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Survey on the Effect of Transmembrane Pressure on Middle Molecules' Excretion in Bicarbonate Base Hemodialysis

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Abstract

Background and Aims: The transmembrane pressure (TMP) is an important factor in removing the molecules during hemodialysis. In this study we explained the effect of ultrafiltration increase on the clearance of middle molecules in the hemodialysis patients of Kashan.

Methods: This clinical trial is a before-after study that was performed on 40 hemodialyzed individuals in 2008. At the first stage, the participants were dialyzed with ultrafiltration equal to the difference of their present weight and their dry weight and in the 2nd stage the ultrafiltration was increased 2 liters and clearance of each solute was mesured in both stages.

Rusults: In the first stage, the amount of reduction in predialysis serum beta 2 microglobulin (beta2M) level was 3.5% (p = 0.05) and in the second stage it was 14.4% (p = 0.001). Excretion of the small molecules (BUN, Cr and P) in the second stage of hemodialysis in comparision with the first stage of dialysis (conventional method) revealed no meaningful change.

In the all previous studies, low flux dialysis membrane had been used in a standard way, and these studies didn't pay attention to ultrafiltration increase but in this research we improved the role of convection in excretion of the middle molecules by ultrafiltration increase through adding TMP. All pores of the low flux membranes are not uniform and unisize. This manufacturing was problem associated with rising hydrostatic pressure through increase TMP help us for removing beta2M with convection.

Conclusions: The results showed that we can increase the amount of excretion of the middle molecules and dialysis capability with increasing the TMP during bicarbonate base hemodialysis through low flux membranes.

Keywords: Hemodialysis, Trans Membrane Pressure, Ultrafiltration, Middle Molecules, Beta 2 mi*croglobulin*

Introduction

Uremic syndrome is identified with the accumulation of poisonous materials that occurs because of the inadequate kidney function. These poisonous materials are classified into three groups: small water-soluble molecules such as urea, Guanidine, phosphorus and oxalate, small lipid-soluble and/or protein-bound-compounds such as p-cresol, indoles, furanopropionic acid,hemocysteine, larger molecules so called middle like Beta2 microglobulin (beta2M), parathyroid hormone, vitamin B12 and advanced glycosylation end products (AGE). Moleculer weight of small molecules is less than 300 daltons and for middle molecules is 300 to15000 Da (1). In

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end stage renal disease (ESRD) patients, dialysis or kidnay transplantation is done for removing uremic toxins. In hemodialysis (HD), the blood of patient comes out through arteriovenous fistula and enters into dialysis system and contacts with semiinfiltrative membrane with dialysis liquid on the other side. Thus, poisons are excreted through diffusion and/or convection from blood of the patient and enter into dialysate. The important point about HD patients is dialysis adequacy. Presently urea is used as a standard index for emiting small molecules and counting in the form of KT/V and urea reduction ratio (URR). That minimum desirable amounts are 1/2 and 65%, in order. This method is not completly efficient for identifying capability of dialysis because urea model only shows removal of small molecules, and it doesn,t consider removing middle molecules that have important role in creating uremic syndrome (2). For the first time, in the middle of 1970, researchers discovered the physio pathologic role of middle molecules (3). The middle molecules with their molecular weight is between 300 to 15000 Da are vitamin B12 (1355 Daltons), beta 2 microglobulin (beta2M) (11800 Daltons), parathyroid hormome and AGE (1). The plasma beta2M concentration is increased in the dialyzed patients ranging from 30 to 50 mg/L much higher than the normal population (4). Studies show that accumulation of middle molecules in long time increases mortality and morbidity. One of the complications of gathering these molecules in the body is dialysis-related amyloidosis (DRA) (5). Because of inaccurate capability of dialysors in complete removal of uremic poisons 90 percent of people that are under dialysis operation show the pathologic finding of DRA after five years (4). Amyloid sedimentation can occur in musculoscleletal system, skin and with fewer spread abroad digestive system, tongue, gluteal region, rectal mucosa, liver, spleen, heart, blood vessels, kidney, testis and lung. Carpal tunel syndrome, bony cysts, spondyloarthropathy, pathologic fractures of bones, swollen and painful joints, periarthritis and destroying scapulohumerous joint are some symptoms of DRA (4, 6-12). Paying attention to the symptoms mentioned above clarifies the importance of using methods that are efficient in removing middle molecules besides small molecules. Up to date there is only one mode of renal replacement therapy available which either prevents the clinical manifestation or arrests the progression of DRA and preserve the normal renal excretory function (13). Different studies have offered different methods such as nightly dialysis (six times in a week, every night eight hours) (4), biocompatible high flux membranes like AN69 (9, 14, 15), hemodiafilteration (16-18), sorbent technology (17), hemodialysis three times a week and eight hours each session (18), peritoneal dialysis (2) for increasing clearance of beta2M and finally decreasing DRA. Base of numerous researches , middle molecules' removal has done only by high flux membranes and risk of DRA is decreased significanty (10, 14, 15, 19). Some researchers beleive that low-flux membranes cannot emit middle molecules because of their small pores (12, 15, 16, 20), but we know that pores of these filters are not uniform and unisize. Some of them are slightly larger or smaller than the standard limit (5, 21). Except for the size of pores, the transmembrane pressure (TMP) is an important factor in removing these molecules(12, 15). In this study we explained the effect of ultrafiltration increase on the middle molecules' removal in Kashan, Iran - 2008.

Note that low-flux membranes are cheaper and more available than high flux membranes in some countries such as Iran, while this is proved that these membranes are efficient in removing the molecules, it is easy to decline complications such as DRA in the hemodialysis patients.

Materials and Methods

Participants

This clinical trial (before-after study) was done on 40 hemodialysis patients who were under

maintenance dialysis for at least five years. The patients who needed urgent hemodialysis or those having an acute and newly onset disease such as infection, acute coronary artery disease or those who needed change in the dose of supportive hemodialysis were excluded from the study. Patients having any evidence of AIDS, lymphoproliferative disorders, and inflammatory disorders such as systemic lupus erythematosus, rheumatoid arthritis and cirrhosis, tuberculosis, chronic osteomyelitis and primary amyloidosis leading to rise in beta2M were also excluded. With these criteria, out of 92 dialysis patients in the ward, 40 agreed to take part in this study.

Apparatus

These patiants were under two stages of hemodialysis. In both the stages, the speed of blood pump (QB=220 cc/min), the speed of dialysis liquid (QD=500 cc/min), the duration of HD (four hours) and dialysis membrane (low-flux poly sulfon), surface of membrane (1.3 m2), the dialysate (bicarbonate) were the same and Gambro AK95 machine made in Sweden was used. We used bicarbonate as a dialysate because compared with acetate, it causes less hemodynamic changes during hemodialysis (5).

Procedures

As mentioned earlier, the patiants were under two stages of hemodialysis; in the first stage, TMP was equal to the difference of the present weight relative to the dry weight. Dry weight of every patient was obtained from the results of previous hemodialysis of the same patient in the same center (5). In the second stage (next session of HD), TMP was adjusted to two litres more than their over weight (relative to dry weight). In other words the TMP at this stage was two litres more than previous stage for each patient, and this extra obtained liquid from patients was compensated with prescribing two litres normal saline during four hours HD session. Before and after each stage, plasma concentration of beta2M, creatinine (Cr), phosphate (P) and blood urea nitrogen (BUN) were measured.

Statistics

We compared the amount of reduction in plasma concentration of beta2M, BUN, Cr and P in both HD stages. Using SPSS version 15.0 and student t-test the data were analyzed and $p<0.05$ was considered significant.

Results

This study was done on 40 patients, 23 men (57%) and 17 women (43%). The average age and weight were 50 9.2 years and 57/2 4 kg, respectively. The mean TMP in the first stage was 3.1 0.3 which was two litres more (5.1 0.3) in the second one. No relationship between age and level of beta2M was seen in this study. In the first stage, the amount of reduction in serum beta2M level was 3.5% ($p = 0.05$) and in the second one it was 14.4% ($p = 0.001$). The findings were shown in table 1 and 2. Excretion of the small molecules (BUN, Cr and P) in the second stage of hemodialysis in comparision with the first stage of dialysis (conventional method) had not a significant change (Cr: $p<0.3$; BUN: $p<0.1$; P: $p<0.9$).

Discussion

The results of this study showed that hemodialysis with low flux polysolfone membranes with increasing TMP in comparision with the conventional HD can decrease the concentration of middle molecules. At the first stage, the amount of reduction in predialysis serum beta2M level was 3.5% ($p = 0.05$) and at the second one it was 14.4% ($p = 0.001$). In contrast Schiff H et al found that the polysulfone membrane eliminates considerable amount of beta2M. This was associated with a sustained reduction of predialysis

Table 1. Pre and post dialysis molecular concentration in the first stage

P value	Amount of reduction	Post dialysis	Pre dialysis	Time / Molecules
0.05	3.5%	1.4 ± 26.2	1.1 ± 27.3	Beta2M (mg/L)
< 0.001	41%	0.3 ± 2.9	1.2 ± 5.1	P (mg/dl)
< 0.001	63.6%	8.8 ± 19.3	10.5 ± 50.2	BUN (mg/dl)
< 0.001	64.5%	0.9 ± 3.1	1.4 ± 8.2	Cr (mg/dl)

Beta2M, Beta 2 Microglobulin; **P**, Phosphate; **BUN**, Blood Urea Nitrogen; **Cr**, Creatinine

serum beta2M levels (20%) (22). In another study that was done 2 years ago, we assesed the effect of ultrafiltration increase in low flux acetate base hemodialysis and could increase beta2M removal. The amount of reduction in beta2M concentration was 7% in the conventional dialysis and 12.1% in HD with ultrafiltration increase (23). In this study, we used bicarbonate as dialysate instead of acetate because bicarbonate causes less hemodynamic changes and acetate may cause vasodilatation (5). Since in the second stage of HD we should get 2 litres more liquid, bicarbonate was considered safer from the point of hemodynamic status. In some studies, removal of middle molecules by low flux filters (filters with finer holes), almost has been reported to be zero (5, 24-26). In a previous study carried out on 89 patiens, the results showed that membranes with high flux capability removed beta2M by adsorption or convection while the entire kinds of low flux membranes were not penetrated into these molecules completely

Table 2. Pre and post dialysis molecular concentration in the second stage

P value	Amount of reduction	Post dialysis	Pre dialysis	Time / Molecules
< 0.001 ⟨	14.4%	2.1 ± 24	1.1 ± 28.1	Beta2M (mg/L)
< 0.001	36.5%	0.8 ± 3.4	0.8 ± 5.3	P (mg/dl)
< 0.001	61.8%	6.9 ± 20	11.1 ± 51	BUN (mg/dl)
< 0.001	62.9%	1.3 ± 3.2	2.3 ± 8.1	Cr (mg/dl)

Beta2M, Beta 2 Microglobulin; **P**, Phosphate; **BUN**, Blood Urea Nitrogen; **Cr**, Creatinine.

(20). Calas in a research in 2000 concluded that standard low flux membranes could not clearup middle molecules, because these membranes act only through diffusion (14). Jeloka et al found that beta2M levels in normal control subjects were 2.6 mg/L while in the patients with chronic renal failure, the levels were 25.6 mg/L. There was a statistically significant fall in the levels of beta2M in those when switching from low flux to high flux HD (26.8 to 25.5 mg/L, p =0.05) as compared to those who were continued on low flux HD for 12 weeks (25.0 to 31.3 mg/L) (13).

The main reasons for the differences in the previous researches with the present study is that basically

two mechanisms have important role in clearance of molecules in dialysis; diffusion and convection or ultrafiltration. Diffusion is the main mechanism in removing small molecules such as BUN, Cr and P. Convection or ultrafiltration is the main mechanism in removing the middle molecules. In all the previous studies, low flux dialysis membrane had been used in a standard way, and these studies didn't pay attention to ultrafiltration but in this research we improved the role of convection in middle molecules' removal by increasing TMP. All the pores of the low flux membranes are not uniform and unisize (5, 21). This manufacturing problem is associated with rising hydrostatic pressure through increase TMP which helped us to remove beta2M. Another finding of this study is that excretion of the small molecules (BUN, Cr and P) in the second stage of hemodialysis in comparision with the first stage of dialysis (conventional method) had no meaningful difference.

This finding shows that the increase of TMP in low-flux membranes cannot increase the clearance of small molecules. This finding is conformable with other researchers`results (5, 9, 26). In our study beta2M was about 25mg/L in most of the patients that had a lower level as compared to other researches. Beta2M level in ESRD patients was 40-70 mg/L in Western America (27), about 40 mg/L in England (28). In a study in India beta2M level (about 25 mg/L) was near to our findings (13).

In general, according to the results of this study with a relatively simple method and with a very little cost by only using two litres of isotonic saline, we can increase the capacity of removing middle molecules. Thus, this method is suitable and feasible for the developing countires where cost of dialysis significantly burdens healthcare system and the patients. However, from the results of this research, it is not clear whether this amount of decrease in plasma levels of middle molecules can be effective in improving symptoms of residual syndrome and decreasing the morbidity and mortality of hemodialysis patients. This needs more consideration and further research.

Conclusions

The results of this study show that we can increase the amount of middle molecules' removal with increasing the TMP during bicarbonate base hemodialysis through low flux membranes.

Conflict of Interest

None declared.

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