Effect of Intranasal DDAVP in Prevention of Hypotension during Hemodialysis

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ABSTRACT

Introduction: The development of intradialytic hypotension during hemodialysis (HD) in which fluid removal is the primary goal, contributes to the excessive morbidity that is associated with the dialysis procedure. **Materials and Methods:** In a double blinded clinical trial, we compared the possible effect of intranasal DDAVP with intranasal distilled water as a placebo in prevention of intradialytic hypotension (IDH) in patients with known symptomatic IDH. In the first month of the study, nasal spray of distill water were administrated 30 minutes before all HD session (Placebo Group, Group 1) and then after a 30-day washout period we were used intranasal DDAVP 30 minutes before HD session (Vasopressin Group, Group 2). Blood pressure was measured just before HD, two hours later and after termination of HD. A hypotensive episode was defined as a decline of systolic blood pressure of more than 10mm Hg. **Results:** In overall Seventeen patients (nine men, eight women; mean age, 47.5 years) with known symptomatic IDH were enrolled in the study. The kind of dialysis membranes, mean of blood flow rate, dialyzate flow rate and ultrafiltration rate were the same in both groups. Each group has 204 HD session (17 * 12). Hypotensive episode occurred 18 times (8.82%) in vasopressin group compared with 125 times (61.27%) in placebo group and there was a significant association between them (p=0.0001). In addition mean arterial blood pressure in vasopressin group was 80.77 and in placebo group was 73.92 and also there was a significant association (p=0.0001). The mean Kt/v in group 1 and 2 were 1.29 and 1.28 without any differences between them (p=0.896). **Conclusion:** These results indicate that Compared with placebo, Vasopressin is significantly associated with a decreased incidence of intradialytic hypotension episodes during hemodialysis.

Keywords: DDAVP. Ultrafiltration Hemodialysis. Intradialytic Hypotension.

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Efecto de la DDVAP intranasal en la prevención de la hipotensión durante la hemodiálisis

RESUMEN

Introducción: *La aparición de hipotensión intradialítica durante la hemodiálisis (HD) en la que el objetivo principal es la eliminación de fluidos, contribuye a una morbilidad excesiva que se asocia con la diálisis. Materiales y métodos: Mediante un ensayo clínico doble ciego, comparamos los posibles efectos de la DDAVP intranasal con los del agua destilada intranasal como placebo en la prevención de la hipotensión intradialítica (HID) en pacientes con HID sintomática diagnosticada. Durante el primer mes del estudio, la pulverización nasal de agua destilada se realizaba 30 minutos antes de todas las sesiones de HD (grupo de placebo, grupo 1) y luego, tras un periodo de reposo de 30 días, utilizamos DDVAP intranasal 30 minutos antes de las sesiones de HD (grupo vasopresina, grupo 2). La presión arterial se medía justo antes de la HD, dos horas después y una vez finalizada la HD. Se definió como episodio de hipotensión la caída de la presión arterial sistólica del más de 10 mmHg.* ***Resultados:*** *Se incluyó en el estudio un total de 17 pacientes (nueve hombres y ocho mujeres de 47,5 años de edad media) con HID sintomática diagnosticada. En ambos grupos, el tipo de membranas de diálisis, la media del flujo sanguíneo, la tasa del flujo dializado y la tasa de ultrafiltración eran los mismos. Ambos grupos se sometieron a 204 sesiones de HD (17 x 12). Los episodios de hipotensión sucedieron en 18 ocasiones (8,82%) en el grupo de vasopresina en comparación con las 125 ocasiones (61,27%) del grupo de placebo y hubo una relación significativa entre ellos (p=0,0001). Además, la presión arterial media en el grupo de vasopresina era de 80.77 y en el grupo de placebo era de 73,92 e igualmente se observó una asociación significativa (p=0,0001). La media Kt/v en el grupo 1 y el 2 fue de 1,29 y 1,28 sin diferencias entre ellos (p=0,896).* ***Conclusión:*** *Estos resultados indican que, en comparación con el placebo, la vasopresina está relacionada de forma significativa con una menor incidencia de los episodios de hipotensión intradialítica durante la hemodiálisis.*

Palabras clave: *DDAVP. Ultrafiltración. Hemodiálisis. Hipotensión intradialítica.*

INTRODUCTION

Although considerable technical improvements have gained since the introduction of hemodialysis in the early 1950's

and life expectancy of patients with End stage renal disease (ESRD) has improved, there are some complications with different underlying mechanisms that commonly occur during hemodialysis (HD) including intradialytic hypotension (IDH), cramps, itching, nausea and vomiting, chest and back pain, headache, and fever and chills.[1-4]

IDH is an important side effect of HD and continues to be a leading problem, especially in the elderly and cardiovascularly compromised patients and it has a negative impact on health-related quality of life.[5-7] In some patients, the development of IDH necessitates decrease of the blood flow rate in HD apparatus and in some times, even discontinuation of HD and therefore it is an important cause of under dialysis. On the other hand, in the patients that they are need to ultrafiltration during HD, the development of hypotention episodes contribute to discontinuation of ultrafiltration and in some times, even necessitate intravenous fluid replacement before they are able to leave the dialysis unit and therefore, this problem can cause volume overload and some other significant complication.[7]

Unfortunately the incidence of this problem is very high especially among patients that they are received ultrafiltration during dialysis. It is occurred in significant percent of ESRD patients during or immediately following HD and its incidence ranges from 15 to 50 percent of dialysis sessions.[7,8]

Although a number of Studies have been evaluated to decrease the incidence of IDH, however because of small number of comparative studies and conflicting results, there are no generally accepted guidelines for prevention of hypotension during hemodialysis.[9-14]

The aim of this study is evaluating the possible effect of intranasal DDAVP for prevention of IDH episodes during hemodialysis.

MATERIAL AND METHODS

In a cross sectional clinical trial from May 2010 to September 2010, the present double blinded study was performed on ESRD patients who underwent hemodialysis treatments at Imam hospital, Ahvaz, Iran.

The ESRD was defined as permanent and irreversible loss of renal function due to any causes with creatinine clearance of less than 10-15ml/min per 1.73m^2 requiring renal replacement therapy.

A standardized questionnaire was used to collect general information such as age, gender, the record of previous diseases and drugs, vital signs, causes of ESRD, date of onset of HD and length of time receiving HD services.

HD patients with known symptomatic episode of IDH in at least 30% of HD session in the 30 days preceding enrollment were included and those with the following characteristics were excluded from the study.

Patients who had used antihypertensive drugs in recent two weeks, those that they didn't need to ultrafiltration during HD, Patients who had used other preventive measure for prevention of hypotention during HD such as cold dialysate, midodrine and others, those with a history of MI in 6 weeks ago, anemic patients with hemoglobin level less than 10 gr/dl, and Patients who were suffered from gastrointestinal bleeding during HD. The study was explained to the subjects and all participants provided written informed consent. The study has approved by the Research Center of Ahvaz Joundishapur University of Medical Sciences.

After selection of patients, in the first month of the study, all participants were received nasal spray of distill water (two puffs) 30 minutes before all HD session (Placebo group, Group 1) and then after a 30-day washout period we were used intranasal DDAVP (two puffs) 30 minutes before all HD session (Vasopressin group, Group, 2).

Blood pressure was measured and recorded by a trained neurse, just before the needles for dialysis access were placed, 2 hour after starting and at the end of each HD session. Mean arterial blood pressure (MABP) was also calculated as the diastolic pressure plus one-third of the pulse pressure. For measurement of blood pressure, the patients were seated for at least 5 minutes and arm supported at heart level. We were used a manual aneroid sphygmomanometer with an appropriate cuff size so that the cuff bladder encircles at least 80% of the arm. An intradialytic hypotensive episode was defined as a fall in systolic blood pressure of at least 10 mm Hg two hour after starting and or after termination of HD compared to pre dialysis.

Statistical analysis: For data analysis, we were used the statistical package for social sciences (SPSS) version 15 software. Chi-square tests or Fishers exact test were performed to evaluate the distribution of variables. Statistical significance was assessed at a probability level of < 0.05 in all analysis.

Hemodialysis Methods

Hemodialysis was performed for 9-12h, three times a week, using Fresenius machines, semi-synthetic (cellulose diacetate), or synthetic (polysulfone) dialyzer membranes, and bicarbonate- buffered dialysate (sodium 135mmol/l, potassium 2mmol/l, calcium 1.5mmol/l, magnesium 0.5 mmol/l and bicarbonate 35mmol/l). Blood flow rate was maintained from 250 to 400 mL/min, and the dialysate flow

rate at 500ml/min. Dialysate temperature was 36.58C throughout the study period. Dry weight and rate of ultrafiltration was determined individually by the patient's attending nephrologist on clinical grounds.

KT/V

KT/V was also calculated for the first and the end HD session in two groups. For evaluation of KT/V, blood sampling for blood urea nitrogen (BUN) was done immediately before HD session and for postdialysis BUN, our practice was to slow the blood pump to 100ml/min and then obtain the blood sample 15 seconds later.

RESULTS

One hundred twenty eight ESRD patients were on HD in Imam Hospital, Ahvaz, Iran. From them, one hundred eleven patients were not assessable because they had no hypotensive episodes and or because they had other exclusion criteria; therefore the study was performed on seventeen HD patients (nine men, eight women) with mean age of 47.5 years (range of 22 yr to 65 yr). The cause of ESRD in the patients on the study was diabetes mellitus in eight patients (four men and four women) and others were non diabetic (Hypertension, 5; Unknown, 3 and ADPKD, 1). In overall 408 HD performed in the period of the study; 204 times (17 X 12) in the placebo group (Group 1) and 204 times (17 X 12) in the vasopressin group (Group 2).

The kind of hemodialysis machines, dialyzer membranes, dialysate were the same in the both groups. The mean rate of blood flow rate, dialysate flow rate and ultrafiltration rate among vasopressin and placebo group in each HD session were 300ml/mim and 290ml/min, 500ml/min and 500ml/min and 2.3 liters and 2.2 liters respectively without a significant difference between them.

Hypotensive episode during HD occurred 18 times (8.82%) in vasopressin group compared with 125 times (61.27%) in placebo group and therefore the rate of IDH was significantly lower in vasopressin group (p=0.001). The mean of systolic and diastolic blood pressure after termination of HD session were 111.854 and 65.228 in vasopressin group and 102.671 and 59.550 in placebo group and there were a significant association between them (p=0.025 in mean of systolic and p=0.033 in mean of diastolic blood pressure).

In addition, the mean of arterial blood pressure after termination of HD session in vasopressin group was 80.77 and in placebo group was 73.92 and also there was a significant difference between them (p=0.0001). The mean of Kt/v in group 1 and 2 were 1.297±0.217 and 1.290± 0.252 without any association between them (p=0.896).

DISCUSSION

The pathogenesis of hemodialysis hypotension is thought to be multifactorial, but generally results from inadequate cardiovascular compensatory mechanisms and impairs autonomic response to the aggressive reduction of circulating blood volume during ultrafiltration.[15,16] In addition there are very strong arguments for an important role of several vasoactive substances such as adenosine (cardiodepressive and endogenous vasodilator) and nitric oxide (endogenous vasodilator) which may be synthesized or released during dialysis in pathogenesis of IDH.[17,18]

Although vasopressin is widely recognized for its role in the regulation of sodium balance and plasma osmolality, it is also a well-recognized vasoconstrictor and the role of vasopressin insufficiency as an important cause of IDH has also demonstrated in recent years by several observations.[19-23] In the first time, the possible role of vasopressin insufficiency as a cause of hemodynamic instability during HD, showed by Friess et al in 1994. They measured plasma AVP level in 23 patients with recurrent **dialysis** hypotension and showed that AVP concentration only increased in six patients with nausea and hypotension and in the remaining 17 patients without nausea AVP level did not increased.[19]

In the setting of hypotension as an example in patients with septic shock, the release of vasopressin is usually increased and in together with other vasoconstrictors cause systemic vascular resistance and elevates blood pressure.[23] It is therefore hypothesized that the inappropriately low vasopressin concentrations due to decreased endogenous AVP synthesis and or secretion may explain recurrent **dialysis** hypotension in the previous study.

Sato et al and Cignareli et al in two separate study in nondialysis diabetic patients with severe *diabetic neuropathy demonstrated that* AVP concentrations do not appropriately increase in the setting of orthostatic hypotension.[24,25] Therefore the results of two studies are supported the important effect of vasopressin in maintenance of blood pressure. In addition because of diabetes mellitus is the most common co morbidities associated with ESRD, the results of these studies also suggested that vasopressin insufficiency may be a part of the underlying mechanism of IDH in diabetic patients.

Mira Rho et al also demonstrated vasopressin insufficiency as a possible mechanism of IDH in ESRD patients and supported the findings of Friess et al.[20] They performed an observational pilot study on 20 chronic hemodialysis patients and observed that AVP concentration did not increase as would normally be expected in patients with symptomatic IDH in response to severe hypotension and therefore they have suggested that intravenous vasopressin

and perhaps intranasal vasopressin administration may improve hemodynamic stability in patients with symptomatic IDH.

Although in our study we were not measured concentration of AVP in HD patients with IDH, however the data from this clinical trial are also supported the findings of the studies of Friess et al and Mira Rho et al. According to the our study, the use of two puffs of intranasal DDAVP 30 minutes before HD session was significantly associated with a decreased incidence of hypotensive episodes among patients that they are received ultrafiltration during dialysis.

Other than our study, there are few clinical trials that they have evaluated the possible effect of vasopressin in prevention of IDH episodes during hemodialysis. As an example, in a study Van der Zee et al measured plasma vasopressin concentration during HD and found that plasma vasopressin levels did not increase during ultrafiltration dialysis. Then they examined 22 ESRD patients in a randomized, double-blinded and placebo-controlled trial and showed that blood pressure was more stable in the patients receiving constant infusion of a non-pressor dose of vasopressin during hemodialysis and the incidence of symptomatic hypotensive episode was significantly lower in comparison to the placebo group. Finally, they concluded that administration of vasopressin improves cardiovascular stability and facilitates fluid removal during hemodialysis.[21]

Jills et al have also showed efficacy of vasopressin in prevention of hypotension during hemodialysis. In this double-blind crossover study, they were used intranasal lysine vasopressin in 6 patients with refractory hemodialysis-induced hypotension and have reported that Systolic, diastolic, and mean arterial blood pressures were more stable with use of vasopressin.[22]

CONCLUSION

Intradialytic hypotension (IDH) continues to be a leading problem in patients with ESRD and it has an important negative effect on health-related quality of life. Unfortunately, because of small number of comparative studies, there are no generally accepted guidelines for prevention of this problem. Some studies have showed that AVP concentration do not increase as would normally be expected in patients with symptomatic IDH. Therefore it is hypothesized that the inappropriately low vasopressin concentrations is a significant part of the underlying mechanism of IDH and perhaps intravenous vasopressin and or intranasal vasopressin administration may prevent hypotension during HD. According to the present clinical trial, the use of two puffs of intranasal DDAVP 30 minutes before HD session Compared with placebo is significantly associated with a decreased incidence of intradialytic hypotension episodes among patients that they are received ultrafiltration hemodialysis. Although the results of our study are interesting but the small number of patients enrolled in the study is a limit factor and therefore further research with larger number of patients is needed to determine the effect of vasopressin administration for prevention of hypotension during HD.

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Conflict of interest

The authors declare they have no potential conflicts of interest related to the contents of this article.

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