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Does continuous renal replacement therapy favourably influence the outcome of the patients?

S. M. Jakob, F. J. Frey and D. E. Uehlinger

Division of Nephrology, Department of Medicine, University of Berne, Inselspital, CH-3010 Berne, Switzerland

Abstract Continuous haemodialysis and continuous haemofiltration are efficient and safe techniques for the treatment of acute renal failure. Theoretical advantages are improved haemodynamic stability and easier fluid removal. All 15 available studies comparing intermittent (522 patients) with continuous (651 patients) renal replacement therapy have been reviewed. From these studies it cannot be established, whether the use of a continuous instead of an intermittent treatment modality improves the outcome in patients with acute renal failure. Reviewing all 67 published studies dealing with continuous renal replacement therapy revealed a trend to a decreasing mortality rate ($P<0.08$) over the last 11 years, whereas the mean age and the severity of illness of the patients, measured by the APACHE II score, did not change. In order to establish whether the quality of treatment has improved as a function of time, two quality factors (QF) were created, i.e. QF for age (mean age/mean mortality rate of the patients treated) and QF for severity of diseases (mean APACHE II/mean mortality rate). Both QF improved from 1984 until 1994, when analyzed for continuous ($P<0.001$) or intermittent ($P<0.001$) treatment modality. Thus the quality of treatment of patients with acute renal failure improved during the last decade. However, there is no evidence with respect to survival rate that a continuous renal replacement therapy is superior to an intermittent one.

Key words: acute renal failure; continuous haemodialysis; continuous haemofiltration; mortality

Introduction

Since the introduction of continuous haemofiltration [1] and continuous haemodialysis [2], these techniques with several modifications have turned out to be efficient and save [3–5]. Despite the theoretical advantages of continuous forms of renal replacement therapy (RRT), such as improved haemodynamics [6], easier fluid removal [6,7] and greater flexibility with parenteral nutrition [7], continuous therapies might have some drawbacks: if the coagulation parameters in the patient are normal and a reasonable life-span of the filter has to be obtained, anticoagulation is compulsory. Possibly, there is an increased frequency of access related complications [3]. Furthermore, once very simple and possibly the cheapest form of RRT, todays continuous methods include highly sophisticated treatment devices to guarantee treatment safety and are thought to be some 2.5 times more expensive than conventional intermittent dialysis and/or haemofiltration [8,9]. This difference might even be more pronounced if one considers the additional manpower required. Thus, in order to be cost effective morbidity and mortality of patients with acute renal failure (ARF) should be better when a continuous instead of an intermittent RRT is applied.

Although there is some evidence that slow continuous techniques in comparison with conventional (intermittent) RRT might improve morbidity and mortality of patients with ARF [10–12], prospective controlled trials comparing the different forms of RRT have not been performed.

This review tries to establish first whether differences in outcome are observed between continuous and intermittent treatment modalities and second, whether an improvement in the outcome of patients with acute renal failure treated with continuous modalities of dialysis and ultrafiltration techniques occurred during the last 10 years. For that purpose all peer-reviewed publications of trials concerning the use of continuous forms of RRT with or without an intermittently treated control group were analysed. Studies available only as an abstract were not considered for the subsequent analysis.

Studies comparing continuous with intermittent forms of renal replacement therapy

Fifteen studies comparing intermittent (522 patients) with continuous (651 patients) forms of RRT have been published (Table 1). Whereas most studies reported observations from patient numbers between

Correspondence and offprint requests to: Dominik E. Uehlinger, Division of Nephrology, Department of Medicine, Inselspital, CH-3010 Berne, Switzerland.

Table. 1. Studies comparing intermittent with continuous renal replacement therapies

Author, year	Number of patients	Mean age age (years)	MAP (mmHg)	APACHE II	Fluid allowance (l/day)	Renal recovery	Mortality	Study characteristics	Filter
Mauritz, 1986 [8]	58	50	uk	uk	uk	34	81	re,nr	
-HD	22	52				27	91		CDAK
-CAVH	9	51				11	89		AMICON
-CVVH	27	47				48	70		AMICON
Bartlett, 1986 [16]	56	57	uk	21	uk	uk	79	re	
-HD	24	56		21			88		C-Acetate
-CAVH	32	59		21			72		AMICON
Simpson, 1987 [7]	32	50	uk	18	uk	uk	60	re,nr	
-cont UF/Dial.	14	48		17			50		F40/F60
-HD	18	52		18			67		Cuprophan
Paganini, 1988 [3]	142	62	75	31	3.2	17	79	re,nr	
-continuous	27	65	65	36	3.8	19	81		uk
-intermittent	47	62	87	27	2.1	19	82		uk
-combined	68	60	71	31	3.8	15	76		uk
Maher, 1989 [18]	90	51	uk		uk	uk	73	re,nr	
-CAVH (ev. +IHD)	65			26					FH55
-CAVHD	22			26					AN69
-HD	3			27				uk	
Favre, 1989 [19]	76	uk	88	uk	uk	uk	uk	re,nr	uk
-CVVH	40		79						
-HD	36		98						
Davenport, 1991 [15]	22	uk	uk	uk	uk	uk	uk	p,pr	
HD									FH77
CAVH/CAVHD									Hosp2400
Bosworth, 1991 [13]	320	60	79	26	uk	uk	68	re,nr	Polyamid/
-continuous	95		70				82		Polyacnitr
-HD	138		85				60		Cuprophan
-combined	87		79				76		as above
Bastien, 1991 [12]	66	57		22	uk	uk	62	p,nr	
-HD	32	54		20			75		uk
-CVVHD	34	60	75	23			50		AN69
Kierdorf, 1991 [11]	146	uk	uk	uk	uk	uk	86	re	uk
-CVVHF	73						78		
-HD	73						93		
McDonald, 1991 [17]	42	46	uk	uk	uk	uk	79	re	
-HD	10	50					70		Cuprophane
-CAVHD	22	45					70		AN69S
-HD/CAVHD	10	44					80		as above
Bellomo, 1993 [4]	167	58	uk	27	uk	uk	65	re,nr	
-CHDF	83	60		28			59		AN69S
-CD	84	56		26			70		Cuprophan
Bellomo, 1993 [5]	160	59	uk	27	uk	uk	65	re+p,nr	
-CHDF	76	62		29			59		AN69S
-CD	84	56		26			71		Cuprophan
Kruczynski 1993 [10]	35	56	uk	27	uk	uk	55	re,nr	
-CAVH	12	45		26			25		Gambro
-HD	23	61		28			82		F6/F60
Davenport 1993 [14]	32	33	77	26	uk	uk	uk	p,pr	
-HF	12	33	82	22					FH77
-CAVH/CAVHD	20	33	74	28					Hosp2400

HD, Intermittent haemodialysis, r, Randomization, CAVH, Continuous arteriovenous haemofiltration, pr, Partly randomized, CVVH, Continuous venovenous haemofiltration, nr, No randomization, CHDF, Continuous haemodiafiltration, re, Retrospective, CD, Conventional dialysis (intermittent haemodialysis or acute peritoneal dialysis), p, Prospective, HF, Intermittent haemofiltration, uk, Unknown, CHF, Continuous haemofiltration, cont UF/Dial., Continuous haemodialysis with ultrafiltration, CAVHD, Continuous arteriovenous haemofiltration with dialysis, MAP, Mean arterial presure.

3 and 36 (intermittently treated groups) and 9–87 (continuously treated groups) respectively, there are some studies with more than a 100 patients [3–5,11,13]. Only four trials were carried out prospectively [5,12,14,15] and there is no published prospective trial with complete randomization available.

The type of filter used was indicated in 12 investigations [4,5,7,8,10,12–18]. No study applied filters with the same material for the continuously and intermittently treated patients. Intermittent treatments were mainly carried out with cellulose-based filters [4,5,7,8,13,16,17], whereas continuous forms of RRT were performed by polyacrylonitrile [4,5,12–15,17,18], polysulphone [7,18] or polyamide [13] filters.

The mean age of the patients was indicated in all but three studies [11,15,19] and ranged from 46 to 62 years. In only one study young patients (mean age 33 years) with a head injury were treated [14].

Results about mean arterial pressure were reported in only four of 15 publications [3,13,14,19]. These values were higher in all studies in the intermittent (88 ± 7 mmHg, mean $\pm$ SD) than in the continuous (72 ± 6 mmHg) groups ($P < 0.05$; Wilcoxon signed rank test). This suggests that patients with low blood pressure and presumably haemodynamic instability were preferentially treated by a continuous dialysis modality.

APACHE II scores were reported in 10 studies [3–5,7,10,12–14,16,18] and the mean values ranged from 18 to 31. Two studies were excluded from further analysis [13,18]. One study reported only a mean APACHE II score for the whole study population [13] and the other study was incomplete with respect to the APACHE II scores [18].

Fluid allowance, often considered to be a criterion for choosing a continuous form of RRT was given in only one report [3]; it was higher in the continuously than in the intermittently treated group (3.8 vs 2.1 l/day).

Two therapeutic end-points were given, renal recovery [3,8] and mortality [3–5,7,8,10–13,16–18] (Table 1). Renal recovery was reported in two studies [3,8]. In none of them was a definition of renal recovery given. As a consequence of the paucity of results, no definite conclusion about the superiority of the method of RRT with respect to renal recovery can be made (Table 1). Mortality rate is known from 12 of 15 studies (Table 1). The values for mortality rate ranged between 55 and 86%. In three investigations a statistically significantly lower mortality was found in continuously than in intermittently treated patients [10–12]. A similar difference was detected in a subgroup of patients from a further study [4].

Despite the non-randomized character of most studies and the many historical control groups (Table 1) for intermittent therapy all available studies [3–5,7,8,10–19] were pooled for further analysis. Weighted multivariate logistic regression analysis was used to examine the influence of APACHE II score, patient age and investigation year on patient mortality in the reviewed trials. Weighted least-squares minimization was done by weighting the loss function with $N*q*(1-q)$ [20], where N is the number of subjects in each pooled study and q is the reported gross mortality rate of the corresponding study. Dummy variables were introduced to test for possible differences between treatment modalities in the relationship of patient mortality and the above-mentioned independent variables [20].

Pooling all the patients from the published trials revealed a mean age of 58 ± 7.1 years in patients with ARF on intensive care units, a mean APACHE II score of 27 ± 4.9 and a mean mortality rate of 69%. In Figure 1 the results are given separately for the years 1986, 1987, 1988, 1991 and 1993. For the other years no studies were available. The analysis of Figure 1 shows a slightly decreasing mortality rate from 80% in 1986 to 64% in 1993 when intermittently and continuously treated patients were considered as a group. Logistic regression analysis, controlled for age, APACHE II score, observation year, and treatment modality, revealed a trend for a better outcome in recent years, independent of treatment modality ($P < 0.07$). However, no differences in mortality rates, APACHE II scores or mean age were detected between intermittent and continuous forms of RRT.

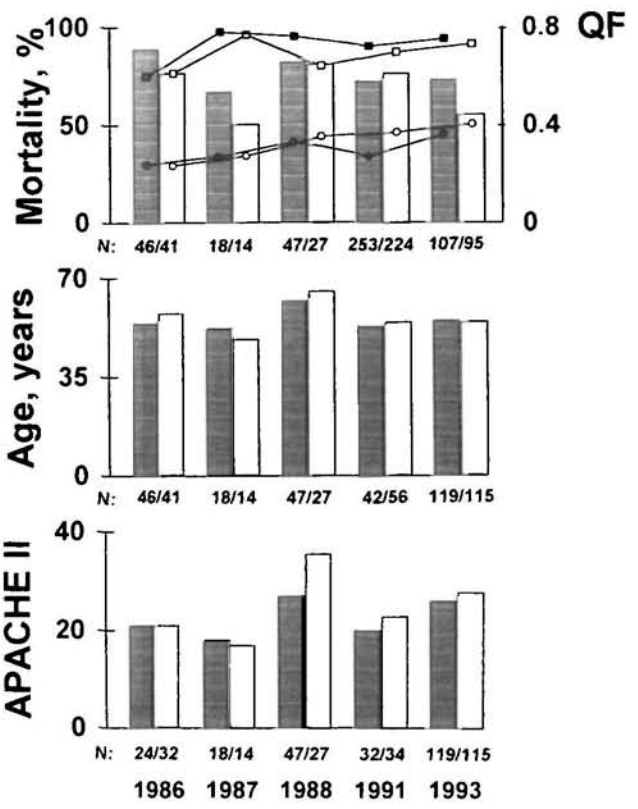

Fig. 1. Comparison of mortality rates, mean age and APACHE II scores between intermittently (hatched bars) and continuously (open bars) treated patients with ARF. The values were derived from studies published in 1986, 1987, 1988, 1991 or 1993. N indicates the number of patients analysed. In the upper part of the figure quality factors of treatment are shown. When age (-■-, intermittently treated patients; -□-, continuously treated patients) or APACHE II (-●-, intermittently treated patients; -○-, continuously treated patients) were considered for the calculation of the quality factors (QF) the values increased with time ($P < 0.001$).

In order to establish whether the quality of treatment of patients with ARF increased in recent years one has to consider both, the severity of the underlying disease states and the mortality rates. The severity of the underlying disease, i.e. the likelihood of not surviving correlates with age and the APACHE II score [21]. Thus dividing age or APACHE II score by mortality rate provides a measure of quality of the treatment. In Figure 1 (upper part) we propose numerical values for such quality factors. For that purpose the weighted mean values of age and APACHE II score respectively, were divided by the corresponding weighted mean values of mortality. High values of those indices suggest

good treatment quality whereas low values suggest the opposite. In Figure 1 the mean values from all studies from where such indices could be derived, are given (1986, 2 studies; 1987, 1 study; 1988, 2 studies; 1991, 5 studies; 1993, 4 studies). When analysed as a function of the year, treatment quality improved ($P<0.001$, weighted logistic regression analysis) as can be clearly shown by the steadily increasing quality factors (Figure 1).

Studies reporting patients on a continuous form of renal replacement therapy without a control group

An additional 52 studies describing only patients treated with continuous RRT without an intermittently treated control group were found in the literature [2,6,9,22–70]. The number of patients included in the reported studies ranged from five [23] to 255 [70] patients. The total number of patients reported in these 52 publications was 1860.

Treatment modalities included continuous haemofiltration, either arteriovenous [23,26,28–32,37,45,-46,50–53,59], venovenous [36,38,47,49,60,66] or both[34,35,44,55], slow continuous ultrafiltration [6], continuous haemodialysis, either arteriovenous[39,41,54,56,58,61,65,68], venovenous [25,31] or both [9,24,42,62,63], continuous haemodiafiltration [40,48,67,69] as well as both continuous arteriovenous haemofiltration and haemodialysis[43,57] respectively. In one study continuous RRT was combined with intermittent haemodialysis [29].

The types of filters used were mostly polyacrylonitrile [9,24,25,28,31,33–35,37–42,48,53,58,61,65,66,68–70], but also polysulphone [6,23,26,30,31,36,43,49–51,57] or polyamide [32,44,46,47,51,55,56,58,70] filters have been used. In some studies the type of filter prescribed was not indicated.

Values for mean age are available from all but three trials [37,45,63] and ranged between 38 years [62] and 73 years [41]. Mean APACHE II scores were available from 12 studies only [9,24,25,33–35,39,58,59,61,64,66]. The reported values were between 21 [46,59] and 33 [39]. Mortality rates were given in all but six [43,45,52,56,57,59] publications. These values ranged from 44% [31] to 100% [50].

Data from the 52 studies without a control group were pooled together with data from the continuous groups of the 15 studies with a control group discussed above (Table 1) in order to analyse the influence of patient age, APACHE II score and investigation year on patient mortality using the same logistic regression analysis as described above. When the mortality rate was analysed as a function of the year a trend to a steady decline was observed ($P<0.08$) (Figure 2). The APACHE II scores and the mean age of the patients did not change during the observation period. However the above defined quality factors of treatment increased as a function of time (Figure 2). For the calculation of these quality factors the following number of studies (year) could be considered: For the quality factor

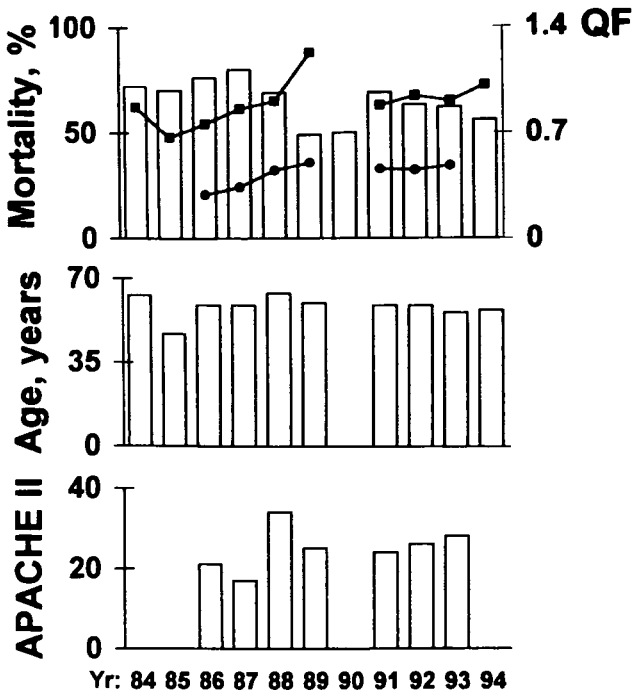

Fig. 2. Mortality rates, mean age and APACHE II scores from 1984 to 1994. Included are all published studies about treatment with a continuous modality of renal replacement therapy (number of patients: 2511). There is a trend to lower mortality rates in recent years, whereas mean age and APACHE II scores did not change. In the upper part of the figure the quality factors (QF) of treatment are shown. When considering age (-■-) or APACHE II scores (-●-) for the calculation of the quality factor a steady increase with time ($P<0.001$) was observed for both parameters.

derived from mean age and mortality 16 (1991), 11 (1993), 8 (1988), 5 (1992), 4 (1989), 3 (1984, 1987), 2 (1986, 1994), 1 (1985), 0 (1990) and for the quality factor derived from mean APACHE II scores and mortality 7 (1993), 3 (1988, 1991, 1992), 2 (1989), 1 (1986, 1987), 0 (1984, 1985, 1990, 1994) respectively.

Conclusions

There is a steadily increasing pressure on the medical community in the western world to demonstrate improving quality of patient treatment. With respect to the treatment of ARF the difficulty to prove unequivocally a decreasing mortality rate over the last decade might be due to methodological problems, because the number of patients treated within a centre was relatively small, the case mix was heterogenous, and the treatment modality as well as the experience of the care providers changed as a function of time. As shown in the present review, a meta-analysis cannot be performed since not enough information about the various studies is available. In an attempt to get some qualitative information about the changes in the outcome all available studies using continuous forms of RRT have been pooled and the outcome analysed. This approach cannot exclude a publication bias and therefore the results have to be interpreted carefully. Within the

limitations of this approach one can conclude that the quality of treatment improved as a function of time when the outcome determinants age and APACHE II score are used to correct for the changing patient population.

In a recent editorial about continuous and intermittent haemodialysis for acute renal failure on the intensive care unit Van Bommel [71] concluded that final proof for the superiority of continuous blood purification techniques to improve outcome in ARF has not been provided until now. That conclusion is supported by the detailed analysis of the literature presented in this paper. It is reassuring how many comparative trials have been performed in that field; however, it is surprising how incomplete these studies are when randomization, description of the patient population investigated, and assessement of therapeutic end-points are considered (Table 1). Furthermore, economic endpoints have virtually never been assessed in these studies. If in the future no advantage for the patients with respect to survival rate can be found when a continuous instead of an intermittent RRT is used, the sum of expenditures for material and labour might ultimately be pivotal for choosing the type of RRT. Thus, future studies designed to investigate the impact of the treatment modality on patient survival rate should comprise an economic assessement.

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