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Neurogenic Orthostatic Hypotension: a Common Complication of Successful Pancreas Transplantation

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Background. Orthostatic hypotension (OH) is a poorly understood complication of simultaneous pancreas–kidney (SPK) transplantation. We sought to determine the incidence, timing, and relationship of OH to rapid glycemic control in the early posttransplant period. **Methods.** This was a nonrandomized retrospective single-center review of 75 SPK and 19 kidney-alone (KA) recipients with type 1 diabetes (DM). **Results.** OH occurred in 57 (76%) SPK versus 2 (10%) KA recipients (odds ratio [OR] 61.72, 95% confidence interval [CI], 9.69-393.01; $P < 0.001$). The median onset of OH was 12 (interquartile range [IQR] 9–18) days posttransplant and resolved in 85% of SPK recipients after a median of 2.5 (IQR 1.2–6.3) months. Among SPK recipients, independent risk factors for OH were a shorter duration of DM (OR 0.85, 95% CI, 0.73-0.98; $P = 0.03$) and rapid glycemic control in the early posttransplant period (OR 1.13, 95% CI, 1.01-1.27; $P = 0.04$), as evidenced by a larger percent change in hemoglobin A1c (HbA1c) from transplant to month 3. OH patients had a higher median baseline HbA1c [8.3% (IQR 7.2–10.0) versus 7.1% (IQR 6.8–8.3); $P = 0.07$], lower median 3-month HbA1c [4.8% (IQR 4.6–5.2) versus 5.2% (IQR 5.0–5.4); $P = 0.02$], and a larger reduction in HbA1c over time as compared to recipients without OH ($P < 0.01$). **Conclusions.** Our results show that OH is more likely to occur following SPK versus KA transplantation and is strongly associated with rapid glucose normalization within the early posttransplant period.

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Simultaneous pancreas and kidney (SPK) transplantation is generally recognized as the optimal treatment for individuals with type 1 diabetes (DM) and end-stage renal disease (ESRD). Typically, successful pancreas transplantation will result in euglycemia within hours of the surgical procedure. Posttransplant, long-term improvement in end-organ complications of DM, such as peripheral neuropathy has been described, but data on autonomic function parameters remain limited and outcomes are mixed.[1-6] Paradoxically, orthostatic hypotension (OH), a manifestation of autonomic neuropathy, is a recognized but poorly understood complication of SPK transplantation that often presents within the early posttransplant period.[7,8] This condition can result in frequent falls related to orthostasis and hospital readmissions, as well as overall reduced quality of life. Current medical management consists of hydration, increasing salt intake, behavioral modifications, and pharmacologic interventions. Although historically OH was believed to be a manifestation of pre-existing autonomic neuropathy, a clear association with posttransplant OH has not been established.[7] Moreover, the incidence, risk factors, and patient outcomes for OH have yet to be described.

Aggressive glycemic control is known to cause treatment-induced neuropathies in individuals with poorly controlled DM. Compared to patients with no change in hemoglobin A1c (HbA1c), a rapid reduction within a 3-month period has been associated with a risk of developing neuropathies,[9,10]

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thus we sought to determine the impact of rapid glycemic control on OH development following SPK transplantation.

MATERIALS AND METHODS

Design and Patient Population

We conducted a retrospective, single-center review of successful enteric-drained SPK recipients transplanted between January 2013 and December 2017 at the Houston Methodist Hospital J.C. Walter Transplant Center in Houston, Texas. A comparator cohort of type 1 DM patients receiving kidney-alone (KA) transplants during the same time period was also included. The majority of these patients had elected to receive a living-donor renal transplant before a deceased donor pancreas transplant. Demographic data, duration of DM, pre-existing OH, clinical course, and management of post-transplant OH were obtained from a chart review. First, we sought to determine the association of OH to pancreas transplantation by comparing the incidence among type 1 DM recipients of either SPK or KA transplant. Second, we examined the incidence and timing of OH after SPK transplantation. Third, we determined the relationship of OH to change in glycemic control after successful SPK transplantation.

Diagnosis and Management of OH

OH was defined as a sustained 20 mm Hg drop in systolic blood pressure within 3 min of standing compared with sitting or in a supine position.[11] Blood pressures were assessed in both a sitting and standing position on a daily basis while recipients were hospitalized and at all weekly clinic visits. Upon diagnosis, anti-hypertensive medications were discontinued, and patients were encouraged to increase fluid and salt intake and use of compression stockings. Initial pharmacologic management consisted of fludrocortisone and/or midodrine, with droxidopa being used in treatment-refractory cases. In severe cases, patients were admitted for treatment with intravenous normal saline infusions. For the purposes of this retrospective analysis, only recipients requiring pharmacologic management of OH were included in this study. Resolution of OH was defined as discontinuation of pharmacologic interventions or initiation of blood pressure medications.

Surgical Procedure

Both kidney and pancreas grafts were placed in an intra-abdominal position. The kidney was anastomosed to the left external iliac vessels with a Lich ureteroneocystostomy over a double-J stent. The pancreas was anastomosed to the right iliac vessels with systemic venous drainage and enteric exocrine drainage.

Immunosuppression Protocol

All recipients received a 5-d induction course of rabbit anti-thymocyte globulin, for a cumulative dose of 7.5 mg/kg. Tacrolimus was initiated when the serum creatinine fell at least 25% from baseline. Tacrolimus doses were targeted to a trough level of 8–10 ng/mL until 3 mo posttransplant, when the range was lowered to 6–8 ng/mL. Mycophenolate mofetil was initiated on the day of surgery at a dose of 500 mg twice daily and then increased to 1000 mg twice daily at completion of all anti-thymocyte globulin dosages (day 6 posttransplant). Methylprednisolone (250 mg) was given on the day of transplantation and then tapered to 30 mg of prednisone by day 3 posttransplantation. Corticosteroids were discontinued by 7 days posttransplantation for SPK recipients considered to be at lower risk of acute rejection (non-African American recipients receiving the first transplant and with a peak pretransplant panel reactive antibody less than 20%). All other SPK recipients were gradually tapered to a maintenance dose of 5 mg/day of prednisone by 1-month posttransplantation.

Postoperative Management of Glycemia

By center protocol, intravenous infusions of dextrose were not routinely used in the early posttransplant period and glucose levels were not tightly controlled using insulin infusions.

Statistical Analysis

Descriptive data were reported as median and interquartile range (IQR) for continuous variables, and as frequencies and proportions for categorical variables. Differences between OH and non-OH groups were compared using the chi-square or Fisher exact tests for categorical variables and Kruskal-Wallis test for continuous variables as appropriate. Comparisons in HbA1c between OH and non-OH groups at each time point were determined by the Kruskal-Wallis test. The difference of the mean change over time in HbA1c between groups was determined by a linear mixed model. The linear mixed model used HbA1c as the dependent variable and the OH versus non-OH groups as the independent variables and employed a random intercept plus random slope model with an unstructured covariance option. The linear mixed model has strength in dealing with missing values, which commonly occurs in longitudinal studies, as well as the unbalance in the number of measurements and the time interval between measurements.[12] Univariate and multiple logistic regression analyses were used to determine the potential risk factors associated with the development of OH. Variables selected for multiple logistic regression models were conducted based on the clinical importance and also by Stata's Lasso command with the cross-validation option. The likelihood ratio test was used to further the model subsets and used to select the best final model based on the smallest Bayesian information criterion, largest area under the receiver operating characteristic curve, and using the smallest number of covariates possible. All analyses were performed on Stata version 16.0 (StataCorp LLC, College Station, TX). A P value of <0.05 was considered statistically significant. This study was approved by the Houston Methodist Hospital Institutional Review Board.

RESULTS

In this retrospective review, our study cohort included 94 transplant recipients with ESRD and type 1 DM, comprised of 75 SPK and 19 KA transplants, performed between January 2013 through December 2017. Only one patient, a recipient of an SPK transplant, required pharmacologic treatment of symptomatic OH before transplantation. All KA and all but one of the SPK recipients were treated with anti-hypertensive agents before transplantation. As shown in Table 1, baseline demographics were similar between SPK and KA groups, including age, gender, and race. Median diabetes duration before transplant, the need for dialysis, duration of dialysis, as well as peak and baseline HbA1c were also equivalent. SPK recipients experienced a significantly higher rate of OH

TABLE 1.

Recipient demographics and incidences of posttransplant orthostatic hypotension in kidney-alone vs kidney–pancreas recipients

Variable	All patients (n = 94)	Kidney-alone (n = 19)	Kidney–pancreas (n = 75)	*P*
Age, median (IQR)	38 (33–47)	38 (34–44)	38 (33–48)	0.78
Male gender, n (%)	55 (59)	11 (58)	44 (59)	0.95
Race, n (%)				
White	43 (46)	10 (53)	33 (44)	0.65
Black	22 (23)	3 (16)	19 (25)	
Hispanic	25 (27)	5 (26)	20 (27)	
Other	4 (4)	1 (5)	3 (4)	
Years of DM, median (IQR)	24 (21–31)	24 (20–27)	24 (21–32)	0.53
Pretransplant dialysis (%)	77 (84)	15 (79)	62 (85)	0.50
Months of dialysis, median (IQR)	12 (4, 24)	12 (12, 24)	11 (5, 18)	0.56
Peak HbA1c before transplant, median (IQR)	8.5 (7.3–10.7)	8.1 (7.3–9.3)	8.5 (7.3–10.8)	0.32
HbA1c at transplant, median (IQR)	7.9 (6.9–9.4)	7.5 (6.9–9.3)	7.9 (7.0–9.4)	0.85
Steroid-sparing immunosuppression, n (%)	29 (31)	2 (11)	27 (36)	0.049
Incidence of posttransplant orthostatic hypotension, n (%)	59 (63)	2 (11)	57 (76)	<0.001

DM, type 1 diabetes; HbA1c, hemoglobin A1c; IQR, interquartile range.

TABLE 2.

Univariate and multiple logistic regression analysis of risk factors for orthostatic hypotension among kidney-alone and kidney–pancreas recipients

	Univariate analysis			Multiple logistic regression analysis		
Variable	No OH (n = 35)	OH (n = 59)	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Transplant type, n (%)						
Kidney-alone	17 (49)	2 (3)	(reference)	<0.001	61.72 (9.69-393.01)	<0.001
Kidney–pancreas	18 (51)	57 (97)	26.92 (5.67-127.84)			
Age, median (IQR)	38 (35-44)	38 (32-48)	0.99 (0.95-1.04)	0.78	1.06 (0.98-1.16)	0.15
Male gender, n (%)	21 (60)	34 (58%)	0.91 (0.39-2.12)	0.82		
Race, n (%)						
White	15 (43)	28 (48)	(reference)	0.24		
Black	11 (31)	11 (19)	0.54 (0.19-1.52)	0.81		
Hispanic	8 (23)	17 (29)	1.14 (0.40-3.25)	0.67		
Asian	1 (3)	3 (5)	0.54 (0.03-9.19)			
Race, n (%)				0.16	3.80 (0.96-15.08)	0.06
Black	11 (31)	11 (19)	(reference)			
Non-Black	24 (69)	48 (81)	2.00 (0.76-5.27)			
Years of DM, median (IQR)	26 (23-35)	23 (20-30)	0.94 (0.89-0.99)	0.02	0.84 (0.75-0.94)	0.002
Pretransplant dialysis (%)	26 (75)	51 (90)	2.94 (0.95-9.16)	0.06		
Months of dialysis, median (IQR)	12 (0-24)	9 (5-21)	1.01 (0.98-1.03)	0.59		
Steroid-sparing immunosuppresson n (%)	4 (11)	25 (42)	5.70 (1.78-18.22)	0.003	2.76 (0.63-12.13)	0.18

DM, type 1 diabetes; IQR, interquartile range.

following transplantation compared to KA recipients (76% vs 10%, $P < 0.001$).

Table 2 shows both univariate and multivariate analyses of perioperative risk factors for OH among KA and SPK transplant recipients. Using multiple logistic regression analysis, only the receipt of an SPK transplant (adjusted odds ratio [OR] 61.72; 95% confidence interval [CI], 9.69-393.01; $P < 0.001$) and a shorter duration of DM before transplant (adjusted OR 0.84; 95% CI, 0.75-0.94; $P = 0.002$) were found to be independent risk factors for OH. Of note, neither the requirement for pretransplant dialysis nor the duration of dialysis pretransplant was a significant risk factor for posttransplant OH. Additionally, both cohorts showed similar and excellent renal function by posttransplant day 3.

To consider the possibility that the increased incidence of OH among the SPK cohort was related to either impaired early renal function or increased surgical stress, we compared both the median estimated glomerular filtration rate (eGFR) at 1-mo posttransplantation and the median length of stay for both groups. At 4 weeks, the median eGFR of the KA cohort was 61 mL/min (IQR 47, 72) versus 69 mL/min (IQR 58–84) for the SPK group ($P = 0.02$). The median length of stay for the KA cohort was 4.5 d (4, 6) versus 7d (6, 9) for the SPK group ($P < 0.001$).

Restricting the analysis to only SPK recipients, we sought to describe the clinical course of OH in the early posttransplant period. OH occurred in 57 of 75 (76%) SPK recipients with a median time to onset of 12 d (IQR 9–18) posttransplant. As previously defined, all 57 patients who developed

OH required pharmacologic management, comprised of fludrocortisone alone in 24 (42%), midodrine alone in 2 (4%), and a combination of fludrocortisone and midodrine in the remaining 31 (54%) patients. One patient with persistent and treatment-refractory OH was initiated on droxidopa at 4.6 mo posttransplant. OH required readmission in 11 (19%) patients, with 5 requiring multiple readmissions. OH completely resolved in 46 of 57 (85%) SPK recipients after a median of 2.5 mo (IQR 1.2–6.3) following onset.

Risk factors for OH, limited to SPK recipients, are shown in Table 3. Again, using multiple logistic regression analysis, a shorter duration of diabetes before transplant (adjusted OR 0.85; 95% CI, 0.73-0.98; $P = 0.03$) and rapid glycemic control (adjusted OR 1.13; 95% CI, 1.01-1.27; $P = 0.04$), as evidenced by a greater percent change in HbA1c value from the time of transplant to month 3, were found to be independent risk factors for posttransplant OH. No differences in OH rates based on steroid avoidance protocols, tacrolimus levels, renal function, or insulin levels were observed.

To determine the relationship of OH to rapid glycemic control after successful SPK transplantation, we performed a linear mixed model of change in HbA1c at 3 mo compared to pretransplant (Figure 1). OH patients had higher median (IQR) HbA1c at baseline (8.3% [7.2–10.0] vs 7.1% [6.8–8.3]; $P = 0.07$) and lower median HbA1c at 3 months (4.8% [4.6–5.2] vs 5.2% [5.0–5.4]; $P = 0.02$), as well as a significant difference in the reduction of HbA1c over time compared to those without OH ($P < 0.01$).

DISCUSSION

In this retrospective analysis, we sought to show that OH after SPK transplantation was linked to a rapid improvement in glucose control posttransplantation, in a patient population that likely has some degree of pre-existing diabetic neuropathy. Although previously described, the etiology of this early posttransplant complication is not well understood. In this review, the largest series presented to date, we found that in the early posttransplant period, fully 63% of patients with type 1 DM who received either a KA or SPK transplant developed symptomatic OH. Moreover, for recipients with type 1 DM, SPK transplantation was a strong predictor of OH, occurring in 76% of SPK patients compared to only 10% of KA recipients.

To exclude the possibility that impaired renal function or greater physical disability in the SPK group was the cause of the increased incidence of OH, we compared both early renal function and length of stay. In fact the SPK cohort displayed better early renal function than the KA group and although the length of stay after SPK surgery was longer than that for the KA recipients, in real terms, the differences were small. Thus, it is unlikely that early renal function or elevated surgical stress played an important role in the increased incidence of OH among the SPK recipients.

OH typically presented early after SPK transplantation, with a median onset at 12 days post-surgery. While symptoms of OH resolved for most recipients, treatment of OH required pharmacologic intervention and frequently resulted in readmission in the early posttransplant period. Management of OH included discontinuation of antihypertensive medications, along with the recommendations to increase fluid and salt intake and use compression stockings. Initial pharmacologic management consisted of fludrocortisone and/or midodrine, with droxidopa being used in treatment-refractory cases. In severe cases, patients were admitted for treatment with intravenous normal saline infusions.

In multivariate analysis, among SPK recipients, a shorter duration of DM before transplantation and a larger reduction

TABLE 3.

Univariate and multiple logistic regression analysis of risk factors for orthostatic hypotension limited to kidney–pancreas recipients

	Univariate analysis				Multiple logistic regression analysis	
Variable	No OH (n = 18)	OH (n = 57)	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Age, median (IQR)	37 (34 to 52)	40 (32 to 48)	0.99 (0.95 to 1.05)	0.85	1.04 (0.93 to 1.17)	0.47
Male gender, n (%)	10 (56)	34 (60)	1.18 (0.41 to 3.45)	0.76	2.13 (0.35 to 12.86)	0.41
Race, n (%)						
White	6 (33)	27 (48)	(reference)	0.07		
Black	8 (44)	11 (19)	0.31 (0.09 to 1.09)	0.87		
Hispanic	4 (22)	16 (28)	0.89 (0.22 to 3.63)	–		
Asian	0 (0)	3 (5)	–			
Race, n (%)				0.04	8.14 (0.72 to 92.39)	0.09
Black	8 (44)	11 (19)	(reference)			
Non-Black	10 (56)	46 (81)	3.35 (1.07 to 10.45)			
Years of DM, median (IQR)	29 (24 to 38)	23 (21 to 30)	0.90 (0.84 to 0.97)	0.01	0.85 (0.73 to 0.98)	0.03
Steroid-sparing immuno-suppression, n (%)	3 (17)	24 (42)	3.64 (0.95 to 13.98)	0.06	1.81 (0.19 to 17.44)	0.61
HbA1c at transplant, median (IQR)	7.1 (6.8 to 8.3)	8.3 (7.2 to 10.0)	1.52 (0.96 to 2.40)	0.07		
Trough insulin level (ng/mL) at month 1, median (IQR)	22.2 (20.4 to 47.9)	23.6 (16.6 to 36.7)	0.98 (0.95 to 1.02)	0.27		
% change of HbA1c from transplant to month 3, median (IQR)	35.7 (23.9 to 40.0)	41.9 (30.9, 47.0)	1.06 (0.99, 1.11)	0.06	1.13 (1.01 to 1.27)	0.04
% change of tacrolimus trough level (ng/mL) from day 1 to day 30, median (IQR)	−26.6 (−35.1 to 12.5)	−4.6 (−61.5 to 20.6)	1.00 (0.98 to 1.01)	0.80	1.01 (0.99 to 1.02)	0.30
% change of eGFR from day 3 to day 28, median (IQR)	−55.5 (−168.4 to 0.0)	−35.3 (−131.2 to 0.0)	1.00 (0.98 to 1.00)	0.68		

DM, type 1 diabetes; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; OH, orthostatic hypotension; SPK, simultaneous pancreas–kidney.

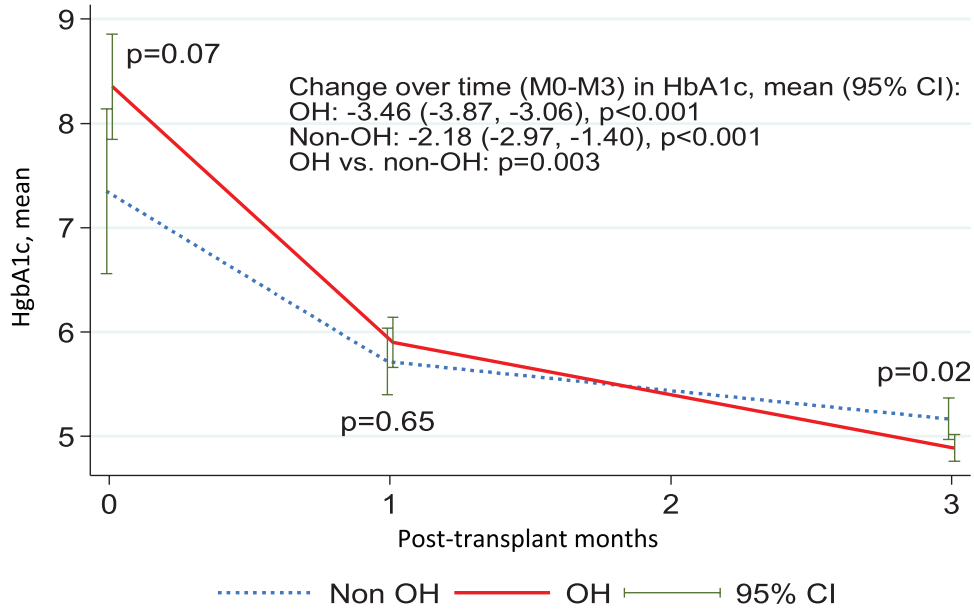

FIGURE 1. Change in hemoglobin A1c from day 0 to posttransplant month 3 between SPK recipients with orthostatic hypotension (OH) vs no orthostatic hypotension (no OH). SPK, simultaneous pancreas–kidney.

in HbA1c in the early posttransplant period were independent risk factors for OH. Again these data suggested that rapid glycemic control was implicated in the development of OH. In short, OH appeared to be an iatrogenic complication of successful pancreas transplantation, as the rapid improvement in HbgA1c in the early posttransplant period resulted in a treatment-induced neuropathy. It is unclear as to why a shorter duration of DM before transplantation should be associated with OH, although it is possible that those patients had a more aggressive progression of disease likely due to relatively poor glucose control.

To date, there are only 2 other single-center studies that have reported their experience with OH after pancreas transplantation. Khurana et al described 7 of 25 SPK recipients who developed OH posttransplantation, typically within the first 2 weeks after surgery and resolved in most cases within 6 wk to 9 mo. They similarly found that this complication was more common after SPK transplantation and speculated that it may be related to hyperinsulinemia after transplant, resulting in vasodilation and a reduction in peripheral vascular resistance.[7] Another single-center report described 7 SPK and 1 pancreas-alone patient with early posttransplant OH, all successfully treated with midodrine.[8]

A similar syndrome, treatment-induced neuropathy in diabetes (TIND), has been observed in patients, newly diagnosed with type 1 diabetes who are initiated on insulin therapy. TIND is a rare iatrogenic small fiber neuropathy caused by an abrupt improvement in glycemic control in the setting of chronic hyperglycemia and is defined by the acute onset of neuropathic pain and/or autonomic dysfunction within 8 wk of a large improvement in glycemic control.[9,10] Previous studies have shown a strong correlation between the magnitude of decrease in HbA1c, the severity of neuropathic pain, and impairment of sympathetic adrenergic function. OH and syncope have been shown to accompany more severe autonomic dysfunction. In addition, in a longitudinal study of 26 individuals with type 1 DM and TIND, followed over an 8-y period, those with stable glycemic control were more likely to show improvement in neuropathy compared to those with poor control.[10] In the experience described herein, although OH was associated with a large improvement in HbA1c percentage, there was no association with neuropathic pain in the SPK recipients. Yet in the majority of transplant recipients, who continued to maintain excellent glucose control, OH tended to resolve, consistent with the findings of the study noted here.

Our study has several limitations inherent to a retrospective chart review, including a relatively small number of subjects and lack of randomization. As we were restricted to data available in the electronic medical record, we cannot comment on the possible contribution of volume status, cardiac function, or alternative endocrine disorders to the development of OH. Similarly, comparing KA recipients, the majority of whom received a living-donor kidney, to recipients of deceased donor SPK transplants is an imperfect comparison, but again, this is a limitation of a retrospective study. Additionally, we were unable to demonstrate the mechanism of improved glycemic control on OH, only to show an association between the two. However, as noted here, 2 potential causes may be direct vasodilation caused by peripheral hyperinsulinemia and/or peripheral neuropathy associated with an abrupt correction of hyperglycemia.

In summary, we have shown that posttransplant OH is a common complication of SPK transplantation presenting within the first 2 wks, requires pharmacologic management and typically resolves within 1–2 mo. Our results point to the finding that this phenomenon is a frequent complication of successful pancreas transplantation, resulting from rapid normalization of glucose levels within the early posttransplant period. We believe that these findings will inform clinicians managing pancreas transplant recipients to be cognizant of OH and proactively eliminate anti-hypertensive agents, encourage salt intake, and introduce midodrine and fludrocortisone early to prevent progression of OH and limit the need for readmission. Further work is required to understand the precise mechanism of this effect.

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