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Monday May 30, 2005

17:00-17:45

Room H

INTRODUCTION

Many intensivists share the opinion that acute renal failure (ARF) presents a rather harmless complication, because renal function can easily and practically indefinitely be replaced by modern renal replacement modalities. This view of ARF must definitely be questioned and possibly refuted as our understanding of ARF has fundamentally changed during the last few years [1]. Several investigations have clearly shown that ARF presents a condition which exerts a fundamental impact on the course of disease, on the evolution of associated complications and on the prognosis, independent of the type and severity of the underlying disease [2]. In the initial stages of ARF the kidneys can be considered as the “victims” of a systemic disease process such as shock or sepsis. Once ARF is established and uraemia has developed, then the kidneys become “offenders” due to the negative effects that pronounced uraemia has upon all organ systems. It must be stressed that ARF is not a problem confined to the kidneys but that the acutely uraemic state has negative consequences for practically all physiological functions, and on all organ systems.

TABLE 1. PATHOPHYSIOLOGICAL CONSEQUENCES OF ARF (EXAMPLES) [1]

| System | Effect of ARF |
|------------------|--|
| Cardiovascular | Hyperdynamic circulation, cardiomyopathy, pericarditis |
| Pulmonary | lung oedema, alveolitis, pneumonia, pulmonary hemorrhage |
| Gastrointestinal | impairment of motility, erosions, ulcerations, hemorrhage, pancreatitis, colitis |
| Neuromuscular | neuropathy, myopathy, encephalopathy |
| Immunological | impairment of humoral and cellular immunity and immunocompetence |
| Haematological | anemia, hemorrhagic diathesis |
| Metabolic | insulin resistance, hyperlipidaemia, activation of protein catabolism, depletion of antioxidants |

Thus, we have to recognize that ARF is not a negligible but rather an ominous complication which, in spite of the potency and availability of modern renal replacement modalities, exerts a profound effect upon morbidity and mortality. ARF is a dangerous condition, the patients do not, as usually is assumed, die with but rather (at least in part) of ARF [3].

This novel understanding of the importance of ARF in ICU patients has several crucial clinical implications [1]. In patient groups at risk of developing ARF preventive measures must be implemented systematically and early to avoid the evolution of renal dysfunction, as avoiding ARF is of the utmost importance. The “sacrifice” of kidney function in favor of other organ systems, especially pulmonary function to improve gas exchange in critically ill patients has to be viewed as a questionable practice. Moreover, if ARF has developed then we have to try to optimize renal replacement therapy in order to minimise the negative repercussions of the acutely uraemic state. In this respect the timing and dosage of extracorporeal renal replacement therapies has been shown to play an essential role.

In this Update on Haemofiltration I want to focus briefly on the timing and the intensity of therapy, but will also discuss citrate anticoagulation, which is increasingly used during continuous renal replacement therapies (CRRT).

THE TIMING OF START OF EXTRACORPOREAL THERAPY

Until recently, the criteria for initiation of a renal replacement therapy in a patient with ARF were similar to those employed in patients with chronic renal failure. However this practice is far from appropriate for patients with ARF. Renal replacement therapy has to be initiated earlier to avoid the development of an acute uraemic intoxication with the many associated side effects.

Unfortunately, few studies have systematically assessed this aspect of treatment for patients with ARF. In a retrospective study in patients on CRRT, Gettings and coworkers have shown that “early starters” (mean BUN 43 mg/dl) had an improved survival as compared to “late starters” (mean BUN 95 mg/dl)(20% vs. 39%, $p < 0.041$)[4].

Similarly, in the study by Claudio Ronco et al on the optimal dose of continuous haemofiltration (CVVH) it was shown that in patients in whom therapy was started early (as assessed by urea concentration at start of therapy) survival was improved [5].

A study published in 2002 by Bowman and coworkers did not support these findings. However, survival in the patients investigated was excellent (70 % and more), and patient selection probably does not reflect the usual case mix in an ICU [6].

Thus, it is reasonable to assume that renal replacement therapy should be initiated before an acute uraemic intoxication has evolved and the potentially untoward systemic side effects can become apparent. Certainly, we should start earlier than has previously been assumed as practice has until now, been based upon the way we treat patients with chronic renal failure.

It must be stressed, that the decision to start a CRRT must be individualized and should integrate various aspects of the patient’s condition, the volume state, haemodynamic and respiratory situation and should not only be based on laboratory parameters such as BUN or creatinine. Usually, the sicker the patient, the earlier RRT should be begun.

TREATMENT DOSE

Similarly, the dose of extracorporeal treatment in ARF must be adjusted so that the systemic consequences are mitigated. Previous practice again was often similar to the strategies used for chronic renal failure. Generation of uraemic toxins in the hypercatabolic patient with ARF can be assumed to be several times higher than in a metabolically stable patient with chronic renal failure. Even in chronic renal failure patients there is ongoing discussion as to whether the dialysis dose should be increased (daily dialysis, over-night dialysis). It can be taken that ARF patients whose dosing is prescribed upon this basis, are being under treated and need a much increased dose of extracorporeal treatment.

In patients with ARF there is an additional problem. They often do not even receive the therapy dose prescribed because of frequent problems encountered in critically ill subjects, such as catheter problems, haemodynamic instability, and the need to perform diagnostic procedures or surgery, all of which mean interrupting therapy [7]. So, often patients on “continuous” therapy receive a lesser treatment dose than a patient on intermittent modalities, or what has been prescribed.

In a study with intermittent haemodialysis in patients with ARF Schifffl et al have convincingly demonstrated that an increase in dialysis dose has a major impact on morbidity and mortality of patients with ARF [8]. A protocol of, what is considered routine, thrice weekly haemodialysis (mean weekly Kt/V of 3.0) was compared with daily haemodialysis (mean weekly Kt/v 5.8). The higher dialysis dose was associated with a lower frequency of complications, such as oliguric ARF, SIRS, sepsis, respiratory insufficiency, coma, and gastrointestinal hemorrhage. There was also a more rapid restoration of renal function and a remarkable improvement in prognosis.

Similarly, Ronco and coworkers have shown that for continuous haemofiltration in critically ill patients with ARF, that an increase in the dose of therapy (i.e. the filtration volume) from 20 ml/kg/h (approximately 1.3 l/h) to 35 ml/kg/h (approximately 2.3 l/h) results in a better survival rate [5]. Interestingly, a further increase in filtration volume to 45 ml/kg/min did not have an additional effect on prognosis.

Again, this has not been uniformly confirmed by all studies. The above mentioned study by Bouman showed that there was no significant influence of the filtration volume (48 vs about 20 ml/kg/h) on survival; however, prognosis was worst in patients on early low volume filtration [6]. A study from Dusseldorf published by Brause and coworkers in 2003 again showed there was no survival advantage in the group with higher filtration rates [9]. In this investigation, the filtration volumes were inadequately low (1 and 1.5 liters/hr only) in both groups, and so a clear-cut difference was hardly to be expected.

To summarize this point, both the pathophysiological considerations and quite convincing clinical evidence support the concept that treatment dose does matter, has an impact on morbidity and mortality and that a higher dose compared to chronic renal failure has to be prescribed.

CITRATE ANTICOAGULATION

From a clinical point of view probably the most relevant obstacle and limitation of CRRT in the ICU patient is the need for a continuous anticoagulation. Filter clotting continues to present a rather annoying aspect of these therapeutic modalities. On the other hand bleeding complications continue to be relevant for patients at risk of haemorrhage, which is often the case in ICU patients. There is no ideal method of anticoagulation for these high risk patients. Prostaglandins have some promising potential (which should not be viewed only as anticoagulants because they also exert many other potential beneficial actions, such as on the microcirculation). Regional anticoagulation using heparin and protamine should not be used in continuous treatment modalities because of unpredictable effects on coagulation during prolonged use.

Citrate presents a potentially very promising method of anticoagulation. Citrate anticoagulation has been in use for intermittent haemodialysis therapy for many years. We have shown excellent anticoagulation using citrate as compared to conventional and low-molecular weight heparin, confirmed by looking at the blood-filter membrane interaction utilising scanning electron microscopy [10].

TABLE 2 . ADVANTAGES OF CITRATE ANTICOAGULATION

- PERFECT quality of anticoagulation (long filter life)
- REGIONAL, extracorporeal anticoagulation with (practically) no systemic effects
- excellent BIOCOMPATIBILITY (inhibition also of cellular components)
- low COMPLICATION RATE (?)
- low COSTS
- easy PERFORMANCE MONITORING

The advantages of citrate (table 2) are that the excellent quality of anticoagulation possible, results in a long filter life and that it is possible to anticoagulate the extracorporeal circuit alone, avoiding any anticoagulation in the systemic circulation and thus minimizing the risk of bleeding complications. There is however a further important advantage: Calcium is also necessary for activation of cellular elements of blood, such as leucocytes and platelets. During citrate induced hypocalcaemia these cellular elements are not activated in the extracorporeal circuit. Thus, citrate anticoagulation is also associated with a dramatic improvement of the biocompatibility of the extracorporeal circuit [11]. During the last decade citrate anticoagulation has also become available for CRRT. Essentially three types of citrate anticoagulation are used for CRRT:

- a. Infusion of concentrated citrate (usually 4 %) to a conventional set-up. This often employed practice should be discouraged because of the excessive load of sodium and base equivalents associated with this procedure.
- b. Infusion of concentrated citrate and the use of an adapted, low sodium and low lactate substitution fluid. This concept is currently the standard in many US centers [12,13].
- c. Use of a citrate based substitution fluid (exchange of lactate by sodium). This is the most simple and potentially the best type of citrate anticoagulation but unfortunately, the appropriate substitution fluids have not become generally available [14-16].

Potential complications of citrate anticoagulation include hypocalcaemia, if calcium is not adequately substituted, metabolic alkalosis, a positive sodium balance and hypomagnesaemia (because citrate not only complexes calcium but also magnesium).

A further disadvantage is the need for a tight monitoring of ionized calcium and the acid-base balance of the patient which should not be a limitation in ICUs. Most modern blood gas analyzers are able to measure ionized calcium.

Are there limitations to the use of citrate in certain patient groups? Clearance of citrate is impaired in presence of hepatic dysfunction but not in ICU patients without hepatic failure [17]. Thus accumulation (which can be detected by increasing gap between total and ionized calcium concentration) should not be a problem in the absence of hepatic dysfunction.

CONSEQUENCES FOR TECHNICAL DEVELOPMENTS OF CRRT MACHINES

These new aspects in the intensity of therapy and citrate anticoagulation will also have an impact of the further development of CRRT machines for critically ill patients. Modern machines for CRRT should enable blood flow rates up to 300 ml/min to achieve the required fluid turnover rates. If the machines should be optimally adapted to citrate anticoagulation, the pumps for blood and substitution fluid should be electronically connected (changes in blood flow should be paralleled by automatic adaptations in the infusion rate of the citrate based substitution fluid). For the future, on-line calcium measurement should become available to facilitate the monitoring of this promising type of anticoagulation.

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