High-frequency external muscle stimulation in acute kidney injury (AKI): potential shortening of its clinical course

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Abstract. Background: The prognosis of acute kidney injury (AKI) is markedly influenced by the degree of muscle protein catabolism. Since the current therapeutic strategies are rather limited, for the first time, we attempted to attenuate the hypercatabolism by high tone electrical muscle stimulation (HTEMS) in AKI patients. This kind of therapy may lower protein degradation via its effect on muscle activity as well as improving insulin resistance. Moreover, electrotherapy may improve renal function due to circulatory effects as well as lowering the sympathetic tone. Methods: 34 patients with AKI Stage 3 were included; all required daily hemodialysis with a dose of Kt/V urea > 1. The patients were randomized into two groups of 17 patients each with and without HTEMS. The groups were comparable with regard to age, gender, underlying diseases, causes of AKI and the baseline biochemistry. HTEMS was performed intradialytically for 1 h. This new electromedical device is characterized by changes in the carrier frequency between 4,100 and 33,000 Hz in short intervals and also the amplitude and frequency are modulated simultaneously. Results: The treatment was well tolerated and associated with an improved clinical outcome. As compared to the untreated patients the HTEMS group showed a significant shorter duration of oliguria, a faster decline of serum creatinine and urea levels, less need of dialysis treatment and a shorter period of hospitalization. The decline of urea was more marked than that of serum creatinine resulting in a significant lowering of the urea/creatinine ratio. This finding suggests a reduced catabolism of muscle proteins which – via a lower release of amino acids into the circulation – results in a decline of hepatic ureagenesis. We hypothesize that in our AKI patients the improved protein catabolism contributed to the shortening of the clinical course of acute renal failure. Conclusion: This study suggests for the first time that HTEMS treatment of patients with AKI during hemodialysis is associated with an improved clinical outcome. To support this novel observation, a randomized controlled trial with a greater number of more homogenous AKI patients should be performed.

Introduction

Acute kidney injury (AKI) is a complex and heterogeneous disorder and occurs in about 5 – 7% of hospitalized patients [1, 2]. In general the mortality of AKI is markedly enhanced if renal replacement therapy is necessary, in particular on intensive care units [3]. However, also slight increases of serum creatinine are associated with increased mortality [4]. The poor outcome is largely due to dysfunction of extrarenal organs such as the heart, liver, lungs and brain [5]. These complications are caused by distant effects of the damaged kidney, the multitude of uremic toxins, superimposed illnesses and/or in the context of multi-organ failure [6, 7, 8, 9, 10].

Biochemical mediators of the bad prognosis are inflammatory cytokines (in particular TNF-α and IL-1), chemokines (MCP-1, IL-8) [11] and reactive oxygen molecules [12, 13, 14]. The plasma concentration of oxidation and nitrogen free products is markedly elevated [15]. In addition, perturbations of the protein, carbohydrate and lipid metabolism constitute a major cause of death [16]. Protein hypercatabolism is a hallmark of the changed metabolic milieu [17, 16, 18] and associated with an excessive release of
amino acids from the muscle [15, 19]. Due to the concomitant suppressed protein synthesis, muscle wasting and a negative nitrogen balance develop. The amino acids released into the circulation are extracted and converted by the liver resulting in an augmented ureagenesis and gluconeogenesis [17, 20]. There is also a stimulated hepatic formation of acute phase proteins, while the synthesis of other proteins is lowered [21].

In the pathogenesis of hypercatabolism, insulin resistance plays a central role [21, 22]. Furthermore, the enhanced formation of catabolic hormones (catecholamines, glucocorticoids and glucagon) and the decreased synthesis of growth factors as well as of 25 (OH) vitamin D3 are involved [18]. Other major factors are uremic toxins, an increased proteolytic activity (23) and metabolic acidosis [24]. Last but not least, the renal replacement therapy stimulates muscle and whole body protein loss [25].

In AKI the blood glucose concentration is frequently elevated and the severity of hyperglycemia correlates with mortality [22]. Disturbances of lipid metabolism include elevated levels of triglycerides and VLDL in the presence of lowered total and HDL cholesterol [26].

The therapy of AKI-associated hypercatabolism is based in particular on an optimal nutritional support and tight glycemic control [18] as well as intermittent or continuous renal replacement therapy. However, the outcome of the patients is still rather poor. Therefore new therapeutic strategies are a challenge. One possibility could be an intervention at the muscular level. It is well known that physical exercise (via enhanced synthesis of proteins and attenuation of protein degradation) increases muscle mass and strength, improves insulin sensitivity and exerts anti-inflammatory effects [27, 28]. For this reason, in maintenance hemodialysis (MHD) patients, aerobic and resistance exercise is generally recommended with great success [29, 30]. However, in the severely ill AKI patients active exercise is mostly impossible. An alternative could be electrical neuro-muscular stimulation which has been shown to be effective in healthy sedentary adults [31] and in patients with congestive heart failure [32]. Electrical muscle stimulation (EMS) by TENS (transcutaneous electrical nerve stimulation) is performed either in the low frequency range (1 – 10 Hz) or at higher frequencies (80 – 120 Hz) resulting in strong muscle contractions. The favorable effects on the muscle is also caused by an improved insulin resistance [33]. In contrast to TENS the new high tone external muscle stimulation (HTEMS) induces extremely high frequencies ranging from 4,100 to 33,000 Hz which is only associated with vibrations and microcontractions of the muscle fibers and well tolerated. HTEMS, as well as TENS improves the insulin resistance as shown by a lowering of HbA1c and improved HOMA-IR index in obese diabetic subjects [34].

The various forms of electrotherapy additionally modulate the local and possibly the systemic microcirculation. TENS increased the blood flow in the intact skin as well as of chronic ulcers of the lower legs [29]. Impressive circulatory effects were observed after chronic spinal cord stimulation in patients with severe coronary heart disease [35] as well as in critical lower limb ischemia [36]. Also HTEMS of the thighs increase the blood flow of the lower limbs [37]. In line with these circulatory effects, HTEMS of the thighs enhances glomerular filtration rate and fractional sodium excretion in healthy subjects [53].

The mechanisms behind the EMS-induced circulatory effects are largely unknown. Beside an enhanced NO production, increased formation of adrenomedullin-2 (intermedin) in skin cells could be involved. This peptide which is a potent vasodilator with reno- and cardioprotective properties [38] is down-regulated in damaged kidneys [39].

In light of these potentially favorable effects of electrical stimulation of muscle metabolism, microcirculation and possibly renal function, we examined in a pilot study the potential influence of HTEMS therapy on the clinical course of AKI patients.

Material and methods

Study population

The study was approved by the Ethics Committee of the University of Naples and conducted in accordance with the current version of the Declaration of Helsinki.
All participants gave their written informed consent prior to the study. We included 34 patients with AKI. According to the new grading system of the Acute Kidney Injury Network (AKIN), they fulfilled the criteria of AKI Stage III [40, 41]. Their characteristics (Table 1a) and blood chemistry data (Table 2b) are presented. The patients were dialyzed daily and the delivered dose, as measured by Kt/V urea, was > 1 according to the current recommendations [42].

Patients were randomized for age, sex and presence of diabetes. They were divided into two groups: treated and non-treated with HTEMS therapy. All patients were oliguric (urine flow < 300 ml/d). Both groups were comparable with regard to the underlying diseases, the causes of AKI and the basal biochemistry data (Table 2a, b). They showed a high rate of heart failure (NYHA > III in 14 treated and 10 untreated patients). Moreover, the incidence of diabetes mellitus Type 2 was rather high (12 vs. 9). A positive history of hypertension was reported in 16 treated and 15 untreated AKI patients.

**Causes of AKI**

Among the causes of AKI nephrotoxic drugs played the major role (Table 2a), 7 patients in the treated and 9 patients in the untreated group. Furthermore, heart failure was a frequent cause of AKI (5 times in the treated and 3 times in the untreated group). In 2 cases of both groups, AKI was induced by dehydration due to acute gastroenteritis. In 3 cases AKI was caused by toxic epidermal necrolysis due to allopurinol.

**Dialysis modalities**

All patients were treated with daily hemodialysis until urine flow was > 700 ml/d
Thereafter intermittent hemodialysis was performed until renal function recovered to Stage 4 of renal impairment (eGFR 15 – 29 ml/min). Hemodialysis sessions were performed over 4 hours with HemoFlow using polymethylacrylamide membranes, surface area 1.6 – 2.0 m². The blood flow averaged 250 ml/min. The dialysate fluid had the following electrolyte concentration: sodium 140 – 145 mmol/l, potassium 2 – 4 mmol/l according to plasma potassium, calcium 1.5 mmol/l and bicarbonate 28 – 30 mEq/l.

**Blood chemical analysis**

Measurement of serum creatinine, urea, uric acid, electrolytes, C-reactive protein (CRP) and albumin was performed by autoanalyzer (Olympus AU 400; Olympus, Italia, Segrate, Italy) and hemoglobin by Coulter counter (Coulter Electronic, Hialeah, FL, USA).

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**Intervention by high tone electrical muscle stimulation**

HTEMS was performed with a HiToP 184 appliance (gbo Medizintechnik, Rimbach, Germany), which is a 230 V. power supply device. In this new electro-medical approach, the frequency varies in short intervals between 4,100 and 33,000 Hz. Another novelty of this method is the fact that the amplitude and electrical frequency are modulated simultaneously. For the therapy, the electrodes were placed around the femoral muscles and in some cases, on the calves as well (Figure 1). HTEMs was performed for one hour during each hemodialysis treatment. The intensity of electrical stimulation was adjusted to suit the comfort level of each individual patient without producing discomfort or pain.

HTEMS currently is widely used in pain treatment of patients of diabetic and uremic polyneuropathy and is well tolerated [43, 44, 45].

**Additional treatment**

To promote diuresis loop diuretics were administered in form of intravenous furosemide in a dose of 0.75 ± 0.3 mg/kg/body weight/d.

In the case of severe acidosis, bicarbonate was administered in a dose to achieve a serum bicarbonate level of about 22 mEq/l.

**Urea generation**

Urea generation (G) was calculated according to Casino and Marshall [46].

\[
G = \frac{V_d \times C_{0(\text{Next})} - V_i \times C_0}{T_i} + K_f \times \frac{C_{0(\text{Next})} + C_0}{2}
\]

\(C_{0(\text{Next})}\) is pre-dialysis BUN for the following treatment, \(V_{0(\text{Next})}\) is pre-dialysis urea distribution volume for the following
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treatment, CEQ is the equilibrated post-dialysis BUN concentration, and TD and TI are the intradialytic and interdialytic duration, respectively. As with all urea kinetic algorithms, G is extrapolated to the preceding dialytic interval, so that a total net urea generation per cycle (Acy) can be computed: Acy = (G × (Td+T1)). The weekly total generation (AWk) is then calculated by simple addition:

\[ \text{Awk} = \text{Acy}_1 + \text{Acy}_2 + \text{Acy}_3 + \ldots + \text{A LAST (n)} \]

CEQ is estimated using the method of Tattersall et al. [33]:

Protein catabolic rate (PCR) was obtained to the generation of urea according to the following formula (46):

\[ \text{nPCR} = \frac{(9.35 + G + 0.294 \times \text{Vt/1000})}{(\text{Vt/580})} \]

However these methods are problematic in the critically ill AKI population since G requires that the urea of the patient is in steady state [46].

Statistics

All values are reported as means ± SD unless otherwise specified. Analysis of variance (ANOVA) was used to compare the two groups. Variable significance was defined as p < 0.05.

Results

No patient died in both groups. Treatment with HTEMS during the hemodialysis session was well tolerated and associated with an improved clinical course of renal failure. Compared to the untreated patients, the HTEMS group had a significant shorter duration of oliguria (13.4 ± 7.7 vs. 19.6 ± 9 d), need of dialysis treatment (14.1 ± 9.3 vs. 20.8 ± 10.1 d), and duration of hospitalization (17.4 ± 8.6 vs. 26.5 ± 11.1 d) (Figure 2).

The duration of oliguria was shorter in the HTEMS as compared to the untreated hemodialysis patients, although the daily dose of furosemide was the same in both groups. Administration of the diuretic was stopped when urine flow was > 800 ml/day.

In Figure 3 and 4 the time course of serum creatinine and urea concentrations are shown. As compared to the untreated group a faster decline of both parameters in the HTEMS treated patients was observed, which was significant after 1 week of therapy. Interestingly, the decline of urea was more marked than that of creatinine. Thereby the urea/creatinine ratio was reduced (Figure 5). From a comparable baseline value of 46.9 ± 12.6 in the HTEMS group and 46.8 ± 11.9 in the untreated group the treated patients displayed a reduction to 31.8 ± 11.1 after 2 weeks, as opposed to 40.6 ± 10.7 in the untreated group.

On admission to the hospital the metabolic acidosis was similar in both patient groups: 15.2 ± 2.6 mEq/l in HTEMS group and 16.0 ± 2.5 mEq/l in no HTEMS group (p = NS). Patients of the HTEMS group received 66 ± 18 mEq/day of bicarbonate for 4 – 6 days while no HTEMS group received 72 ± 21 mEq/d of bicarbonate for 8 – 10 d. Altogether HTEMS patients received 330 ±
70 mEq of bicarbonate and the no HTEMS patients 648 ± 70 mEq (p < 0.0001).

Urea generation was 4.1 ± 1.1 g/d in HTEMS Group (corresponding 0.70 g/kg/d in Protein catabolic rate) and 5.3 ± 1.2 g/d in No HTEMS Group (corresponding 0.82 g/kg/d in Protein catabolic rate) (p < 0.005 for urea generation). These measurements were performed on the 3rd day of hospitalization.

Nutritional support due to anorexia and nausea was necessary for 3 – 5 days in 7 patients in the HTEMS and 8 patients in the no HTEMS group. These patients received 30 – 35 kCal/kg/d, with lipids (40 g/d) and essential amino acids (44 g/d).

Discussion

The evolution of AKI is classically divided into three phases: the initiation, the maintenance and the recovery phases. Recently, a fourth phase (the extension phase) has been described between the initial and maintenance phases [14]. According to Schrier et al. [47] an attenuation or prevention of AKI can only be achieved if the therapy starts before the insult as has been shown e.g. in radiocontrast-induced AKI. An intervention after the ischemic or nephrotoxic insult does not alter the clinical course and the high mortality.

To the best of our knowledge, only one study so far investigated the effect of electrotherapy on established ischemic renal failure in rats [48]. In this study, electrotherapy with Rebox apparatus was performed directly on the ischemic kidney at a frequency of 1 – 10 kHz. The results showed a significant enhanced diuresis and sodium excretion, however, without improving the clinical course. In contrast to this experiment, in our patients with AKI, electrical stimulation of the thigh muscle was performed during the daily hemodialysis treatment. The results of this pilot investigation suggest that the recovery was accelerated by HTEMS treatment. The mechanism of this favorable action is entirely unknown. Our hypothesis deals with the concept of an attenuated protein catabolism which is supported by the decline of the urea/creatinine ratio in serum of the active treated group. This finding could indicate a lower hepatic ureagenesis as consequence of a decreased muscle protein catabolism resulting in a smaller release of amino acids into the circulation. Of course, the urea/creatinine ratio is a weak parameter of muscle catabolism and depends also on other factors, such as the nutritional protein intake and the fractional urea excretion. As far as we could evaluate our patients, the dietary protein intake was not different between both groups. For evaluation of the protein catabolism measurement of urea nitrogen appearance (G) was performed. In the HTEMS Group G was lower than in the no HTEMS group 4.1 ± 1.1 g/d and 5.3 ± 1.2 g/d respectively (p < 0.005). However, in AKI patients these measurements are less reliable due to the missing steady state of urea. Moreover, determinations of pro-inflammatory cytokines and parameters of oxidative stress would be helpful in the evaluation of the different response in both groups.

Besides the potential effects on protein break-down, it is conceivable that HTEMS therapy could increase the renal perfusion rate and its excretory function as suggested by the
recent findings of an increased GFR as measured by creatinine clearance [53]. These observations are so far of interest, since in the pathogenesis of intrinsic or toxic AKI, an intensive and persistent renal vasoconstriction plays a key role of its manifestation [49]. There is clear evidence of a reduced renal blood flow, in particular of the outer medulla in AKI. This results in damage of tubular regions with a very high energy requirement such as the thick ascending limb and the S2 segment of the proximal convoluted tubule, as well as of endothelial cells [49]. Surprisingly, normalization of the impaired renal blood flow during the maintenance phase of AKI by systemic or intrarenal application of a vasodilator (dopamine) did not reverse the experimental or clinical outcome of AKI [50]. Among other factors, this missing effect could be a consequence of tubular obstruction due to cast formation in the distal nephron – an important maintenance factor of AKI [50]. An additional explanation could be the genotoxic action of dopamine [51] which prevents the beneficial action on the clinical course despite its vasodilatory effect. Another potential effect could be a consequence of a sympotymatic action of electrotherapy as demonstrated by Sanderson et al. [52].

The present study is limited by various factors: 1) the small and heterogeneous sample size, 2) the different causes of AKI, 3) missing determination of parameters of inflammation and oxidative stress and 4) measurement of muscle volume of the thighs by computer tomographic scan in the course of AKI in the treated and untreated group.

Summarizing the results of our study suggest that HTMEMS in AKI patients during the daily hemodialysis treatment improves the clinical outcome, probably via an attenuated muscle protein break-down and possibly an improved renal function. To confirm this novel observation of a shortening of the clinical course of AKI by electrotherapy with treatment (without relevant side effects) recommends performing a large controlled clinical study in more homogenous AKI patients.

Conflict of interest

B. D. I received lecture honoraria from Genzyme. No conflict of interest was present in the preparation of this manuscript. A. H. received honoria from gbo.

References


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