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Using ultrapure water in hemodialysis delays carpal tunnel syndrome

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ABSTRACT: Since 1977, our patients have undergone chronic HD with ultra-pure dialysate (UPD), defined as having endotoxin levels below 0.008 ng/ml and less than 1 bacteria/ml of dialysate. We evaluated the incidence of carpal tunnel syndrome (CTS) in three groups of patients. Group I (GI), 84 patients, dialysed for 6.1 ± 3.2 years (mean ± SD) with UPD only; Group II (GII), 39 patients, first dialysed for 3.7 ± 2.3 years with non-UPD and afterwards for 8.4 ± 2.1 years with UPD; Group III (G III), 103 patients treated for 6 ± 5.9 years exclusively with non-UPD. All patients were dialysed with cuprophan or cellulose acetate membranes.

Results, expressed by Kaplan-Meier actuarial survival curves as the percent of patients without CTS, show that CTS occurred significantly less in GI than in GIII. This may be due to less stimulation of monocytes resulting from the absence of bacteria, endotoxins and pyrogens in the dialysate which would reduce the stimulation of cytokines release, interleukin 1 and 6, and tumor necrosis factor, known to stimulate β2 microglobulin synthesis. (Int J Artif Organs 1991; 14: 681-5)

KEY WORDS: Carpal tunnel syndrome, Hemodialysis, β2 microglobulin, Amyloidosis, Ultrapure dialysate

INTRODUCTION

Carpal tunnel syndrome (CTS) is a common complication in patients treated by hemodialysis (HD) for a long period (1-4). Compression of the median nerve is a consequence of amyloid material deposits derived from β2 microglobulin (β2M) (5). The prevalence of CTS in hemodialysed patients is about 30% after nine years (4) and nearly all patients treated for more than 15 years suffer from this syndrome (6).

The pathogenesis of CTS is debated: it is partly by the consequence of accumulation of B2M during hemodialysis with cellulosic membranes (5). Recently (7, 8) it was proposed that B2M accumulation might also be the consequence of repeated stimulation of monocytes by bacteria and pyrogens in the dialysate. The present study evaluated the impact of the use of ultrapure dialysate (UPD) for a long period on the incidence of CTS.

MATERIALS AND METHODS

Patients

We evaluated the incidence of CTS in 226 patients treated by HD in two hemodialysis centers. Since 1977 ours has been equipped with a UPD production and distribution unit permitting the distribution of UPD. The other center uses conventional individual dialysis material.

Patients were separated into three groups according

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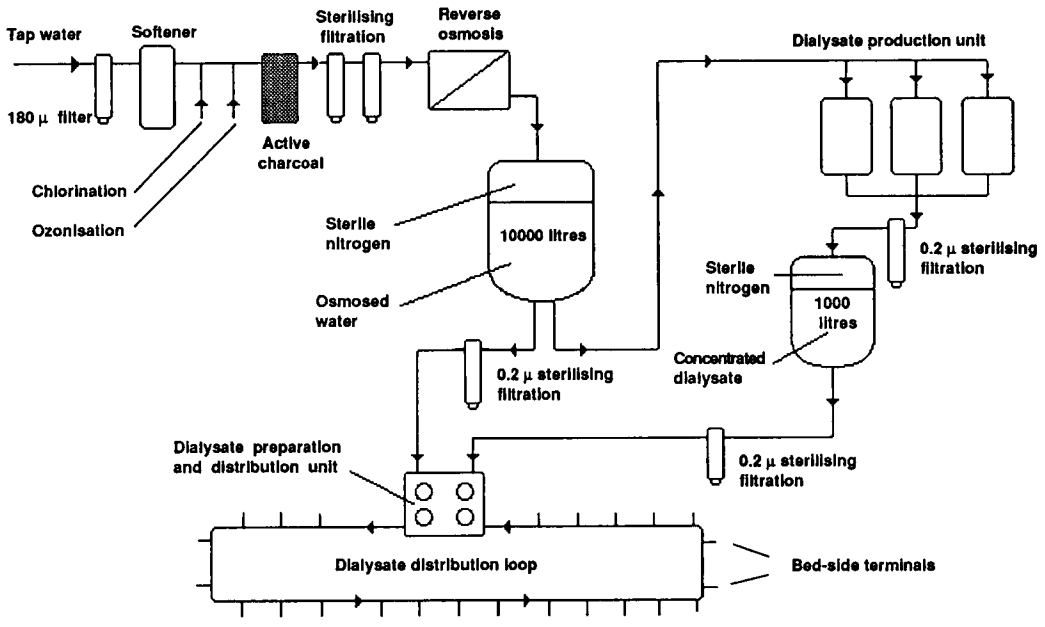

Fig. 1 - *Ultrapure dialysate fabrication and distribution control unit.*

TABLE I - CHARACTERISTICS OF THE PATIENTS IN THE THREE GROUPS AND DURATION OF HEMODIALYSIS TREATMENT WITH ULTRAPURE DIALYSATE (UPD) AND NON-ULTRAPURE DIALYSATE

Group	GI	GII	GIII
Patients	84	39	103
Men	52	20	47
Women	32	19	56
Age (years)	57.5	54.5	58.3
Duration of dialysis (years)			
with UPD	6.1 ± 3.2	3.7 ± 2.3	—
without UPD	—	8.4 ± 2.1	6.0 ± 5.6

to the type of dialysate used for hemodialysis sessions (Tab. I). Group I consisted of 84 patients, with a mean age of 57.5 years (range 27-77 years) treated for 6.1 ± 3.2 years exclusively with UPD in the first center. Group II was composed of 39 patients, with a mean age of 54.5 years (range 28-83 years) also dialysed in the first center but with non-UPD before 1977 and after that with UPD. The last, group III, comprised 103 patients, with a mean age of 58.3 years (range 22-85 years) treated in the second center exclusively with non-UPD.

Methods

All patients underwent 4 to 6 h hemodialysis sessions, twice weekly. Only cuprophan or cellulose acetate membranes were used.

CTS was diagnosed clinically and confirmed by electromyography. Surgery was performed 1 to 12 months after diagnosis. Amyloidosis deposits were not documented in all patients.

Ultrapure dialysate (UPD): since 1977, UPD has been made in our unit as follows (Fig. 1): tap water is filtered through a 180 μ membrane then treated by a softener, chlorination and ozonisation. Afterwards the water is filtered through charcoal and treated by reverse osmosis before storage under sterile nitrogen atmosphere. Osmosed water is filtered through a 0.2μ sterilising membrane before use.

Concentrate for hemodialysis is prepared with osmosed water and ultra-pure materials, stored under sterile nitrogen atmosphere and kept sterile by a very high ionic concentration (autosterilisation by hyperosmolarity). Concentrate is filtered through a 0.2 μ sterilising filter before use.

Dialysate is prepared by two central units, and distributed by a distribution loop to 32 bedside terminals. Dialysate fabrication and distribution units and all bedside terminals are sterilised daily by

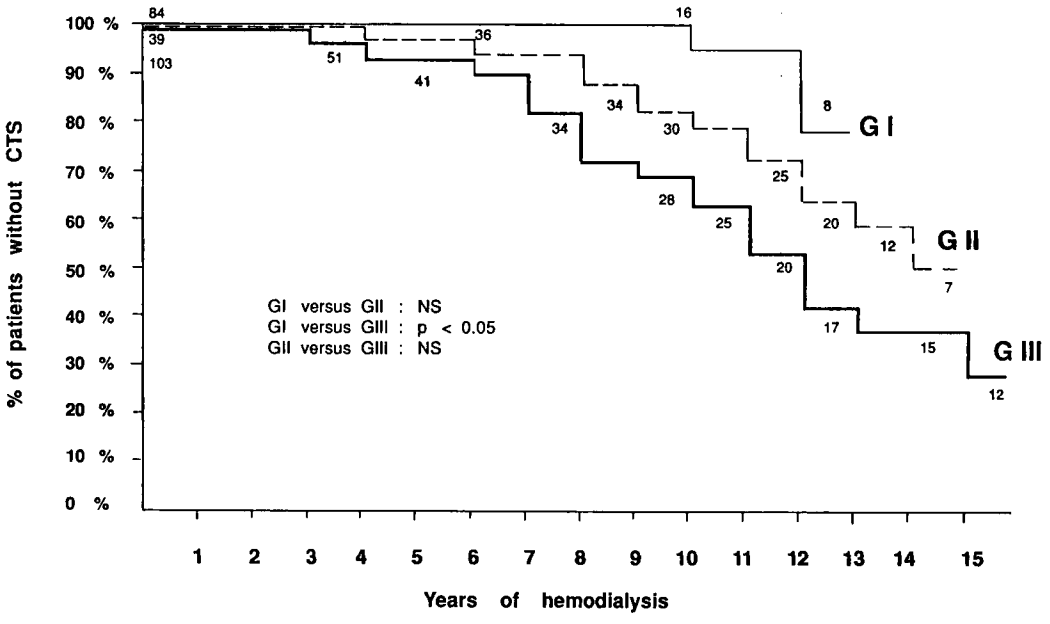

Fig. 2 - *Actuarial occurence of CTS expressed as the percentage of patients without CTS. The occurrence of CTS is significantly lower in group I (GI) than in group III (G III).*

sodium hypochlorite for 15 min, followed by 125°C steam at 1.5 bar for 30 min before rinsing with osmosed water.

Endotoxin levels never exceeded the sensivity threshold of the Limulus lysate assay (0.008 ng/ml). The bacterial control showed less than 1 colony/ml of dialysate liquid.

Non-ultrapure dialysate: tap water is treated by a softener then by reverse osmosis immediately before use. Concentrate is prepared as described above. Dialysate is prepared individually by a dialysis generator, which keeps it within the limits set by the French standards for endotoxins (< 0.025 ng/ml) and international standards for bacteria (1000 colonies/ml of dialysate).

Statistical analysis: the values are expressed as mean ± SD. The three groups were compared by a log-rank test on the three Kaplan-Meier actuarial survival curves. A p value < 0.05 was regarded as statistically significant.

RESULTS

In group I, treated exclusively with UPD, only two patients developed CTS, in the 10th and 12th year of treatment (Tab. II). In group II, treated with non-UPD then with UPD, 15 patients developed CTS. In group III, treated only with non-UPD, 24 patients presented CTS. Figure 2 shows the Kaplan-Meier actuarial survival curves of CTS in the three groups, expressed as the percentage of patients without CTS. The probability of CTS was significantly lower ($p<0.05$) in group I than in group III.

TABLE II - TIME OF OCCURRENCE OF CTS IN THE THREE GROUPS AFTER THE ONSET OF HEMODIALYSIS

Years	1-2	3-4	5-6	7-8	9-10	11-12	13-14	>15
GI	0/11	0/19	0/15	0/15	1/16	1/8	—	—
GII	0/0	1/4	1/1	2/5	3/3	4/7	2/8	2/11
GIII	0/45	3/10	1/10	6/9	3/3	6/6	0/5	5/5

DISCUSSION

The use of UPD appears to postpone the occurrence of CTS in hemodialysis patients. Dialysis-related amyloidosis has been reported to occur with a higher frequency in the HD population (1-4). Amyloidosis is always associated with increased serum B2M, 10-30 times the normal values (9).

Protein analysis of CTS tissue from biopsies shows there is a high concentration of B2M (5). This accumulation is due to a lack of renal elimination of this molecule, inadequacy of dialysis membrane elimination, and overproduction of β2M by cellulosic membranes and/or dialysate contaminated with bacterial endotoxins.

Floege et al. (6) reported that HD with regenerated cellulosic membranes increased serum β2M by 10-15%. Dialysis with polycarbonate lowers serum β2M by 8% and, with PAN, by 53%. The use of highly permeable AN 69 membranes may prevent CTS (10), while HD with cuprophan membranes retains β2M and may induce an increased production of this molecule (11, 12). Recently, however, Chanard et al. (13) demonstrated that AN 69 prevents the occurrence of CTS but not that of juxta-articular bone cysts.

In experimental conditions, the contact of blood or monocytes with cuprophan led to no increase in β2M concentration (14). *In vivo* dialysis with no dialysate flow confirmed these results (15). These data show that cuprophan adherence of monocytes or macrophages is not a sufficient stimulus of β2M synthesis and release, and that the highly permeable membrane does not suffice to prevent HD-related amylosis. Monocytes, in fact, may be activated during cuprophan HD and then produce β2M, particularly when dialysate is contaminated with bacterial endotoxin (16).

Bacterial products, including endotoxins, induce human monocytes to produce several monokines (IL1, IL6, interferon and TNF) (17, 18). Monocytes produce IL-1 *in vitro* when incubated with endotoxin. Bernick and al. (19) detected no bacteria or endotoxin in the blood compartment during HD with bacteria-contaminated dialysate. Thus the intact cellulosic membrane is considered an effective barrier to bacteria and endotoxin. Bernick (20) investigated the effect of endotoxin recirculation in the dialysate loop on human monocytes. The maximum endotoxin transfer rate through cellulosic membrane was less than 2.5 ng/h; this quantity was not pyrogenic and it was not detectable by the Limulus lysate assay, which has a minimum sensitivity of about 0.015 ng/ml.

Jones et al. (21) detected a circulating antibody to endotoxins extracted from bacteria present in the dialysate during HD. The presence of the antibody was explained by trace amounts of endotoxin passing through an intact dialysis membrane. The transfer of an undetectable amount of endotoxin through micro-ruptures in the dialysis membrane or the passage of endotoxin fractions through the intact membrane, undetectable by the Limulus lysate assay, has been reported by Bingel (22) who considers this sufficient to induce monocytes to release IL1.

Man (23) demonstrated, in experimental conditions *in vitro*, that backfiltration of contaminated bicarbonate dialysate through highly permeable membranes gives a positive pyrogen test with no evidence of endotoxin transfer. Microbiological contamination of dialysate and the increasing use of high-flux membranes cause potentially unsterile dialsyis fluid or pyrogens to enter the patient's blood.

In conclusion, our results show that the probability of CTS is significantly lower in patients treated exclusively with UPD than in those treated with non-UPD. The use of UPD in HD treatment appears to delay the occurrence of CTS thus stressing the importance of UPD in improving the quality of HD therapy. UPD might minimise the production and release of β2M since it allows the use of highly permeable membranes, thus enhancing β2M elimination. The simultaneous use of UPD and highly permeable membranes prevents and delays CTS.

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