Clinical Predictors of Acute Renal Replacement Therapy in Critically Ill Patients with Acute Renal Impairment

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ABSTRACT

Objective: *To investigate the early predictors of acute renal replacement therapy (RRT) in critically ill patients with acute renal impairment.*

Methods: *A retrospective study of the clinical and laboratory records of all critically ill adult patients with acute renal impairment admitted to a 6-bed multidisciplinary intensive care unit of a general teaching hospital between 1st January 2000 and 31st December 2001 were reviewed to determine risk factors for RRT. Acute renal impairment was defined as an acute increase in plasma creatinine of > 0.12 mmol/L and urea of > 8mmol/L or an increase in plasma creatinine of > 0.06 mmol/L from the baseline level in patients who had chronic renal impairment.*

Results: *A cohort of 179 critically ill patients with acute renal impairment were identified. The mean APACHE II score was 23.4 and RRT was required in 11.2% of patients. The final logistic regression model showed that the requirement for noradrenaline (OR 29.0; 95% CI: 1.92 - 436.4, p = 0.015) was a positive risk factor and an increase in the average hourly urine output after intravenous frusemide (post-frusemide average hourly urine output/pre-frusemide average hourly urine output, OR 0.08; 95% CI: 0.02 - 0.32, p = 0.0004) was a negative risk factor for the requirement of RRT (area under the ROC curve = 0.88, 95% CI: 0.82 - 0.94, p = 0.001).*

Conclusions: *After adequate fluid resuscitation, poor urinary output response to intravenous frusemide coupled with requirement for noradrenaline predicted the requirement for RRT in critically ill patients with early acute renal impairment in our intensive care unit.* (**Critical Care and Resuscitation 2003; 5: 97-102**)

Key words: Renal replacement therapy, frusemide, noradrenaline, acute renal impairment

Acute renal failure in critically ill patients is associated with an increase in mortality.[1] While there is some evidence that early high flux renal replacement therapy (RRT) may improve clinical outcomes in critically ill patients,[2] there is often no agreement on how best to define acute renal failure or when to initiate acute renal replacement therapy.[3-5]

Many studies have confirmed that an increase in age, sepsis, circulatory or respiratory failure and cirrhosis are risk factors for acute renal failure in critically ill patients who previously have had normal renal function.[6,7] However, the predictive values of these factors are generally low because the prevalence of acute renal failure requiring RRT in such patients is low.[8,9] On the other hand, the prevalence of acute renal failure requiring RRT is usually higher in critically ill patients who initially develop acute renal impairment. Predictors for RRT derived from such cohorts are therefore likely to have higher predictive values.

Because of limited health resources and complications associated with RRT, many critically ill patients with acute renal failure are often managed conservatively with mechanical ventilation, inotropes, diuretics and intravenous fluids; RRT is usually only initiated when

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major complications of fluid overload, acidosis, uraemia or hyperkalaemia develop. While early prediction of the requirement for acute RRT is useful, the standard method of assessing renal function using creatinine clearance is limited. For example, the requirement of an accurate 2 - 24 hour urine collection to determine the clinical course of acute renal dysfunction is laborious and the results are often delayed.[10] In practice, most intensivists assess renal function by monitoring the urine output and plasma urea and creatinine levels.[3]

We decided to investigate the early predictors for development of severe acute renal failure requiring RRT in critically ill patients with acute renal impairment. In particular, we wished to evaluate the role of intravenous frusemide as a diagnostic test in predicting the requirement of acute RRT in these patients.

METHODS

This was a retrospective observational study of patients admitted to a 6-bed multidisciplinary intensive care unit of a general teaching hospital. The hospital provides general surgery, internal medicine, coronary care, orthopaedic surgery and obstetrics services to a population of about 400,000. There are no cardio-thoracic surgery, neurosurgery, burns or spinal trauma services in this hospital. After obtaining approval from the hospital ethics committee, two independent investigators examined the electronic and clinical records of all patients who were admitted to the intensive care unit (ICU) from 1st January 2000 to 31st December 2001. Acute renal impairment was defined using criteria previously described[3] (i.e. a plasma creatinine level of greater than 0.12 mmol/L and urea level greater than 8 mmol/L when the patient's normal creatinine level was less than 0.12 mmol/L). Patients with pre-existing renal impairment were included if there was a significant increase in the plasma creatinine level (i.e. > 0.06 mmol/L) during their ICU admission. The laboratory results in the 12 months before and after the ICU admission determined the patient's normal renal function.

Patients with plasma creatinine level less than 0.12 mmol/L during their stay in ICU but with raised creatinine level before or after their ICU stay were excluded. A standardised management protocol for acute renal impairment included fluid resuscitation by colloid infusion (gelofusine®, succinylated gelatin solution 4%, B. Braun, Switzerland) and, if intravascular volume status was clinically judged to be adequate, maintenance of a mean arterial pressure greater than 75 mmHg using a noradrenaline infusion (0 - 1.0 μg/kg/min). Dopamine, dextran, albumin, and hydroxyethyl starch were not used. If oliguria persisted, an intravenous dose of frusemide (40 mg to 120mg) was used. The hourly urine output was replaced intravenously with 0.45% solution of sodium chloride.

When intravenous frusemide had been used before the commencement of RRT, the timing of its administration in relation to RRT, the dose and the average hourly urine output over a period of 8 hours before (i.e. pre-frusemide urine output) and 8 hours after the frusemide was given (post-frusemide urine output) were recorded. Renal ultrasound was performed to exclude obstructive renal failure. Data including history of pre-existing renal impairment, diabetes mellitus, cirrhosis, requirement for noradrenaline, mechanical ventilation (other than continuous positive airway pressure) and the decision to withdraw or limit therapy were also recorded.

Using univariable analyses, all potential risk factors and confounders for requiring acute RRT were tested for association with occurrence of RRT. Analysis of variance (ANOVA) was used for all continuous variables (if they were normally distributed) and Chi-square test or Mann-Whitney test was used for categorical variables (also for continuous variables if they had different variances between the two groups or if the data was not normally distributed). Stratified analyses were performed to test for confounding between categorical variables that were derived from the univariable analyses with a p-value of less than 0.10. The principle of intention to treat analysis was used when considering whether a particular variable should be included in the final logistic regression model. As the decision to withdraw or limit therapy might have been affected by some of the clinical risk factors in the model, we have included withdrawal of therapy in the final logistic regression model, creating a more conservative rather than an over-optimistic model. The five significant variables analysed in the logistic regression were age, chronic renal impairment, noradrenaline requirement, ratio of urine output before and after frusemide and withdrawal of therapy.

In this study, a p-value less than 0.05 was regarded as significant in the univariable analyses and multivariable analyses, and all statistical tests were 2-tailed tests unless stated otherwise. Statistical analyses were performed using EPI 2000 software (version 1.12a 2002, CDC, USA). Confidence intervals were calculated by confidence interval analysis (version 2.0.0 BMJ 2000) if they were not generated by EPI 2000 software. Because the ratio of the average hourly urine output before and after frusemide is a continuous variable, we assess the reliability of this parameter to predict RRT by the means of a receiver operating characteristic (ROC) curve. The ROC curve was plotted by SPSS for windows statistical software (version 9.0, 1998 SPSS Inc. IL, USA).

RESULTS

The cohort identified 179 critically ill adult patients with a mean APACHE II score of 23.4. The final regretssion model was based on a total of 127 study subjects; 52 subjects of the original cohort were not included in this analysis because they had pre-renal failure and their urine output had responded to fluid resuscitation alone without the requirement of intravenous frusemide during their stay in ICU.

A significant proportion of patients had diabetes mellitus (26.3%) and chronic renal impairment (8.4%). Sepsis was the main primary diagnosis in 80% of patients. A significant proportion had a raised plasma creatinine level of greater than 0.12 mmol/L when they were admitted to the ICU. The average mortality rate of the entire cohort was 39.7%. The characteristics of the entire cohort are detailed in Table 1. The characteristics of twenty of 179 patients who required RRT during their ICU stay are described in Table 2.

The patients who had RRT had a significantly higher pre-dialysis creatinine level (mean 0.43 mmol/L) and urea level (25.8 mmol/L) than those who did not have RRT. They also received higher doses of frusemide, indicating that the RRT group had a more severe acute renal impairment than the group that did not receive RRT (Table 2 and 3). Univariable analyses showed that age, chronic renal impairment, noradrenaline therapy and urinary output ratio after frusemide (post-frusemide to pre-frusemide average hourly urine output) were significantly associated with requirement for acute RRT (Table 3).

The final logistic regression model consisted of 127

Table 1. Characteristics of the cohort of patients with acute renal impairment

Age (years, mean ± SD)	65.7 ± 16.1
Sex (ratio of male/female)	61.5/38.5
APACHE II score (mean ± SD)	23.4 ± 11.7
Predicted mortality % (mean ± SD)	43.2 ± 29.7
Actual mortality %(95% CI)	39.7 (32.4 - 47.2)
Diabetes mellitus % (95% CI)	26.3 (20.0 - 33.3)
Chronic renal impairment % (Cr > 0.12mmol/L, 95% CI)	8.4 (4.8 - 13.4)
Patients mechanically ventilated % (95% CI)	60.3 (52.8 - 67.6)
Usual creatinine level (mmol/L, mean ± SD)	0.09 ± 0.05
Creatinine level (mmol/L) when admitted to ICU (mean ± SD)	0.20 ± 0.20
Highest potassium (mmol/L, mean ± SD)#	5.0 ± 0.8
Lowest bicarbonate (mmol/L, mean ± SD) #	17.8, 17.9, 5.5
Highest creatinine (mmol/L, mean ± SD) #	0.28, 0.20, 0.25
Highest urea (mmol/L, mean ± SD) #	19.7, 16.5, 11.8
Patients requiring noradrenaline % (95% CI)	76.5 (69.6 - 82.5)
Patients receiving frusemide before RRT % (95% CI)	70.9 (63.7 - 77.5)
Patients receiving 40/80/120mg of frusemide (%)	80.3/15.0/4.7
Patients who underwent withdrawal of therapy % (95% CI)	21.2 (15.5 -28.0)
ICU stay in days (mean ± SD)	5.0 ± 6.5
Patients requiring RRT % (95%CI)	11.2 (7.0-16.7)

= the worst laboratory test results before renal replacement therapy was used.

Table 2. Characteristics of patients receiving renal replacement therapy (N = 20)

Proportion of patients who received frusemide	95%
Timing of frusemide before renal replacement therapy (h) mean ± SD	39 ± 32
Number of patients with 40/80/120 mg frusemide administered	0,14,6
Highest predialysis potassium (mmol/L, mean ± SD)	5.2 ± 1.0
Highest predialysis creatinine (mmol/L, mean ± SD)	0.43 ± 0.5
Highest predialysis urea (mmol/L, mean ± SD)	25.8 ± 19.5
Days of renal replacement therapy needed (mean ± SD)	7.7 ± 5.1

Table 3. Risk factors for requiring renal replacement therapy

Variables	*RRT n=20*	*No RRT n=159*	*Difference (95% CI)*	*p-value*
Mean age (years ± SD)	54.6 ± 13.7	68.0 ± 15.8	13.4 (6.1 - 20.7)	0.0009
Mean APACHE II score (± SD)	20.9 ± 8.4	23.7 ± 12.1	2.8 (-2.7 - 8.3)	0.31
Chronic renal failure (% Cr > 0.12 mmol/L)	20.0	6.9	13.1 (9.2 - 19.6)	0.047
Diabetes mellitus (%)	10.0	28.3	18.3 (-2.8 - 28.7)	0.08
Mechanical ventilation (%)	75.0	58.5	16.5 (-6.6 - 32.4)	0.16
Highest F_IO_2 (± SD)	67% ± 28	58% ± 22	9.0% (-1.6 - 19.6)	0.11
Requirement for noradrenaline (%)	95.0	74.2	20.8 (1.2 - 29.2)	0.039
Highest noradrenaline dose (mg/h ± SD)	2.2 ± 1.7	1.3 ± 1.9	0.9 (-0.02 - 1.8)	0.10
Urine output ratio after frusemide*	0.91 ± 0.46	4.15 ± 4.2	3.2 (1.4 - 5.1)	0.001
Highest pre-dialysis potassium (mmol/L)	5.2 ± 1.0	5.0 ± 0.8	0.2 (-0.2 - 0.5)	0.45
Highest pre-dialysis creatinine (mmol/L)	0.43 ± 0.5	0.26 ± 0.2	0.17 (0.1 - 0.3)	0.006
Highest pre-dialysis urea (mmol/L)	25.8 ± 19.5	19.0 ± 10.3	6.8 (1.3 - 12.3)	0.01
Withdrawal of therapy (%)	0.0	21.4	21.4 (4.3 - 28.4)	0.02
Survival (%)	70.0	61.8	8.4 (-14.7 - 25.7)	0.48

* = post-frusemide/pre-frusemide average hourly urine output ± SD (analysis was performed in the 127 patients who received frusemide during the course of acute renal impairment but before renal replacement therapy.

Table 4. Risk factors and confounders for patients requiring acute renal replacement therapy*

Variables	*Beta-coefficient*	*Odds Ratio (95% CI)*	*p-value*
Requirement for noradrenaline	4.149	29.0 (1.9-436.4)	0.015
Chronic renal impairment	-0.351	0.70 (0.1-7.5)	0.77
Urine output response to frusemide**	-3.231	0.08 (0.02-0.32)	0.0004
Age	-0.034	0.97 (0.92-1.01)	0.13

* final logistic regression model, ** ratio of post-frusemide to pre-frusemide hourly urine output

Table 5. Risk of requiring renal replacement therapy if there is no withdrawal of therapy

Risk factors	*Probability of requiring RRT*
Double hourly urine output after frusemide and no need for noradrenaline	1.0%
No change in hourly urine output after frusemide and no need for noradrenaline	21.1%
Double hourly urine output after frusemide but requiring noradrenaline	46.7%
Hourly urine output reduced to half after frusemide but no need for noradrenaline	57.3%
No change in urine output and requiring noradrenaline	94.4%
Hourly urine output reduced to half after frusemide and requiring noradrenaline	98.8%

patients with the significant variables (Table 4) of requirement for noradrenaline (OR 29.0, 95% CI: 1.92 - 436.4, p = 0.015) and urinary output response ratio to frusemide (i.e. ratio of post-frusemide hourly urine output to pre-frusemide hourly urine output, OR 0.08, 95% CI: 0.02 - 0.32, p = 0.0004).

To facilitate clinical interpretation, we summarised the risks of requiring RRT when certain clinical risk factors were present. The probabilities of requiring acute RRT in the presence of one or two of the predictors are shown in Table 5.

We found that the reliability of urinary output response to frusemide (the ratio of post-frusemide hourly urine output to pre-frusemide hourly urinary output, both averaged over a period of 8 hours) to predict requirement for RRT was high, with an area under the ROC curve = 0.88 (95% CI: 0.82 - 0.94, p = 0.001, see Figure 1).

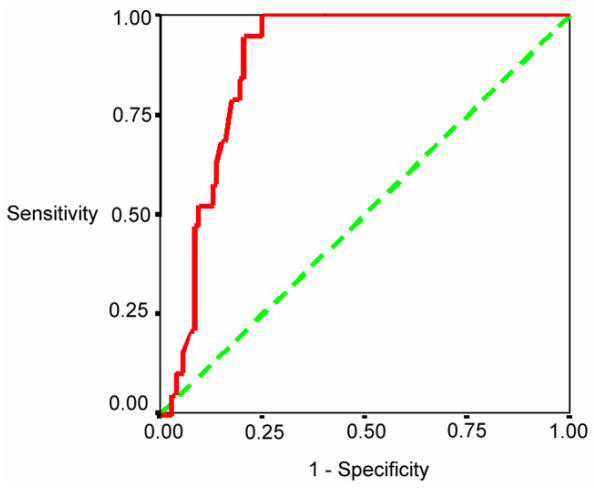

Figure 1. Receiver operating characteristic (ROC) curve of urinary output response to frusemide in predicting requirement for acute renal replacement therapy (Area under ROC = 0.88 95% CI 0.82 - 0.94, p = 0.001)

DISCUSSION

It has been reported that non-oliguric acute renal failure has a better prognosis than oliguric acute renal failure.[8,11,12] While frusemide is still being used to facilitate fluid and electrolytes management in critically ill patients with acute renal dysfunction[12,13], its use in preventing acute renal failure, both in experimental and clinical settings, have been disappointing.[11,14-16]

The results of this cohort study have demonstrated a different approach to the use of frusemide. In critically ill patients with acute mild renal impairment or who are in the early stage of acute renal failure, a poor urinary output response to intravenous frusemide, especially if the patient also requires inotropic support, has a strong association with requirement for acute RRT later in the course of their illness. Previous studies have shown that responders to intravenous frusemide are in general not as ill as non-responders,[11,14] and that responders usually have a higher creatinine clearance than the non-responders.[11]

Our results showed that those who did not respond to frusemide early in the course of acute renal impairment subsequently had higher plasma creatinine and urea levels and required RRT. As frusemide is largely excreted unchanged in the urine and influences tubular reabsorption from the luminal side, it is the urinary tubular excretion of the drug, not its plasma concentration that determines the efficacy of its diuretic action.[18-20] Therefore, the diuretic response to frusemide may represent a clinical 'surrogate' for the underlying degree of acute renal impairment, which ultimately determines whether acute RRT is required during the illness.

While our results have demonstrated a high predictive value of urinary output response to intravenous frusemide in predicting the requirement for acute RRT, overuse or misuse of frusemide can cause potential problems in critically ill patients, especially when hypovolaemia exists.[21] We believe that aggressive fluid resuscitation, which was the standard management for all patients in this study, should be undertaken both before and after the use of frusemide, even when frusemide is used as a diagnostic test.

There are several limitations to our study. Observational studies, especially retrospective studies, are prone to biases. We used two independent investigators to collect data from both electronic and clinical records to reduce selection and detection biases. However, we cannot exclude significant performance bias in this study. While we have a standardised management protocol for patients with acute renal dysfunction in the ICU, there were no standardised criteria for RRT initiation. Also, clinicians were not blinded to the urinary output response to frusemide. However, our results indicated that the attending intensivists had been conservative in terms of initiating RRT as the mean plasma creatinine of 0.43 mmol/L and urea of 25.8 mmol/L were high before RRT was commenced. The other factor that may have affected our results was the variable doses of frusemide used in this cohort. While 40 mg of intravenous frusemide was used in 80.3%, some patients received 80 mg (15%) and others 120 mg (4.7%). The response between urine output and frusemide dose from 0 to 1 mg/kg is steep in children who have normal renal function. In children with acute renal failure, there is a broad but more variable relationship between diuretic response and the dose of frusemide (1.2 to 30.8 mg/kg).[22] However, the dose response of frusemide in adults with acute renal impairment has not been thoroughly investigated. In our study, those patients who received higher doses of frusemide were those who had least response to frusemide (see table 2) and subsequently required RRT.

In conclusion, in patients with early acute renal impairment and after adequate fluid resuscitation, a poor urinary output in response to intravenous frusemide, especially if the patient also requires inotropic support, is associated strongly with the need for RRT later in the course of their disease. While frusemide cannot prevent acute renal failure, we believe that its use as a diagnostic test to predict the degree of acute renal impairment and subsequent requirement for acute RRT deserves further investigation.

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