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CLINICAL RESEARCH

Addition of a Loop Diuretic to Norepinephrine During Treatment of Hepatorenal Syndrome Type 1

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Introduction: Diuretics are commonly discontinued in patients with cirrhosis with acute kidney injury (AKI) because they are presumed to trigger hepatorenal syndrome type 1 (HRS-1). We hypothesized that if HRS-1 is adequately treated with a vasoconstrictor (mean arterial pressure [MAP] effectively increased), diuretics are safe and effective.

Methods: Records of hospitalized patients with cirrhosis who received i.v. furosemide while receiving i.v. norepinephrine as a vasoconstrictor to treat HRS-1 were examined. We assessed change in urine output (UOP), trajectory of serum creatinine (sCr), and impact of portopulmonary hypertension (PoPHTN) on the therapeutic response.

Results: Twenty-six patients with HRS-1 received i.v. furosemide (median: 2 days, 160 mg boluses every 6–24 hours) added to i.v. norepinephrine. Median age was 51 years; 91% were of White race, 36% were women, and median model for end-stage liver disease score was 32. The median initial sCr was 4.0 mg/dl. Before treatment, median UOP was 358 ml/d. Norepinephrine alone led to a median increase in UOP to 850 ml/d. Addition of furosemide to norepinephrine induced a subsequent increase in median UOP to 2072 ml/d ($P < 0.0001$), which was not observed in a control group ($n = 22$) who did not receive furosemide. Nineteen patients (73%) treated with norepinephrine plus furosemide (median MAP increase, 16 mm Hg) either maintained or improved their sCr trajectory. The magnitude of norepinephrine-induced increase in MAP correlated with the norepinephrine plus furosemide-induced UOP ($r = 0.67$, $P = 0.0002$), and the correlation coefficient was numerically stronger among those with PoPHTN.

Conclusion: In patients with HRS-1 who are adequately treated with norepinephrine and achieved an optimal MAP increment, addition of i.v. furosemide enhances diuresis without negatively affecting renal recovery.

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Immediate withdrawal of diuretics, along with administration of i.v. albumin, has been a standard recommendation for patients with cirrhosis presenting with AKI. The rationale behind this recommendation by the International Club of Ascites was to eliminate and address prerenal azotemia as a cause of AKI.[1] Because of the vulnerability of patients with cirrhosis to acquire a state of hypovolemia, this recommendation was deemed reasonable and was fairly well-adopted in clinical practice. In addition, it is commonly assumed that diuretics can potentially trigger the development of HRS-1, also called HRS-AKI, as a result of diminishing effective arterial blood volume, triggering a hormonal cascade that causes maladaptive renal vasoconstriction.[2] Thus, once the diagnosis of HRS-1 is made, diuretics are rarely utilized because of concerns of aggravating the clinical course by further enhancing a maladaptive hepatorenal physiology. However, data supporting such potentially detrimental effect of diuretics in HRS-1 are lacking.

Vasoconstrictors constitute the mainstay of pharmacological therapy for HRS-1. Multiple lines of evidence demonstrate that the therapeutic response to vasoconstrictors is directly proportional to the

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achieved increase in MAP.[3] The greater the magnitude in MAP increase upon administration of a vasoconstrictor, the greater the likelihood of achieving improvement in kidney function.[4-6] This concept applies to all vasoconstrictors used in HRS-1, including the combination of midodrine and octreotide, norepinephrine and terlipressin.

Challenging the default assumption that patients with cirrhosis and AKI are often hypovolemic, evidence has emerged suggesting that these patients frequently present in a hypervolemic state.[7,8] Before establishing a diagnosis of HRS-1 or HRS-AKI, patients almost universally receive i.v. volume expansion with albumin for at least 1 to 2 days as per the 2015/2017 International Club of Ascites guidelines.[9] The new consensus recommendations from a combined effort by the Acute Disease Quality Initiative and the International Club of Ascites has removed the mandatory 2-day requirement of albumin administration to all comers and has now proposed individualized volume assessment and limited the i.v. volume challenge to 1 day, if indicated.[10] However, these new recommendations have not been widely adopted yet. Therefore, patients who fail a fluid challenge with i.v. albumin and assigned to a diagnosis of HRS-1, are often in a hypervolemic state at the time of initiation of vasoconstrictor therapy. At that stage, upon initiation of a vasoconstrictor, it seems prudent to limit additional administration of volume expanders and instead consider reintroduction of diuretic therapy.

Thus, we hypothesized that after a prerenal state is ruled out and HRS-1 is diagnosed and properly treated with a vasoconstrictor, that is, the MAP is effectively increased, use of diuretics during the course of the AKI could be safe and effective.

METHODS

Study Design

We searched for medical records of adult patients with cirrhosis hospitalized at Ochsner Medical Center between 2017 and 2023 who were diagnosed with AKI and received treatment with i.v. norepinephrine for >24 hours, specifically as a vasoconstrictor, for a presumed diagnosis of HRS-1 or HRS-AKI. Cases were captured through an established prospective data collection study protocol. All patients met the International Club of Ascites criteria for HRS-1. In addition, for a more stringent diagnosis to be included, all patients were required to have a urinary sodium <10 mEq/l and a urinary sediment without abundant muddy brown granular casts. This study was an ancillary investigation from a larger dual-center cohort study, evaluating the relationship of MAP increase and clinical outcomes.[6] We selected patients who were treated with norepinephrine infusion for HRS-1. Norepinephrine was dosed to target an increase in MAP ≥15 mm Hg from baseline, starting at a dose of 4 μg/min. However, administration of the prescribed dose was not uniformly adopted at all times, resulting in variability in achieved MAP target. To eliminate cases with insufficient norepinephrine-mediated MAP increase, we included in our study only those who achieved a minimum of 5 mm Hg increase within the first 24 to 48 hours of treatment. We then selected those who received at least 1 dose of i.v. furosemide concomitant with the norepinephrine infusion. The decision to add furosemide was independently made by the treating physician in cases in which patients were deemed hypervolemic and the UOP was deemed insufficient for optimal volume management. Exclusion criteria included the following: (i) use of a vasoconstrictor for treatment of shock, (ii) need for renal replacement therapy (RRT) before the initiation of HRS-1 treatment; and (iii) liver transplantation within 24 hours of initiation of furosemide. Patients treated with norepinephrine for HRS-1 during the same study period who did not receive furosemide were included as a control group.

Clinical Parameters

Basic demographic and clinical variables were collected. Clinical response to treatment was assessed by extracting daily values of sCr, UOP, and need for RRT. Daily mean MAP was estimated by the average of 12 to 24 MAP values per day.

Echocardiography

We searched for cases in which echocardiography was performed during the index hospitalization and before initiation of norepinephrine, to identify cases of PoPHTN or cirrhotic cardiomyopathy. PoPHTN was defined as echo-based mean pulmonary artery systolic pressure (PASP) ≥45 mm Hg and absence of reduced left ventricular ejection fraction or left ventricular diastolic dysfunction, or a right heart catheterization–based mean PASP > 25 mm Hg with a pulmonary capillary wedge pressure <20 mm Hg.[11] Cirrhotic cardiomyopathy was defined as either presence of reduced left ventricular ejection fraction, left ventricular diastolic dysfunction, or electrophysiological abnormalities.[12]

Treatment Periods

We defined 3 treatment periods; first period: pre-initiation of norepinephrine as vasoconstrictor; second period: treatment with norepinephrine alone; third period: treatment with i.v. furosemide added to

norepinephrine. For each treatment period, we assessed daily value of UOP and sCr concentration, and the change in mean MAP. For the first period, we estimated the slope of change in kidney function by averaging the daily change of up to 3 daily measurements of sCr before initiation of norepinephrine. Similarly, the mean UOP for this period was estimated by averaging up to 3 daily measurements of UOP before initiation of norepinephrine. The mean MAP for this period was defined by averaging the daily mean MAP values for up to 2 days before initiation of norepinephrine. For the second and third periods, all the daily values of sCr change, UOP, and MAP documented during the corresponding treatment period were extracted and divided by the number of days. For the control group of patients who did not receive diuretics, there was no third period of norepinephrine plus furosemide. Thus, the interval of treatment with norepinephrine alone was divided into early period (days 1–3) and late period (days 4–7).

End Points

We examined the change in kidney function and UOP between periods and the relationship between MAP increase and UOP. We also examined the relationship between PoPHTN or cirrhotic cardiomyopathy and the interdependence of norepinephrine-mediated MAP increase and the furosemide-enhanced volume of diuresis. The proportion of patients achieving >30% reduction in sCr without need for RRT or death or discharge to hospice by day 14, as well as the proportion of patients who progressed to require RRT, were also examined.

Statistics

Descriptive statistics were performed by calculating medians and interquartile ranges (IQRs). To assess changes in UOP and kidney function between treatment periods, we performed 1-way analysis of variance of repeated measures. Spearman correlations were performed to assess the relationship between MAP and UOP and presence of PoPHTN.

Ethics

The study was conducted with approval of the institutional review board and waiver of informed consent. The study was conducted in accordance with the Declaration of Helsinki.

RESULTS

Among 51 patients with cirrhosis and AKI who were treated with norepinephrine for HRS-1 during the study period, 24 did not receive concomitant furosemide, 2 of whom were excluded: 1 because MAP increase ≥5 mm Hg was never achieved, and 1 because UOP was not recorded. Thus, 22 patients who were treated with norepinephrine alone were available for comparison. In addition, among 27 patients who were treated with norepinephrine and received furosemide concomitantly, 1 patient was excluded because furosemide was administered only after norepinephrine was discontinued. Therefore, a total of 26 patients with HRS-1 treated with i.v. norepinephrine who simultaneously received i.v. furosemide during the norepinephrine infusion were included in the study (Figure 1). The overall baseline characteristics of the groups treated or untreated with diuretics were similar (Table 1). Specifically for the norepinephrine plus furosemide group, the median age was 51 (IQR: 40–63) years; 92% were of White race, 38% were women, and the median model for end-stage liver disease score was 32 (IQR: 28–36). Eighty-two percent of patients had failed to respond to the combination of midodrine and octreotide before receiving norepinephrine (Table 1). At the time of initiation of norepinephrine, the median sCr was 4.0 (IQR: 2.7–5.0) mg/dl. The median baseline MAP was 71 (IQR: 68–73) mm Hg. Exposure to norepinephrine alone before addition of furosemide lasted a median of 2 (IQR: 0–3) days. Furosemide was added to norepinephrine at a median of 1 (IQR 0–4) day after initiation of norepinephrine. The median duration of treatment with furosemide was 2 (1–8) days). The median dose of furosemide was 160 (80–240) mg boluses every 6 to 24 hours for a median of 2 (IQR: 1–3) doses per day.

UOP

The median MAP increase in response to norepinephrine was similar in both groups: 15 (IQR: 9–17) mm Hg and 16 (IQR: 11–18) mm Hg for the norepinephrine-only and the norepinephrine plus furosemide groups, respectively. Similarly, the median achieved absolute MAP values were comparable: 86 (IQR 83–89) and 87 (IQR: 81–88) mm Hg. Before initiation of norepinephrine, the median UOP was 328 (IQR: 200–500) ml/d for the norepinephrine-only group and 358 (IQR: 200–450) ml/d for the norepinephrine plus furosemide group. Norepinephrine alone led to a median increase in daily UOP to 743 (IQR 420–900) ml/d ($P = 0.005$) in the norepinephrine-only group and to 850 (IQR: 300–1465) ml/d ($P = 0.008$) in the norepinephrine plus furosemide group. Subsequently, in the norepinephrine-only group, no significant further increase in UOP was observed in the late period compared with the early period when norepinephrine alone was continued (Figure 2). However, in the norepinephrine plus furosemide group, addition of furosemide to norepinephrine induced a subsequent significant increase in

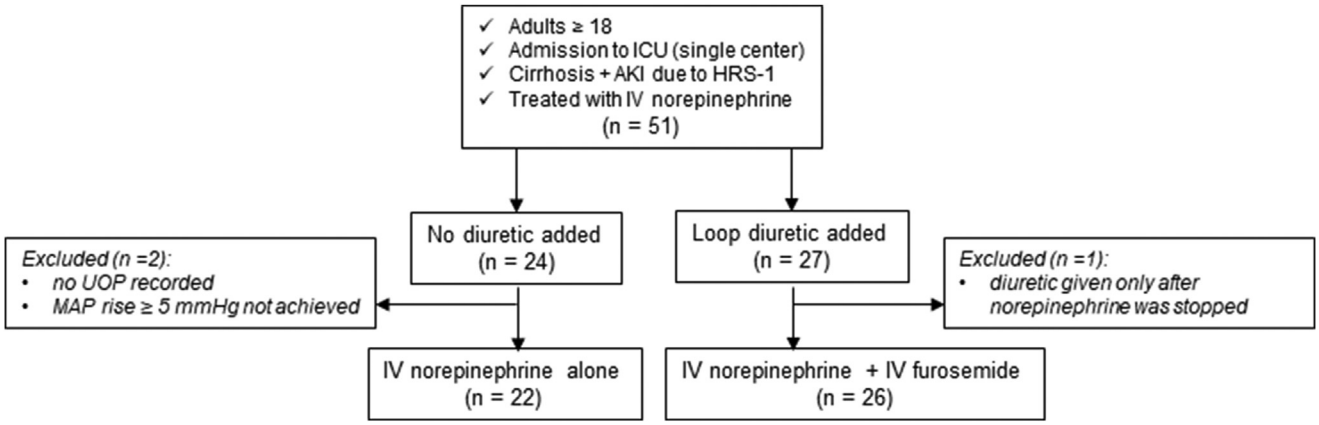

Figure 1. Study design and patient identification and categorization. AKI, acute kidney injury; HRS-1, hepatorenal syndrome type 1; ICU, intensive care unit; MAP, mean arterial pressure; UOP, urine output.

median UOP to 2073 (IQR: 1400–3400) ml/d ($P < 0.0001$) (Figure 2). In 6 cases, there was no norepinephrine-only period since furosemide was initiated at the same time that norepinephrine infusion was initiated; thus, all 3 data time points were available for only 20 of the 26 patients (Figure 2). When the analyses were restricted to those with data in all 3 treatment periods, the observation was similar (Figure 2d) in that, the UOP progressively increased in the norepinephrine plus furosemide group from 250 (IQR: 175–520) ml/d during prenorepinephrine period (first), to 875 (IQR: 275–1500) ml/d during the norepinephrine alone period (second), to 2500 (IQR: 1400–3400) ml/d during the norepinephrine plus furosemide period (third). Thus, within those with data in all 3 treatment periods, addition of furosemide to norepinephrine resulted in a median gain in UOP of 1400 (IQR: 450–2570) ml/d compared with norepinephrine alone period and a median gain of 2410 (IQR: 900–3265) ml/d compared to the prenorepinephrine period.

Table 1. Baseline characteristics of the study cohort of patients with cirrhosis and HRS-1 treated in the ICU with i.v. norepinephrine

Parameter	Norepinephrine	Norepinephrine + Furosemide
Number of patients	22	26
Age (yrs)	53 (43–65)	51 (40–63)
Gender (male/female)	12 (55%)/10 (45%)	16 (62%)/10 (38%)
Race (White/Black/Hispanic/Asian)	18 (82%)/2 (9%)/2 (9%)/0	24 (92%)/1 (4%)/0/1 (4%)
Etiology of ESLD		
Alcohol-related/cryptogenic/NASH/Other	12 (55%)/1 (5%)/4 (18%)/5[a] (23%)	18 (69%)/4 (15%)/2 (8%)/2[b] (8%)
MELD score	33 (29–39)	32 (28–36)
Laboratory values		
Serum creatinine (mg/dl)	3.9 (2.8–4.9)	4.0 (2.7–5.0)
Serum sodium (mEq/l)	131 (129–134)	132 (128–136)
Serum albumin (g/dl)	3.2 (2.0–3.3)	2.7 (2.3–3.3)
Total bilirubin (mg/dl)	10.3 (4.8–23.5)	7.5 (3.5–10.1)
Platelet count (x10^3/mm^3)	68 (55–113)	72 (57–119)
INR	1.9 (1.4–2.2)	1.8 (1.4–2.1)
AKI stage		
2	4 (18%)	5 (19%)
3	18 (82%)	21 (81%)
MAP (mm Hg)	72 (67–74)	71 (68–73)
Urine output (ml/d)	328 (200–500)	357 (200–450)
Prior midodrine/octreotide, *n* (%)	20 (91%)	23 (88%)
Prior albumin therapy, *n* (%)	18 (82%)	20 (77%)

AKI, acute kidney injury; ESLD, end-stage liver disease; INR, international normalized ratio; MAP, mean arterial pressure; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis.
[a]3 cases of hepatitis C virus and 2 cases of hepatitis B virus.
[b]1 case of hepatitis C virus and 1 case of primary biliary cirrhosis;
Data are presented as median (interquartile range).

Kidney Function

To determine whether furosemide-induced diuresis is associated with a detrimental effect in renal recovery, we assessed the sCr slope among those treated with the combination of norepinephrine and furosemide. Before administration of norepinephrine, the median daily slope in sCr change was +0.4 (IQR: +0.25 to +0.67) mg/dl/d. This slope of sCr trajectory was improved with the use of norepinephrine alone to a median daily change in sCr of +0.05 (IQR: +0.35 to −0.33) mg/dl/d ($P = 0.009$). When furosemide was added to norepinephrine, the favorable trajectory of change in kidney function was maintained with a median daily change in sCr of −0.16 (IQR +0.05 to −0.35) mg/dl/d ($P = 0.23$) during this treatment period (Figure 3). Nineteen patients (73%) treated with the combination of norepinephrine and furosemide either maintained or improved the sCr trajectory consistent with kidney recovery and not needing RRT. By the end of therapy, 12 (46%) achieved a >30% improvement in kidney function and 6 (23%) had complete HRS-1 reversal to a sCr ≤1.5 mg/dl. By day 14, 7 (27%) required RRT. There was no significant difference in the change in slope of sCr trajectory between the norepinephrine-only and the norepinephrine plus furosemide groups (Figure 3).

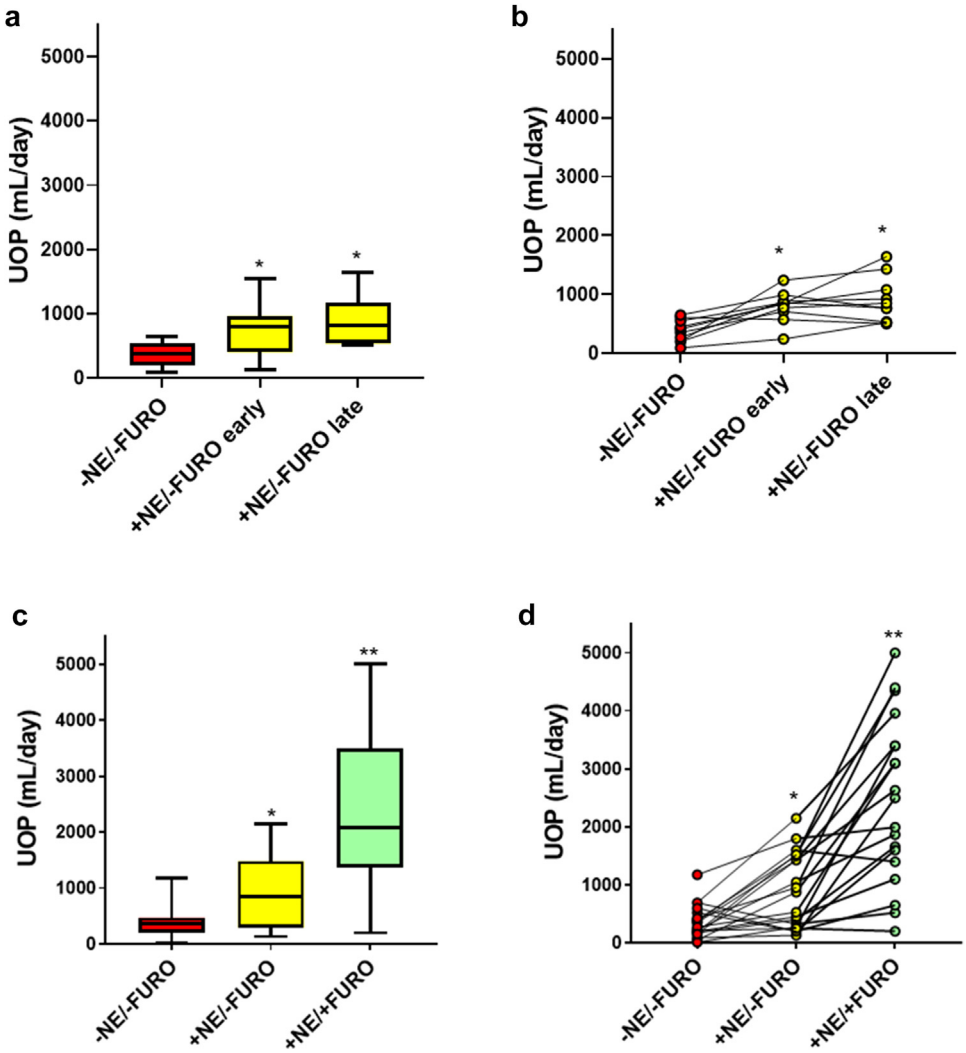

Figure 2. Change in urine output (UOP) between baseline (red) and the subsequent treatment periods with norepinephrine (NE) alone (yellow) and with the combination of NE and furosemide (FURO) (green). Panels a and b: control group (norepinephrine alone), panels c and d: norepinephrine plus furosemide group. Data are presented as medians per treatment period for each cohort (panels a [$n = 22$] and c [$n = 26$]) as well as in individual values only restricted to patients with all 3 data points (panels b [$n = 12$] and d [$n = 20$]). *$P < 0.001$, **$P < 0.0001$.

Relationship of UOP with MAP and PoPHTN in Patients Treated With Furosemide

The volume of diuresis generated by the combination of norepinephrine and furosemide, significantly correlated with the magnitude of the norepinephrine-mediated increase in MAP ($r = 0.67$, $P = 0.002$) (Figure 4). Twenty-five of the 26 patients (96%) underwent echocardiography. PASP was estimated in 24 patients (92%). Echo-based diagnosis of PoPHTN was made in 6 patients (25%). PoPHTN was confirmed by right heart catheterization in 5 patients (21%). Four patients (15%) had reduced right ventricular systolic function, 2 patients (8%) were categorized as having cirrhotic cardiomyopathy: 1 had reduced left ventricular ejection fraction and 1 had left ventricular diastolic dysfunction. The correlation coefficient between the magnitude of furosemide-enhanced diuresis and norepinephrine-mediated MAP increase was numerically stronger among those with PoPHTN ($n = 6$, median PASP = 49, $r = 0.79$, $P = 0.058$) compared to those without PoPHTN ($n = 18$, median PASP = 29, $r = 0.62$, $P = 0.006$) (Figure 4). Furthermore, echo-based central venous pressure (CVP) was reported in 18 patients (75%). PoPHTN with concomitant estimated CVP of 8 to 15 mm Hg ($n = 3$) (congestion) was associated with greater diuretic response to MAP increase compared with the absence of PoPHTN and a CVP of 3 mm Hg ($n = 8$) (no congestion), with a median of 238.4 versus 127.1 ml of UOP per mm Hg of MAP increase, respectively, ($P = 0.0002$) Seven patients were deemed equivocal regarding congestion because either PoPHTN was associated with a CVP of 3 mm Hg or absence of PoPHTN was associated with a CVP of 8 or 15 mm Hg (Figure 4). Radiological evidence of overt

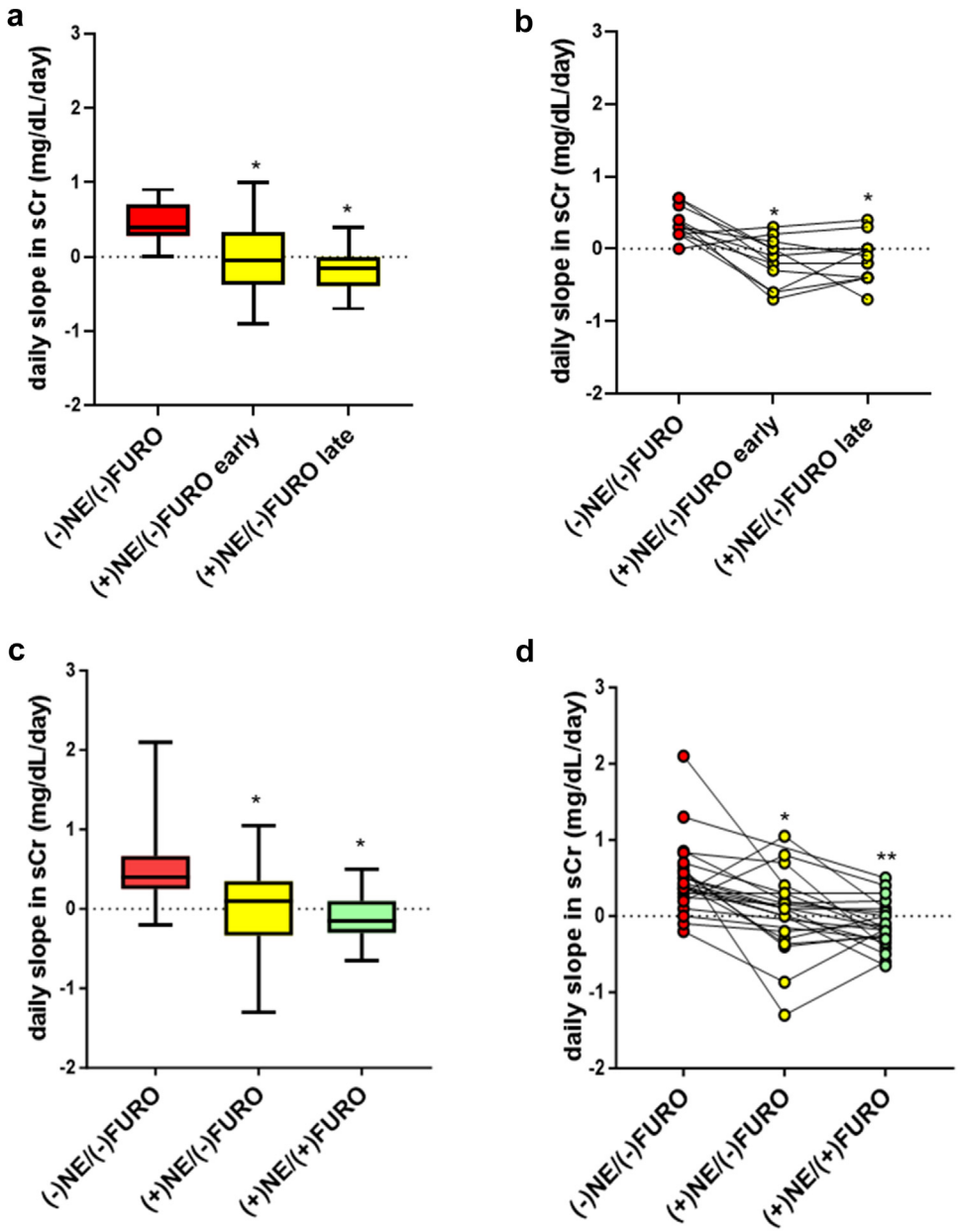

Figure 3. Change in daily serum creatinine slope between baseline (red) and the subsequent treatment periods with norepinephrine (NE) alone (yellow) and with the combination of NE and furosemide (FURO) (green). Panels a and b: control group (norepinephrine alone), panels c and d: norepinephrine plus furosemide group. Data are presented as medians per treatment period for each cohort (panels a [$n = 22$] and c [$n = 26$]) as well as in individual values only restricted to patients with all 3 data points (panels b [$n = 12$] and d [$n = 20$]). *$P < 0.001$, **$P < 0.0001$.

pulmonary edema prior to initiation of furosemide was present in 3 cases, and it improved in 2 of those cases after the addition of furosemide.

DISCUSSION

Our findings demonstrate that in patients with HRS-1 or HRS-AKI effectively treated with a MAP-increase targeted i.v. norepinephrine infusion, addition of i.v. loop diuretics results in increase in diuresis without compromising the clinical response to norepinephrine. Thus, a diuretic-induced increase in UOP was not associated with deterioration of kidney function, suggesting that utilization of diuretics is a safe and likely beneficial intervention in vasoconstrictor-treated HRS-1.

Guidelines for the diagnosis and management of HRS-1 or HRS-AKI dictate that before HRS-1 can be considered as a potential etiology of AKI, prerenal azotemia must be ruled out. To do so, when patients with cirrhosis present with AKI, it is recommended to first discontinue all diuretics, administer i.v. albumin, if indicated, and assess clinical response. For patients unresponsive to this initial intervention of diuretic withdrawal and volume expansion, a diagnosis of HRS-1 or HRS-AKI can be entertained, provided that the

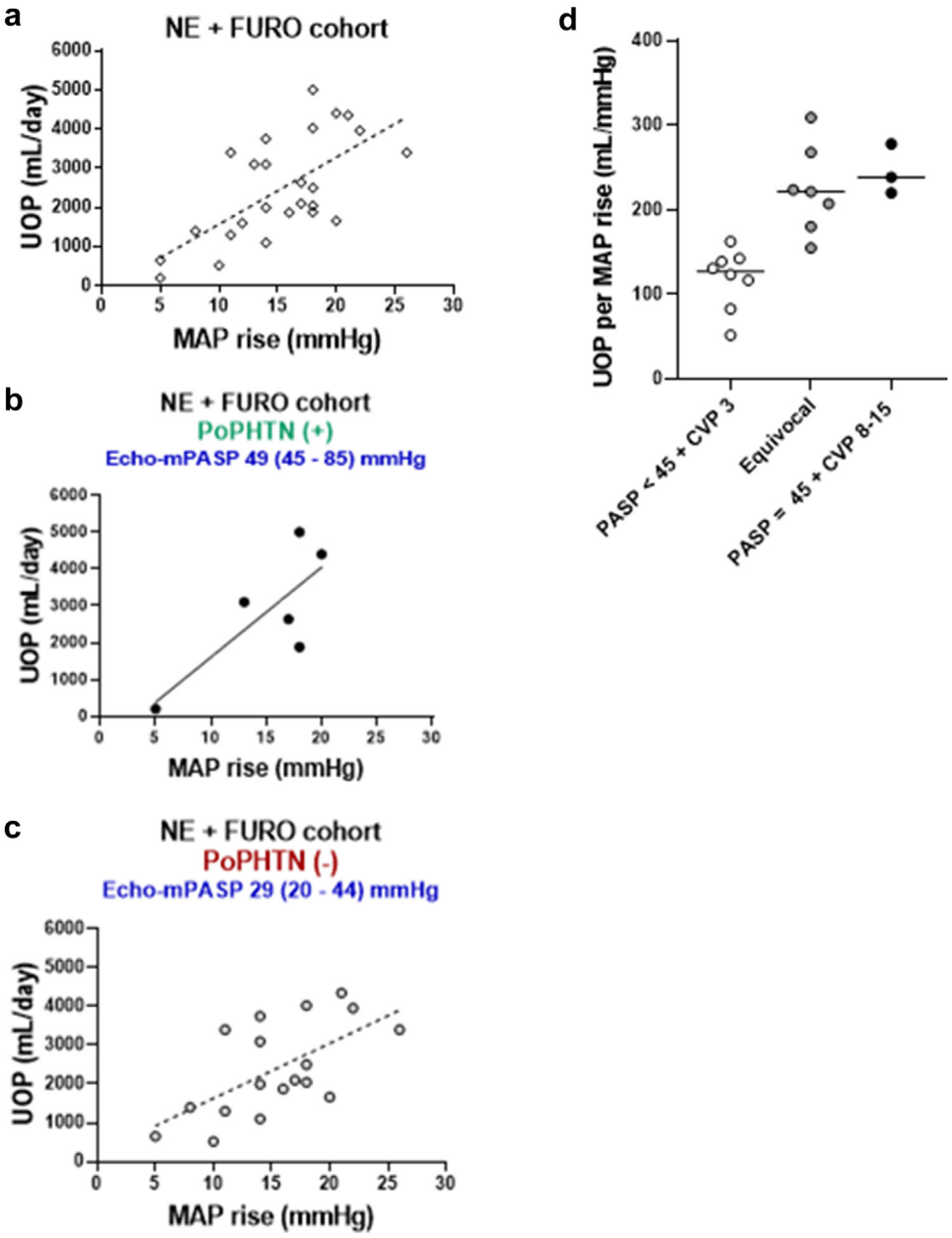

Figure 4. Correlation between achieved increase in mean arterial pressure (MAP) and achieved volume of urine output (UOP) in patients with HRS-1 treated with the combination of norepinephrine (NE) and furosemide (FURO). Data presented for (a) the overall NE + FURO cohort, and the subgroups of patients with (b) or without (c) portopulmonary hypertension (PoPHTN). Echo-mPASP, echocardiography-based mean pulmonary artery systolic pressure. Panel d shows the UOP (ml) per mm Hg of MAP increase among those with suspected congestion versus those without congestion. Cases with equivocal status are presented separately. CVP, central venous pressure.

remainder of the diagnostic criteria are met. Once a diagnosis of HRS-1 or HRS-AKI is made, the standard of care is to consider initiation of a vasoconstrictor, either norepinephrine or terlipressin.[13] When a vasoconstrictor is started, it is also recommended to consider concomitant administration of i.v. albumin. The rationale for the addition of albumin to a vasoconstrictor is supported by a study that reported greater efficacy of the combination of terlipressin and albumin compared to terlipressin alone.[14] However, the study was not randomized, it combined patients with HRS-1 and HRS-2 (HRS-CKD), and only included 16 patients with HRS-1. Furthermore, the subjects randomized to the terlipressin alone arm did not achieve a significant increase in MAP, whereas those who received terlipressin plus albumin achieved a 9 mm Hg increase in MAP. Therefore, in HRS-1, superiority of the combination of albumin and a vasoconstrictor over a vasoconstrictor alone has not been demonstrated in the context of effectively increased MAP by the vasoconstrictor alone.

Although discontinuation of diuretics is a therapeutic measure recommended specifically for the initial phase prior to establishing a diagnosis of HRS-1, concerns about potentially harmful effects of diuretics are

commonly carried over well into the subsequent phase of management, when a diagnosis of HRS-1 is made. As a result, clinicians are often reluctant to introduce diuretics when a patient is actively treated for HRS-1 with a vasoconstrictor. Rather, albumin is commonly used concomitantly as a volume expander. However, recent observations have revealed that overzealous administration of albumin could be associated with a risk for pulmonary edema and respiratory failure. In the ATTIRE trial, individuals randomized to normalization of serum albumin with treatment with i.v. albumin experienced a 3-fold increase in pulmonary edema events.[15] Similarly, in the CONFIRM trial, the combination of terlipressin and albumin was associated with greater risk for respiratory failure compared with the combination of placebo and albumin.[16] Although an inherent effect of terlipressin may have driven such adverse event, aggressive use of albumin before trial enrollment might have also increased the risk.[17] In our study, the observation of preserved trajectory of improvement in kidney function in patients treated with the norepinephrine plus furosemide combination demonstrates that addition of diuretics to vasoconstrictor therapy in HRS-1 is not only not harmful, but likely beneficial. Notably, initiation of norepinephrine alone resulted in a significant increase in UOP compared with that of the prevasoconstrictor phase. While significant, the increase in volume of urine with norepinephrine alone was not robust. Stimulation of α-adrenergic receptors by norepinephrine upregulates the sodium-hydrogen exchanger in the proximal convoluted tubule and promotes tubular reabsorption of sodium.[18] Thus, the pressor natriuretic effect of norepinephrine may be limited by simultaneous stimulation of proximal tubular reabsorption. Consequently, diuretics are necessary to properly enhance diuresis in patients with HRS-1 who are hypervolemic, as observed in our study.

During the treatment period in which norepinephrine infusion was given without diuretics, it was noted that the sCr trajectory changed from a daily increase to a phase of stabilization of kidney function. It has been previously shown that when norepinephrine effectively increases the MAP, improvement in kidney function may ensue in about 43% of patients.[6] Such benefit is observed after 3 to 5 days of therapy. In this ancillary study, the average treatment period in which norepinephrine was administered alone only lasted 2 days, which may explain why the average sCr trajectory did not fully revert to improvement during this period. When furosemide was added to norepinephrine, not only was the sCr trajectory maintained but it also revealed a trend for improvement (Figure 2), suggesting that renal congestion often complicates HRS-1.

PoPHTN is a complication of cirrhosis that can lead to venous congestion. It affects 5% to 20% of patients with advanced cirrhosis.[19–21] In our HRS-1 cohort, one-quarter of the patients met our echocardiographic definition of PoPHTN and most of them were confirmed to have PoPHTN by right heart catheterization. This enrichment of PoPHTN within a cohort of patients with HRS-1 is a novel observation and it is in line with proposed pathophysiological connection between pulmonary and renal vascular maladaptation.[22] Furthermore, a state of hypervolemia resulting from AKI is expected to aggravate PoPHTN-induced venous congestion. Not surprisingly, the relationship between MAP increase and response to diuresis was numerically stronger among those with PoPHTN. Thus, presence of PoPHTN may help in guiding decongestive strategies in the management of AKI due to HRS-1. In addition, in contrast to other reports,[23] we found a low incidence of cirrhotic cardiomyopathy in our cohort. However, our findings are in agreement with a recent study using cardiac magnetic resonance imaging that revealed that the cardiac output in patients with HRS-1 is markedly elevated and consistent with high-output heart failure.[24]

Our study has limitations. It is a retrospective observational study of prospectively collected data with a small sample size and a contemporaneous nonrandomized control group. Therefore, our results should be seen primarily as hypothesis-generating. The strengths of the study include the granularity of the data, the homogeneity of MAP-targeted treatment with i.v. norepinephrine, the clear signal favoring the safety of diuretics, and the novelty of the observation. It also supports growing evidence that challenges the safety of aggressive use of i.v. albumin in AKI in cirrhosis.

In conclusion, this report constitutes evidence against the paradigm that views the use of loop diuretics in the context of HRS-1 as potentially deleterious. In patients with HRS-1 who are adequately treated with norepinephrine, and likely other vasoconstrictors, and achieved an optimal MAP increment, addition of high-dose i.v. loop diuretic enhances diuresis without negatively affecting recovery of kidney function. Not only the overzealous use of i.v. albumin should be revisited, but loop diuretics should be safely introduced in vasoconstrictor-treated patients who exhibit signs of hypervolemia and are at risk of pulmonary insufficiency.

DISCLOSURE

JCQV has served as advisor and consultant for Mallinckrodt Pharmaceuticals, maker of terlipressin. He has also provided consultative work for Bayer

Pharmaceuticals, Travere Therapeutics, and Calliditas. All the other authors declared no conflicting interests.

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REFERENCES

1. Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *J Hepatol*. 2015;62:968–974. https://doi.org/10.1016/j.jhep.2014.12.029
2. Baraldi O, Valentini C, Donati G, et al. Hepatorenal syndrome: update on diagnosis and treatment. *World J Nephrol*. 2015;4:511–520. https://doi.org/10.5527/wjn.v4.i5.511
3. Velez JCQ, Therapondos G, Juncos LA. Reappraising the spectrum of AKI and hepatorenal syndrome in patients with cirrhosis. *Nat Rev Nephrol*. 2020;16:137–155. https://doi.org/10.1038/s41581-019-0218-4
4. Velez JC, Nietert PJ. Therapeutic response to vasoconstrictors in hepatorenal syndrome parallels increase in mean arterial pressure: a pooled analysis of clinical trials. *Am J Kidney Dis*. 2011;58:928–938. https://doi.org/10.1053/j.ajkd.2011.07.017
5. Velez JC, Kadian M, Taburyanskaya M, et al. Hepatorenal acute kidney injury and the importance of raising mean arterial pressure. *Nephron*. 2015;131:191–201. https://doi.org/10.1159/000441151
6. Velez JCQ, Karakala N, Tayebi K, et al. Responsiveness to vasoconstrictor therapy in hepatorenal syndrome type 1. *Kidney360*. 2023;4:e448–e456. https://doi.org/10.34067/KID.0000000000000068
7. Pelayo J, Lo KB, Sultan S, et al. Invasive hemodynamic parameters in patients with hepatorenal syndrome. *Int J Cardiol Heart Vasc*. 2022;42:101094. https://doi.org/10.1016/j.ijcha.2022.101094
8. Velez JCQ, Petkovich B, Karakala N, Huggins JT. Point-of-care echocardiography unveils misclassification of acute kidney injury as hepatorenal syndrome. *Am J Nephrol*. 2019;50:204–211. https://doi.org/10.1159/000501299
9. Wong F, Angeli P. New diagnostic criteria and management of acute kidney injury. *J Hepatol*. 2017;66:860–861. https://doi.org/10.1016/j.jhep.2016.10.024
10. Nadim MK, Kellum JA, Forni L, et al. Acute kidney injury in patients with cirrhosis: Acute Disease Quality Initiative (ADQI) and International Club of Ascites (ICA) joint multidisciplinary consensus meeting. *J Hepatol*. 2024;81:163–183. https://doi.org/10.1016/j.jhep.2024.03.031
11. Jasso-Baltazar EA, Pena-Arellano GA, Aguirre-Valadez J, et al. Portopulmonary hypertension: an updated review. *Transplant Direct*. 2023;9:e1517. https://doi.org/10.1097/TXD.0000000000001517
12. Liu H, Naser JA, Lin G, Lee SS. Cardiomyopathy in cirrhosis: from pathophysiology to clinical care. *JHEP Rep*. 2024;6:100911. https://doi.org/10.1016/j.jhepr.2023.100911
13. Kanduri SR, Velez JCQ. Kidney dysfunction in the setting of liver failure: core curriculum 2024. *Am J Kidney Dis*. 2024;83:386–401. https://doi.org/10.1053/j.ajkd.2023.08.013
14. Ortega R, Gines P, Uriz J, et al. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomized study. *Hepatology*. 2002;36:941–948. https://doi.org/10.1053/jhep.2002.35819
15. China L, Freemantle N, Forrest E, et al. A randomized trial of albumin infusions in hospitalized patients with cirrhosis. *N Engl J Med*. 2021;384:808–817. https://doi.org/10.1056/NEJMoa2022166
16. Wong F, Pappas SC, Curry MP, et al. Terlipressin plus albumin for the treatment of Type 1 hepatorenal syndrome. *N Engl J Med*. 2021;384:818–828. https://doi.org/10.1056/NEJMoa2008290
17. Belcher JM, Parada XV, Simonetto DA, et al. Terlipressin and the treatment of hepatorenal syndrome: how the CONFIRM trial moves the story forward. *Am J Kidney Dis*. 2022;79:737–745. https://doi.org/10.1053/j.ajkd.2021.08.016
18. Liu F, Nesbitt T, Drezner MK, Friedman PA, Gesek FA. Proximal nephron Na+/H+ exchange is regulated by alpha 1A- and alpha 1B-adrenergic receptor subtypes. *Mol Pharmacol*. 1997;52:1010–1018. https://doi.org/10.1124/mol.52.6.1010
19. Li J, Zhuang Q, Zhang X, et al. Prevalence and prognosis of portopulmonary hypertension in 223 liver transplant recipients. *Can Respir J*. 2018;2018:9629570. https://doi.org/10.1155/2018/9629570
20. Krowka MJ, Swanson KL, Frantz RP, McGoon MD, Wiesner RH. Portopulmonary hypertension: results from a 10-year screening algorithm. *Hepatology*. 2006;44:1502–1510. https://doi.org/10.1002/hep.21431
21. Gurghean AV, Tudor IA. Pulmonary hypertension in patients with hepatic cirrhosis and portal hypertension. An echographic study. *Clujul Med*. 2017;90:161–165. https://doi.org/10.15386/cjmed-705
22. Zardi EM, Zardi DM, Giorgi C, Chin D, Dobrina A. Portopulmonary hypertension and hepatorenal syndrome. Two faces of the same coin. *Eur J Intern Med*. 2017;43:22–27. https://doi.org/10.1016/j.ejim.2017.05.028
23. Anikhindi SA, Ranjan P, Kumar M, Mohan R. A prospective study of prevalence and predictors of cirrhotic cardiomyopathy and its role in development of hepatorenal syndrome. *J Clin Exp Hepatol*. 2022;12:853–860. https://doi.org/10.1016/j.jceh.2021.11.005
24. Danielsen KV, Wiese S, Busk T, et al. Cardiovascular mapping in cirrhosis from the compensated stage to hepatorenal syndrome: a magnetic resonance study. *Am J Gastroenterol*. 2022;117:1269–1278. https://doi.org/10.14309/ajg.0000000000001847