THE EFFECTS OF VASOPRESSIN ON ACUTE KIDNEY INJURY IN SEPTIC SHOCK

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ABSTRACT

Objective: To compare the effects of vasopressin versus norepinephrine infusion on the outcome of kidney injury in septic shock.

Design and Setting: Post-hoc analysis of the multi-centre double-blind randomized controlled trial of vasopressin versus norepinephrine in adult patients who had septic shock (VASST).

Patients and Intervention: 778 patients were randomized to receive a blinded infusion of either low-dose vasopressin (0.01-0.03U/min) or norepinephrine infusion (5-15μg/min) in addition to open-label vasopressors and were included in the outcome analysis. All vasopressors were titrated and weaned to maintain a target blood pressure.

Measurement and results: RIFLE criteria for acute kidney injury were used to compare the effects of vasopressin versus norepinephrine. In view of multiple simultaneous comparisons a p-value of 0.01 was considered statistically significant. Kidney injury was present in 464 patients (59.6%) at study entry. In patients in the RIFLE "Risk" category (n=106) vasopressin as compared with norepinephrine was associated with a trend to a lower rate of progression to renal "Failure" or "Loss" categories (20.8% v 39.6% respectively, p=0.03), and a lower rate of use of renal replacement therapy (17.0% v 37.7%, p=0.02). Mortality rates in the "Risk" category patients treated with vasopressin compared to norepinephrine were 30.8% v 54.7%, p=0.01, but this did not reach significance in a multiple logistic regression analysis (OR=0.33, 99%CI 0.10-1.09, p=0.02). The interaction of treatment group and RIFLE category was significant in predicting mortality.

Conclusions: Vasopressin may reduce progression to renal failure and mortality in patients at risk of kidney injury who have septic shock.

Key words: Sepsis; kidney failure; vasopressins; shock, septic

INTRODUCTION

Acute kidney injury is a common complication of sepsis that is associated with high mortality [1]. The incidence ranges from 15-50% [2-4], and is associated with a mortality rate of 30-75% [2-5]. This variation in reported incidence and outcome is partly due to heterogeneous patients and different definitions of kidney injury used in these studies. Recently, the acute dialysis quality initiative (ADQI) group recommended a consensus definition for kidney injury called the RIFLE criteria [6]. Patients are defined as being at "**R**isk" of kidney injury, having renal "**I**njury" or "**F**ailure", having "**L**oss" of renal function or having "**E**nd-stage" renal failure based on decreased glomerular filtration rate (or increased serum creatinine) and urine output.

Despite the high prevalence of acute kidney injury during critical illness in general, and severe sepsis specifically, success has been limited in improving the outcome of this complication [7]. The mainstays of prevention and treatment include avoidance of nephrotoxins and ensuring adequate renal perfusion. In addition to its potent vasoconstrictor effects, vasopressin may also have specific beneficial effects on renal function secondary to its binding to a family of vasopressin receptors [8]. In several small studies of vasodilatory shock, vasopressin increased glomerular filtration rate, urine output and creatinine clearance [9-12]. However, to date no large studies have assessed the effect of vasopressin, as compared with norepinephrine, on the outcome of acute kidney injury.

Therefore, we studied patients who had septic shock recruited to the randomized controlled trial of vasopressin versus norepinephrine (VASST: Vasopressin and Septic Shock Trial) to compare the effects of vasopressin versus norepinephrine on

the outcome of acute kidney injury using the RIFLE criteria. Some of this data has been presented in the form of an abstract at the American Thoracic Society International Conference, San Francisco, in 2007 [13].

MATERIAL AND METHODS

Patients

All patients (n = 779) randomized and infused with study drug from the VASST study were included. The study protocol has been previously described [14]. In summary, this was a multi-center randomized double-blind controlled trial of vasopressin versus norepinephrine in addition to standard vasopressors for the treatment of septic shock. Patients were greater than 16 years of age and had septic shock, defined by the presence of two or more of the systemic inflammatory response syndrome (SIRS) criteria [15], proven or suspected infection, new dysfunction of at least one organ, and hypotension despite adequate fluid resuscitation requiring vasopressor support of at least 5 μg/min of norepinephrine (or equivalent) for six hours. Important clinical exclusion criteria were unstable coronary syndromes, acute mesenteric ischemia, severe chronic heart disease (New York Heart Association class III and IV) and vasospastic diathesis [14]. Patients were randomized to receive a blinded infusion of study drug, either vasopressin (0.01 - 0.03 U/min) or norepinephrine (5 – 15 μg/min). The study drug and all other vasopressors were titrated and weaned according to protocols. The initial target mean arterial pressure was 65 – 75 mmHg. Other treatment decisions (including the need for renal replacement therapy) were at the local physician's discretion.

All patients were classified into one of the RIFLE categories at study baseline (see Table 1 for RIFLE classification definitions) based on the rise in serum creatinine measured at baseline (i.e., just prior to study drug infusion) compared to the patient's "normal" creatinine. For patients with known chronic renal failure their "normal" creatinine was taken as the lowest creatinine measured in the previous 24 hours. For

patients without chronic renal failure the “normal” creatinine was taken as the lower of: the lowest creatinine measured in the previous 24 hours or the estimated creatinine calculated using the MDRD (Modification of Diet in Renal Disease) equation as in the original RIFLE description [6]. Patients without end-stage renal failure who were receiving renal replacement therapy at study baseline were assigned to the “Failure” category as previously described [16]. Patients with known end-stage kidney disease at study inclusion were classified as class “E” within RIFLE and were excluded from analyses of change in renal function. Details of fluid balance and diuretic therapy were available for the first four days of the study only. Data were not available to use the urine output criteria for the RIFLE definition.

Statistics

Outcome measures were 28-day mortality (the primary endpoint of the main trial), rate of progression to renal “Failure” / “Loss”, the use of renal replacement therapy and serum creatinine over time up to day 28. Survival status at day 90 was also recorded. Comparison of outcome between the two treatment groups, vasopressin and norepinephrine patients, was performed using the chi-squared test. A multiple logistic regression model including age, sex, APACHE II score (measured in the 24 hours prior to study inclusion), medical / surgical admission, dose of norepinephrine at baseline and treatment group was used to adjust for possible imbalances at baseline between the two treatment groups within the patient subgroups in each RIFLE category. As the analyses were repeated in each of the five RIFLE classes at baseline a Bonferroni correction for multiple testing was applied and a p-value of 0.01 was considered statistically significant.

A linear mixed effects model was used to analyze longitudinal data (i.e., creatinine over time). Serum creatinine values were not normally distributed and so the values

were log transformed for analysis. This analysis was also repeated adjusting for the dose of norepinephrine over time. A differential response to vasopressin compared to norepinephrine according to RIFLE category was tested using the interaction terms in the regression analyses. Other continuous variables are presented as mean (± standard deviation) or median (interquartile range) and tested using the T-test, ANOVA or Mann Whitney U test, as appropriate.

RESULTS

A total of 779 patients were randomized and infused with study drug, 397 with vasopressin, and 382 with norepinephrine. One patient in the vasopressin group was lost to follow up at day 28 and therefore only 778 patients were included in the outcome analysis. All patients had septic shock and at baseline required a mean norepinephrine dose of 20.7 ± 20.2 μg/min to maintain a mean arterial pressure of 72.7 ± 9.5 mmHg. The average baseline APACHE II score was 27.1 ± 7.3 and patients had 3.4 ± 1.1 organ failures, using the Brussels scoring system [17]. Full details of patient characteristics have previously been published [14].

We compared clinical outcomes between vasopressin-treated patients and norepinephrine-treated patients within each RIFLE category (Table 2). Within the "Risk" category, there was a trend for less patients to progress to renal "Failure" or "Loss" over the 28-day study period in the vasopressin-treated group than the norepinephrine group (11 [20.8%] v 21 [39.6%] respectively, p = 0.03). Within the "Risk" category, the use of renal replacement therapy at any time during the study period was less than half in the vasopressin group compared to the norepinephrine group (9 [17.0%] v 20 [37.7%], p = 0.02). There was no significant difference in progression of kidney injury between treatment groups in any other RIFLE category.

Serum creatinine decreased more in the "Risk" category of patients who were treated with vasopressin as compared with norepinephrine (p = 0.02) despite similar baseline creatinine values (Figure 2). This difference remained the same after adjusting for dose of norepinephrine (p = 0.02). There was no difference in serum creatinine over

time between vasopressin and norepinephrine treated patients in any other RIFLE category (Figure 2). There was no significant difference in fluid input, fluid balance or diuretic use over the first four days between vasopressin and norepinephrine treated patients (data not shown).

We also compared 28-day mortality rates between vasopressin-treated patients and norepinephrine-treated patients within each RIFLE category (Table 2). Of those patients who were in the "Risk" category, mortality in the vasopressin-treated patients compared to norepinephrine-treated patients was 16/52 (30.8%) versus 29/53 (54.7%), $p = 0.01$. There were no significant differences in mortality between treatment groups in any other RIFLE category. The interaction of treatment group and RIFLE category ("Risk" versus "non-risk") for 28-day mortality rate was statistically significant ($p = 0.03$). However, after adjusting for baseline characteristics (Table 3) using a logistic regression model, the odds ratio for mortality in patients randomized to receive vasopressin in the Risk category was not statistically significant (OR = 0.33, 99% confidence intervals 0.10 – 1.09, $p = 0.02$). The Kaplan-Meier survival curves demonstrate that the variation in mortality rates between vasopressin-treated and norepinephrine-treated patients began at about day 2 and then persisted throughout the full 90-day follow-up period ($p = 0.007$, log rank statistic) (Figure 1).

In the "Risk" category, vasopressin was associated with a significant decrease in norepinephrine infusion rate from a median of 20 (IQR 8 – 27) μg/min to 9 (IQR 4 – 23.5) μg/min and the total norepinephrine infusion rate remained lower in the vasopressin-treated group throughout the study (Figure 3, Panel A). This vasopressin infusion rate maintained mean arterial pressure at values similar to the mean arterial pressure in the norepinephrine-treated group (Figure 3, Panel B).

Kidney injury (as defined by "Risk" category or worse) was present in 464 (59.6%) of patients at baseline (Table 2) and was associated with significantly higher 28-day mortality than patients with no kidney injury (44.3% v 27.0%, $p < 0.001$). A further 117 patients who had "normal" renal function (non-AKI) at baseline had a deterioration in renal function so that in total, 581 (74.6%) patients had kidney injury ("Risk" category or worse) at some time during the 28-day study period.

Excluding the 49 patients who had end-stage renal failure prior to inclusion, 532 of 730 (72.9%) had acute kidney injury during the 28-day study period. Of these 730 patients, 247 (33.8%) required renal replacement therapy. One hundred and fifty nine patients underwent continuous renal replacement therapy, 31 underwent intermittent hemodialysis and 57 underwent both types of replacement therapy. Nineteen (4.1%) of the 466 survivors without pre-existing end-stage renal failure were still dependent on renal replacement therapy at day 28. Of the 49 patients who had end-stage renal failure at baseline, 19 were managed with continuous renal replacement therapy, 8 with intermittent hemodialysis and 22 with both, during the study period.

DISCUSSION

Comparison of vasopressin v norepinephrine

In this large multi-center study of patients who had septic shock, we found that acute kidney injury was very common, found in 73% of patients, and was associated with a high mortality rate. In patients who were at risk of kidney injury who had septic shock, we found that vasopressin compared to norepinephrine was associated with a trend to reduced creatinine over time, reduced progression to renal failure / loss and reduced mortality. As a result, fewer patients treated with vasopressin compared to norepinephrine required renal replacement therapy.

These results are consistent with previous small studies showing that vasopressin compared to norepinephrine increased urine output and creatinine clearance [9-12]. The findings in the "Risk" category contrast to those patients who had already sustained more severe kidney injury (RIFLE categories "Injury" or "Failure") at the time of study drug infusion; there was no difference in renal function or mortality according to vasopressin or norepinephrine allocation. Similarly, there was no significant beneficial effect of vasopressin in patients who had no acute kidney injury at baseline.

The interaction between treatment group and RIFLE category on mortality was significant, suggesting that the response to vasopressin treatment in the "Risk" category was significantly different to the response of patients in the other categories of RIFLE. These findings raise the possibility that patients classified in the RIFLE "Risk" category could be targeted for future therapeutic trials.

Incidence and outcome of acute kidney injury

Numerous studies have evaluated the RIFLE criteria in various critically ill populations [3, 16, 18-26]. The incidence of acute kidney injury varied between 11% and 67% in studies of general ICU patients [16, 18, 20-22]. To our knowledge, the current study is the largest study using RIFLE criteria in patients who have septic shock.

The 73% incidence of acute kidney injury in this cohort is slightly higher than in previous studies. However, this is not surprising, as we studied only severely ill patients who had septic shock. Previous studies have shown that the severity of sepsis correlates with the incidence of kidney injury [4]. The incidence of acute kidney injury we report is substantially higher than the incidence in the most severely ill patients described by Rangel-Frausto *et al* [4], which may reflect between study differences due to case mix, or a true increased incidence of acute kidney injury in sepsis today compared with the past, as has been suggested by others [20]. The high incidence we observed may also reflect greater sensitivity of the RIFLE definitions compared to older definitions of renal failure. In RIFLE, a rise in serum creatinine of only 50% from baseline is defined as "Risk" [6]. In agreement with previous studies examining outcomes using the RIFLE criteria [27, 28], we found that mortality was markedly higher among patients who were in the "Risk" category compared to patients with non-AKI at enrollment (43% versus 27%, $p = 0.002$). Our study also suggests that patients in the RIFLE "Risk" category were indeed at increased risk of renal failure. Half of patients in the "Risk" category had deterioration in renal function. Interestingly, it was in the "Risk" subgroup of patients where a beneficial effect of vasopressin treatment was observed.

Study limitations

There are several limitations of this study. Although we used the consensus RIFLE definitions, like many other studies [19, 20] we were not able to asses the urine output criteria of the RIFLE definition; thus, the incidence of acute kidney injury using RIFLE may actually be higher than the 73% that we observed. Second, we did not examine the mechanisms of potential benefit of vasopressin in this study. Vasopressin has complex effects on renal function because of its global hemodynamic effects and because of its binding to the vasopressin family of receptors. The renal-specific effects of vasopressin include binding to AVPR1a receptors of glomerular efferent arterioles which causes glomerular efferent arteriolar vasoconstriction and thus increases glomerular filtration [29]. Furthermore vasopressin analogues have been shown to increase renal perfusion in decompensated liver cirrhosis [30] and are a standard of care in this condition. In contrast, norepinephrine binds to alpha-1 receptors of renal afferent arterioles and decreases glomerular perfusion pressure and filtration [31], although effects may vary between normal healthy states and sepsis [32]. Vasopressin-treated patients (Figure 3) had significantly lower norepinephrine infusion rates compared to the norepinephrine-treated patients. Mean arterial pressure was similar between the two treatment groups (Figure 3). Thus, differences between vasopressin and norepinephrine-treated patient outcomes may be due to beneficial effects of vasopressin or, alternatively, due to reduction in detrimental effects of norepinephrine.

Third, the findings of this post-hoc subgroup analysis should be interpreted cautiously [33] since they may represent a chance finding. Although we did correct for multiple comparisons some of the RIFLE categories are quite small and there were some imbalances in baseline characteristics. Adjusting for these baseline characteristics in a multiple logistic regression model resulted in the mortality rates within the “Risk”

category no longer reaching statistical significance. However, the RIFLE criteria have been previously defined by an independent expert group [6] and have been well described in a number of other studies of critically patients [27]. Furthermore, the trend to a lower mortality rate in the vasopressin-treated patients at “Risk” of acute kidney injury was also accompanied by an improvement in renal function. This may provide a biologically plausible explanation for the finding of improved outcome associated with vasopressin treatment. This result is also consistent with the primary subgroup analysis of the VASST study in which vasopressin treatment was associated with decreased mortality in patients who had less severe shock and not in patients who had more severe shock [14].

Taken together, these data raise the hypothesis that if there is any benefit of treatment using vasopressin in septic shock, it may occur before significant organ failure is established. This hypothesis will need further testing. Strategies to improve the outcome of established renal failure have so far not provided any convincing benefit [34].

CONCLUSION

In a post hoc analysis of this large randomized controlled multicenter study, we found that vasopressin was associated with a trend to improved renal function, lower mortality and less renal replacement therapy in patients at “Risk” of acute kidney injury, but not in those who had already sustained significant renal injury. These results will need further testing in another randomized trial before adoption into routine clinical practice.

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VASST CLINICAL CENTERS:

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Table 1. RIFLE criteria definitions used in this study [6]

	Serum creatinine change criteria
Risk	Increased serum creatinine x1.5
Injury	Increased serum creatinine x2
Failure	Increased serum creatinine x3 or Increased serum creatinine ≥44μmol/l if baseline ≥350μmol/l
Loss	Persistent acute renal failure = complete loss of renal function for > 4 weeks
End stage	End-Stage Kidney Disease (>3 months)

GFR = Glomerular filtration rate. Serum creatinine 88μmol/l = 1 mg/dl

Table 2. Baseline characteristics at time of study drug infusion, 28 day mortality rates and other outcomes according to RIFLE categories, and comparing the vasopressin and norepinephrine treatment groups according to RIFLE category.

	Non-AKI				Risk			
	Total	**NE**	**AVP**	**p-value[#]**	**Total**	**NE**	**AVP**	**p-value[#]**
Number	315 (40.4)	160	155		106 (13.6)	53	53	
Age	57.8 ± 16.6	59.8 ± 16.7	56.2 ± 16.1	0.06	61.2 ± 16.8	64.3 ± 16.8	58.1 ± 16.4	0.06
Sex – male	203 (64.4)	101 (63.1)	102 (65.8)	0.70	69 (65.1)	37 (69.8)	32 (60.4)	0.42
APACHE II	23.7 ± 6.4	24.5 ± 6.0	22.8 ± 6.7	0.007	27.0 ± 6.2	26.9 ± 6.3	27.0 ± 6.2	0.91
Recent Surgery	120 (41.7)	62 (38.8)	58 (37.4)	0.81	38 (38.0)	16 (30.2)	22 (41.5)	0.22
Ethnicity – Caucasian	266 (84.4)	134 (83.8)	132 (85.2)	0.73	92 (86.8)	47 (88.7)	45 (84.9)	0.57
Serum creatinine at enrollment (µmol/l)	101 ± 66	100 ± 64	102 ± 69	0.73	154 ± 34	156 ± 37	152 ± 30	0.55
Mean arterial pressure at baseline (mmHg)	74.3 ± 8.4	74.6 ± 8.4	74.1 ± 8.4	0.86	72.2 ± 9.8	72.9 ± 10.4	71.5 ± 9.2	0.49

More severe shock (NE >15µg/min)	131 (41.6)	72 (45.0)	59 (38.1)	0.26	66 (62.3)	33 (62.3)	33 (62.3)	1.0
Cardiac Index at baseline (l/min/m^2)**	4.1 ± 1.5	4.0 ± 1.4	4.3 ± 1.5	0.43	3.6 ± 1.3	3.6 ± 1.4	3.5 ± 1.3	0.79
Mechanically ventilated at inclusion	301 (95.6)	157 (98.1)	144 (92.9)	0.03	96 (90.6)	45 (84.9)	51 (96.2)	0.05
Comorbidities								
Ischemic heart disease	45 (14.3)	25 (15.6)	20 (12.9)	0.49	15 (14.2)	8 (15.1)	7 (13.2)	0.78
Congestive heart failure	20 (6.3)	13 (8.1)	7 (4.5)	0.19	7 (6.6)	4 (7.5)	3 (5.7)	0.70
Diabetes	55 (17.5)	32 (20.0)	23 (14.8)	0.22	20 (18.9)	11 (20.8)	9 (17.0)	0.62
COPD	65 (20.6)	38 (23.8)	27 (17.4)	0.16	14 (13.2)	8 (15.1)	6 (11.3)	0.57
28-day mortality	85 (27.0)	45 (28.1)	40 (25.8)	0.64	45 (42.9)*	29 (54.7)	16 (30.8)	0.01
Adjusted OR[##] (99% CI)			1.07 (0.52-2.22)	0.81			0.33 (0.10-1.09)	0.02
Need for RRT during 28-day study period	36 (11.4)	20 (12.5)	16 (10.3)	0.54	29 (27.4)	20 (37.7)	9 (17.0)	0.02
ICU length of stay (days)	18 (10-36)	18 (11-33.5)	17 (9-37)	0.73	14 (6–26)	14 (4-26)	14 (11-25)	0.60

	Injury				Failure			
	Total	**NE**	**AVP**	**p-value[#]**	**Total**	**NE**	**AVP**	**p-value[#]**
Number	130 (16.7)	62	68		179 (23.0)	82	97	
Age	64.0 ± 14.8	64.8 ± 13.6	63.4 ± 16.0	0.63	61.9 ± 16.4	62.4 ± 16.0	61.5 ± 16.7	0.74
Sex – male	75 (57.7)	32 (51.6)	43 (63.2)	0.25	99 (55.3)	43 (52.4)	56 (57.7)	0.58
APACHE II	28.0 ± 7.7	27.1 ± 6.4	29.2 ± 7.8	0.06	31.3 ± 6.5	31.7 ± 6.5	31.1 ± 6.5	0.53
Recent Surgery	49 (41.5)	20 (32.3)	29 (42.6)	0.22	62 (35.6)	25 (30.5)	37 (38.1)	0.28
Ethnicity – Caucasian	113 (86.9)	51 (82.3)	62 (91.2)	0.28	147 (82.1)	66 (80.5)	81 (83.5)	0.60
Serum creatinine at enrollment (µmol/l)	205 ± 39	203 ± 36	207 ± 42	0.53	321 ± 123	333 ± 135	310 ± 112	0.21
Mean arterial pressure at baseline (mmHg)	72.0 ± 8.9	72.9 ± 8.2	71.2 ± 9.4	0.28	71.6 ± 11.4	72.2 ± 12.7	71.0 ± 10.2	0.46

More severe shock (NE >15µg/min)	75 (57.7)	35 (56.5)	40 (58.8)	0.92	105 (58.7)	47 (57.3)	58 (59.8)	0.86
Cardiac Index at baseline (l/min/m^2)**	3.5 ± 1.0	3.9 ± 1.1	3.3 ± 0.9	0.19	4.1 ± 1.3	4.3 ± 1.1	4.0 ± 1.3	0.42
Mechanically ventilated at inclusion	118 (90.8)	54 (87.1)	64 (94.1)	0.17	169 (94.4)	81 (98.8)	88 (90.7)	0.02
Comorbidities								
Ischemic heart disease	28 (21.5)	11 (17.7)	17 (25.0)	0.31	35 (19.6)	15 (18.3)	20 (20.6)	0.69
Congestive heart failure	12 (9.2)	5 (8.1)	7 (10.3)	0.66	13 (7.3)	5 (6.1)	8 (8.2)	0.58
Diabetes	26 (20.0)	13 (21.0)	13 (19.1)	0.79	45 (25.1)	22 (26.8)	23 (23.7)	0.63
COPD	11 (8.5)	6 (9.7)	5 (7.4)	0.63	31 (17.3)	18 (22.0)	13 (13.4)	0.13
28-day mortality	51 (39.2)	22 (35.5)	29 (42.6)	0.47	82 (45.8)	39 (47.6)	43 (44.3)	0.67
Adjusted OR$^{\#\#}$ (99% CI)			1.44 (0.50-4.10)	0.37			0.87 (0.38-1.98)	0.67
Need for RRT during 28-day study period	47 (36.4)	23 (37.7)	24 (35.3)	0.78	135 (75.4)	60 (73.2)	75 (77.3)	0.52
ICU length of stay (days)	12 (7-31)	13 (8-33)	12 (5-23.5)	0.15	15 (7-29.5)	15 (8-31)	16 (6-28)	0.55

	End-stage				p-value[$] between RIFLE categories
	Total	**NE**	**AVP**	**p-value[#]**	
Number	49 (6.3)	25	24		
Age	62.3 ± 13.3	61.9 ± 12.2	62.6 ± 14.7	0.87	0.002
Sex – male	29 (59.2)	16 (64.0)	13 (54.2)	0.68	0.25
APACHE II	31.5 ± 6.1	30.1 ± 6.4	33.0 ± 5.4	0.09	<0.001
Recent Surgery	14 (28.6)	9 (36.0)	5 (20.8)	0.24	0.37
Ethnicity – Caucasian	38 (77.6)	22 (88.0)	16 (66.7)	0.07	0.48
Serum creatinine at enrollment (µmol/l)	472 ± 207	463 ± 181	480 ± 235	0.78	<0.001
Mean arterial pressure at baseline (mmHg)	70.1 ± 8.4	69.1 ± 10.2	71.2 ± 6.0	0.40	0.002

More severe shock (NE >15µg/min)	24 (49.0)	13 (52.0)	11 (45.8)	0.88	<0.001
Cardiac Index at baseline (l/min/m^2)**	3.3 ± 0.4	3.4 ± 0.5	3.2 ± 0.3	0.48	0.10
Mechanically ventilated at inclusion	45 (91.8)	23 (92.0)	22 (91.7)	0.97	0.21
Comorbidities					
Ischemic heart disease	10 (20.4)	6 (24.0)	4 (16.7)	0.52	0.29
Congestive heart failure	6 (12.2)	3 (12.0)	3 (12.5)	0.96	0.60
Diabetes	19 (38.8)	10 (40.0)	9 (37.5)	0.86	0.03
COPD	6 (12.2)	2 (8.0)	4 (16.7)	0.14	0.01
28-day mortality	27 (55.1)	15 (60.0)	12 (50.0)	0.48	<0.001
Adjusted OR[##] (99% CI)			0.67 (0.13-3.47)	0.53	
Need for RRT during 28-day study period	49 (100)	25 (100)	24 (100)	-	<0.001
ICU length of stay (days)	15.5 (7-27.5)	14 (2-25.5)	20 (7.5-48.5)	0.25	0.006

Values are numbers (%) or mean ± SD or median (25-75th centiles). Patients' "normal" creatinine was estimated in 394 / 779 (50.6%) of cases for RIFLE classification. *One patient in the "Risk" group was lost to follow up and therefore not included in the mortality analysis. **Cardiac index was measured in a subset of 153 patients at baseline. $^{\#}$ p-values compares variable between NE and AVP group within RIFLE category. $^{\#\#}$ Adjusted OR refers to multivariate logistic regression model of 28-day mortality rates. $^{\$}$Compares variable between RIFLE categories in all patients. RRT = renal replacement therapy, NE = norepinephrine, AVP = vasopressin.

Table 3. Multivariate logistic regression model for 28-day mortality in "Risk" category patients

	Odds ratio	99% CI		p-value
Age	1.01	0.97	1.06	0.38
Male sex	0.87	0.24	3.14	0.87
APACHE II	1.04	0.94	1.16	0.31
Surgical admission	0.61	0.18	2.08	0.30
Dose of NE at baseline	1.03	1.00	1.06	0.02
Vasopressin treatment	0.33	0.10	1.09	0.02

NE = norepinephrine. For the continuous variables the odds ratio refers to each year of age, each point of APACHE II score, and each μg/min of norepinephrine. For dichotomous variables comparison references are male v female sex, surgical v medical admission, and vasopressin v norepinephrine treatment allocation.

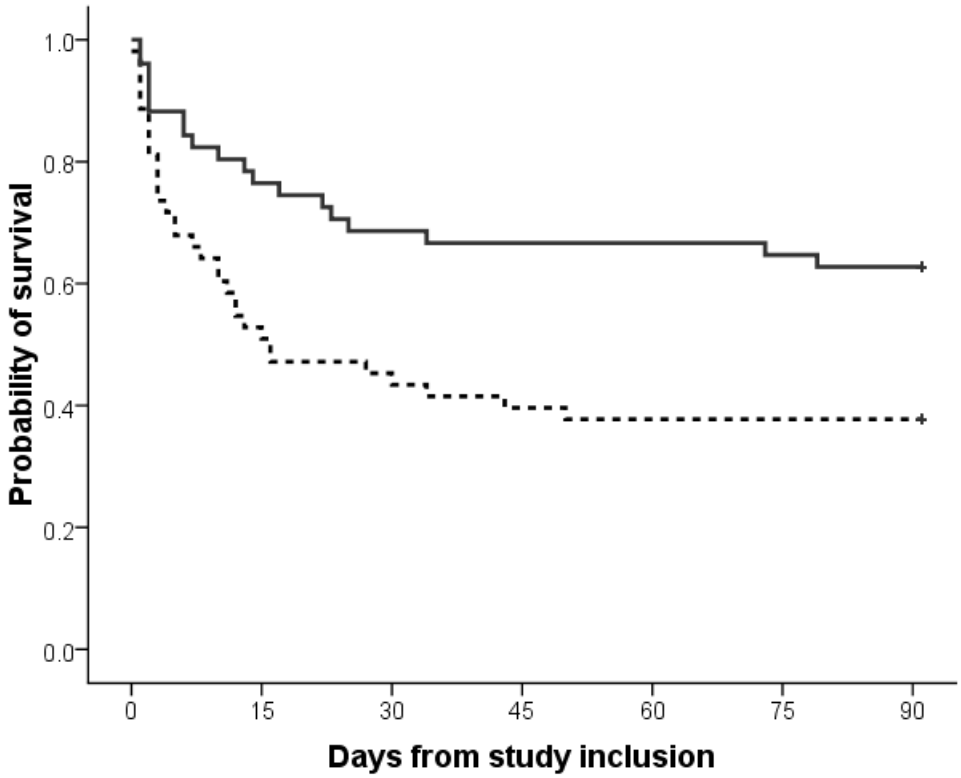
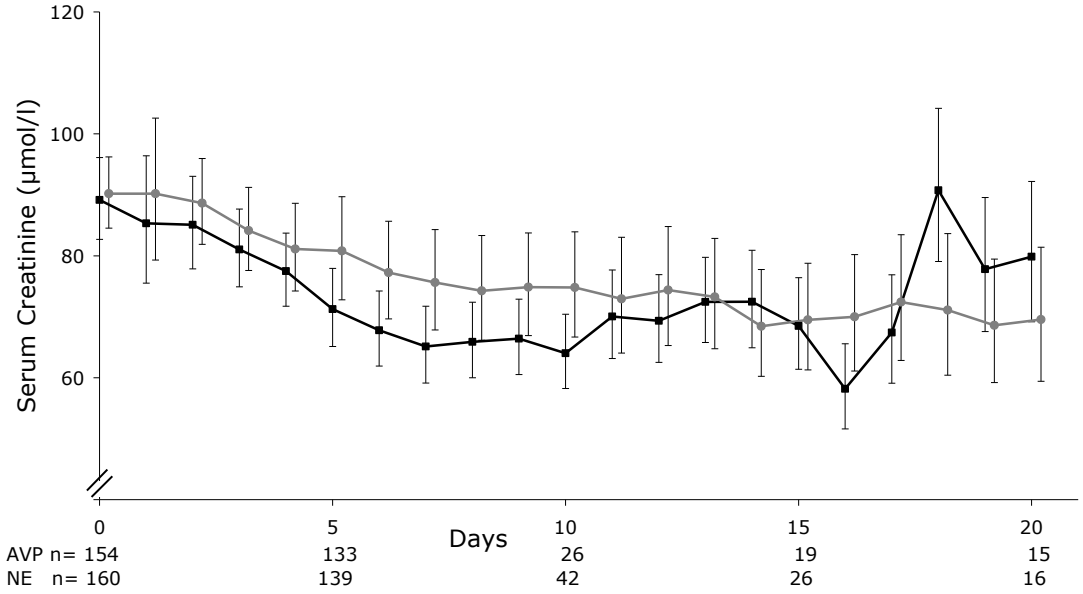
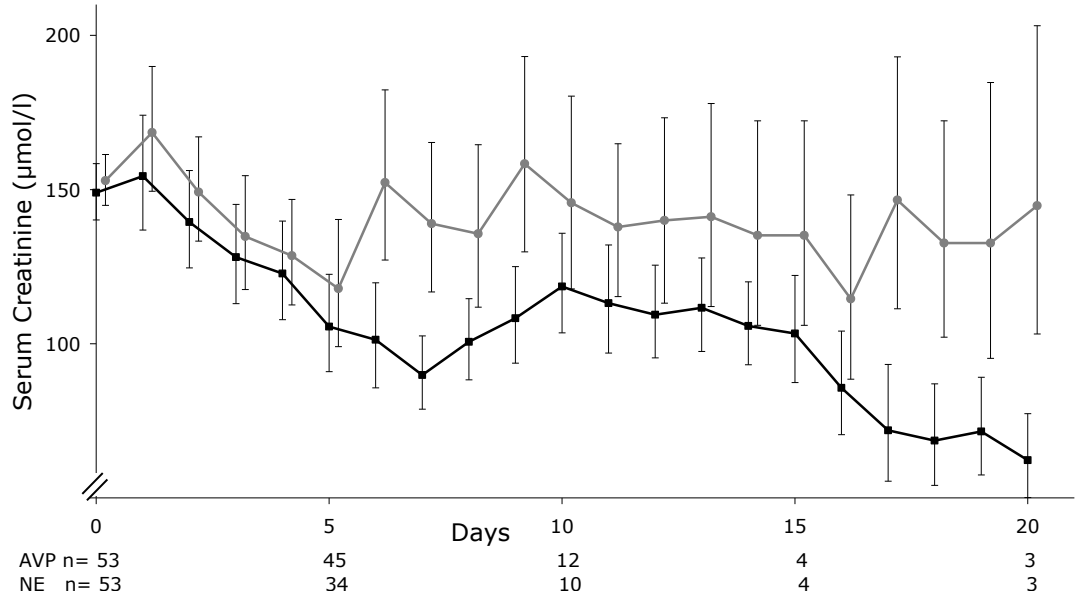


Figure 1. Kaplan Meier survival curves for at "Risk" patients in the vasopressin-treated group, solid black line, and the norepinephrine-treated group, dotted line (p = 0.007). P value was calculated using the log rank statistic.

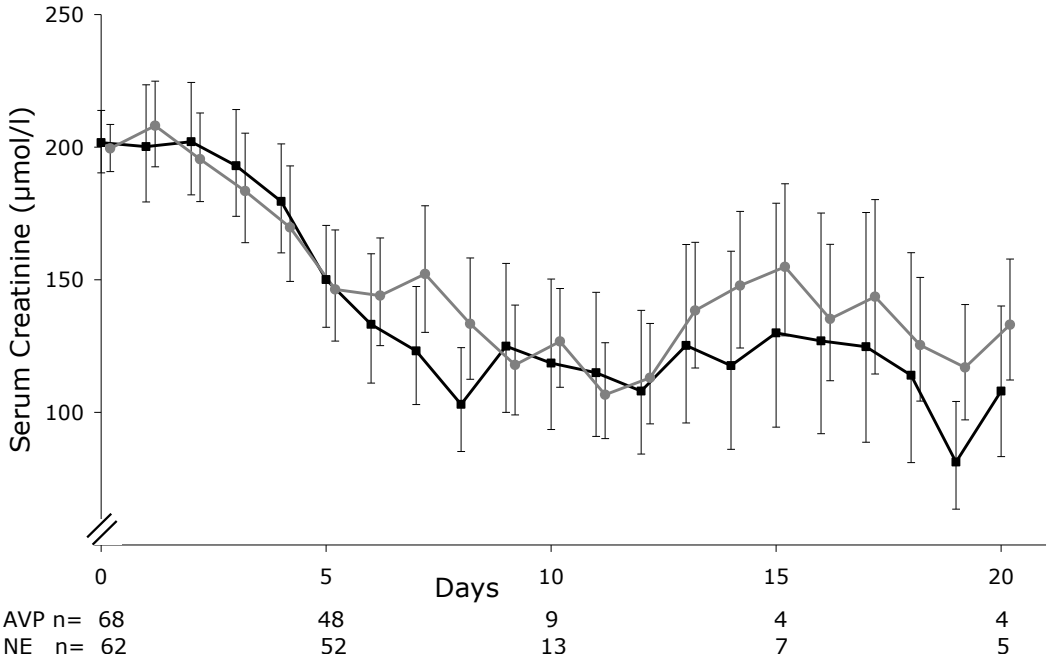
A


120
100
80
60
Serum Creatinine (µmol/l)
0
5
10
15
20
Days
AVP n= 154
133
26
19
15
NE n= 160
139
42
26
16

B


200
150
100
Serum Creatinine (µmol/l)
0
5
10
15
20
Days
AVP n= 53
45
12
4
3
NE n= 53
34
10
4
3

C



D

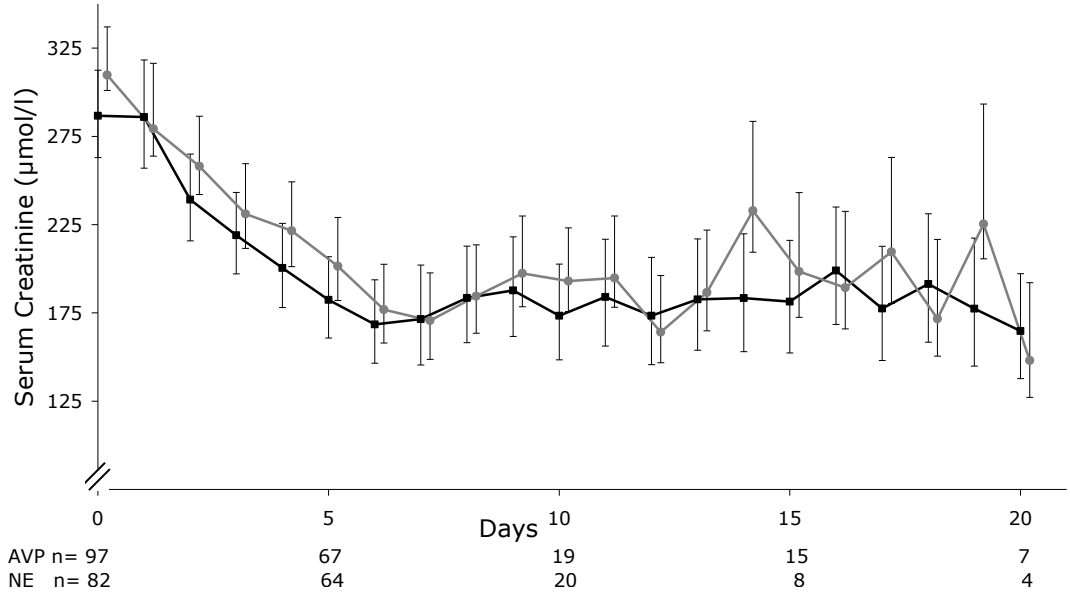
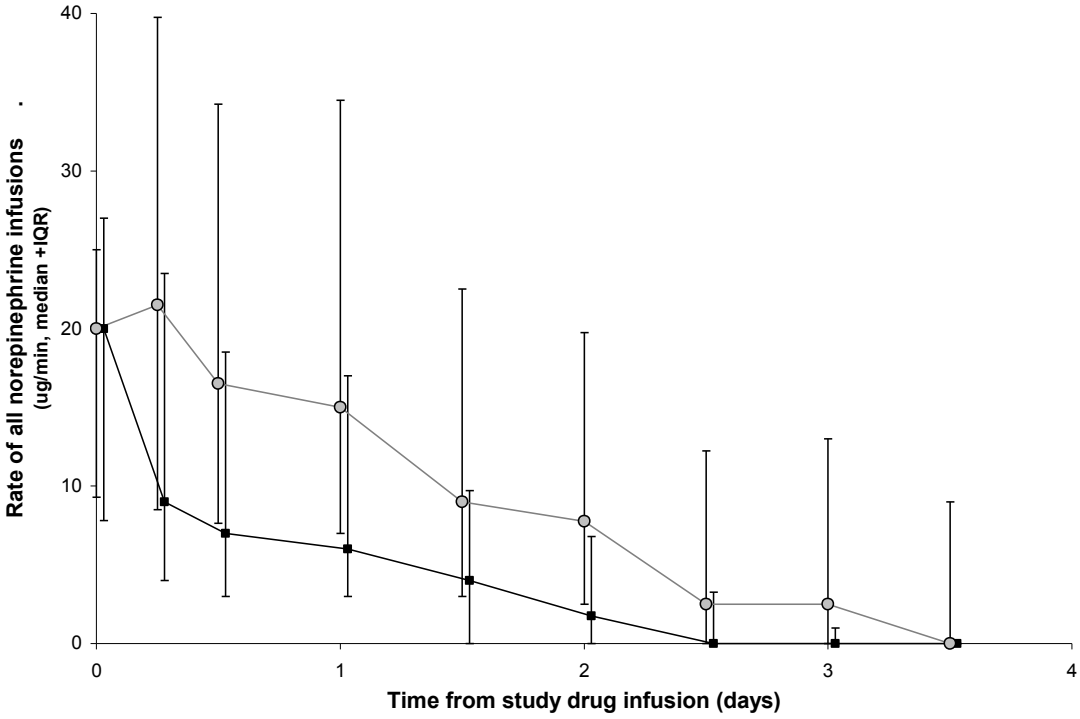


Figure 2. Mean serum creatinine (and 95%CI) over the first 20 days from start of study drug infusion in A – "Non-AKI" category, B – "Risk" category, C – "Injury" category, D – "Failure" category of RIFLE. Grey circles represent norepinephrine group, black squares represent vasopressin group. Serum creatinine values recorded whilst receiving renal replacement therapy have been excluded from the analysis.

Data after day 20 has not been shown due to small numbers in each group. AVP = vasopressin, NE = norepinephrine

A.



B.

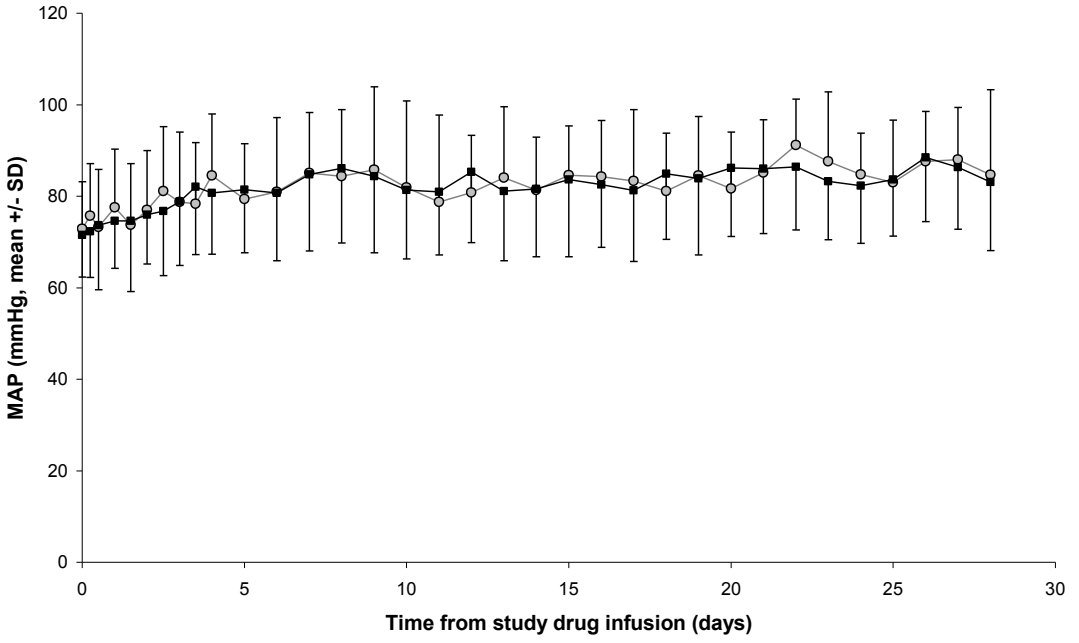


Figure 3. Median (±IQR) norepinephrine infusion rates are shown (Panel A) for patients receiving open-label norepinephrine at baseline in vasopressin and in norepinephrine treatment groups of patients in VASST who were in the "Risk" category of acute kidney injury according to RIFLE. Vasopressin-treated patients (black squares) had significantly reduced norepinephrine infusion rates compared to

the norepinephrine-treated patients (grey circles) ($p < 0.001$). Mean arterial pressure was similar between the two treatment groups (Panel B).