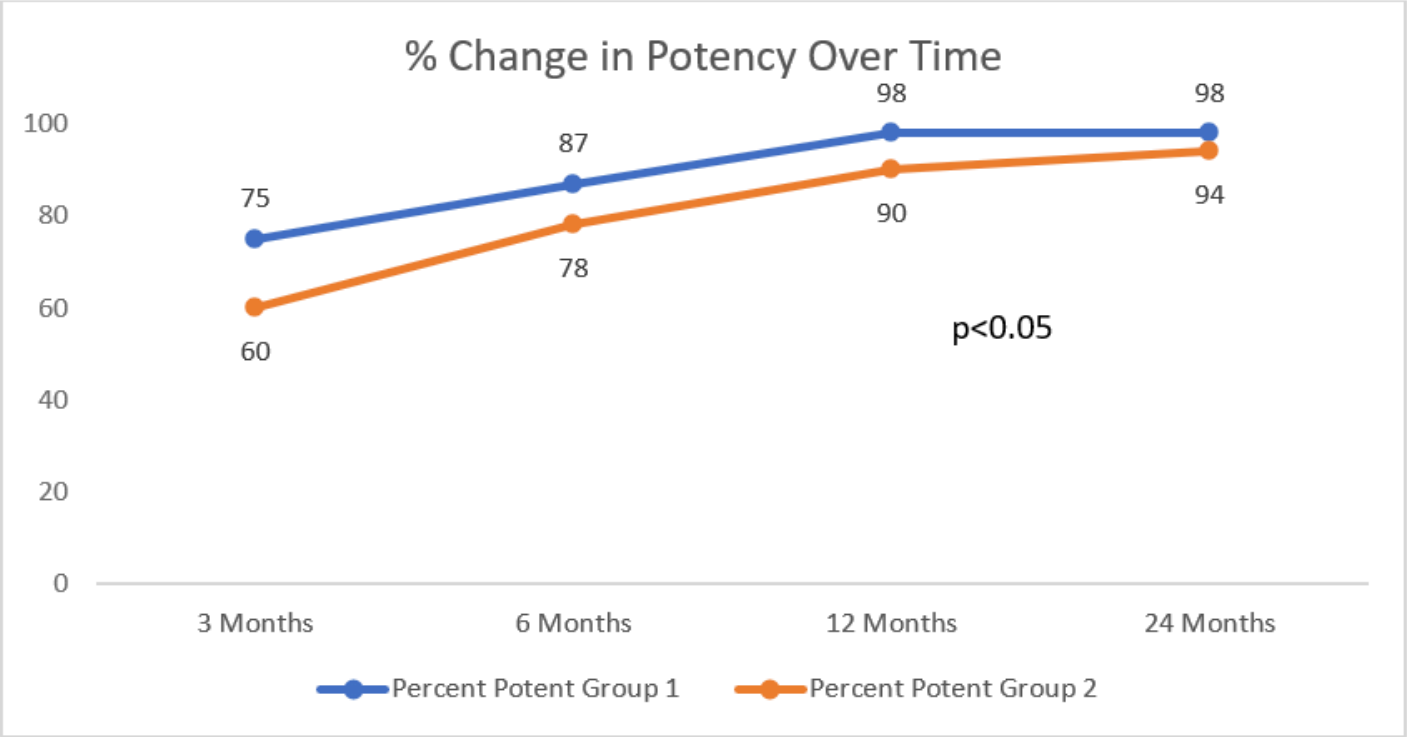

Figure 2

Change in Potency Over Time

Supplementary Files

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- SupplementalFigure1.docx