Intraocular Pressure, Ocular Perfusion Pressure and Blood Pressure in Patients with End Stage Renal Disease Undergoing Hemodialysis

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ABSTRACT

Purpose: The aim of this study was to evaluate the effects of hemodialysis (HD) on intraocular pressure (IOP), ocular perfusion pressure (OPP), and blood pressure (BP) in patients with end stage renal disease (ESRD).

Material and Methods: The study included 106 eyes of 54 patients (32 women and 22 men) undergoing HD for ESRD. Systolic and diastolic blood pressure (SBP and DBP) were measured by sphygmomanometer; IOP was measured with a Tonopen before HD (pre-HD), at hour 2 of HD (mid-HD), and at the end of HD (post-HD). OPP was estimated by measuring the difference between two-thirds of the mean arterial pressure and the IOP value. Blood samples were obtained before and after HD for analysis of blood urea nitrogen (BUN), creatinine (Cr), and potassium (K) levels.

Results: There was no statistically significant change in IOP between the three time points ($p_{pre-mid}$=0.080, $p_{pre-post}$=0.328, $p_{mid-post}$=0.582). SBP, DBP, and OPP decreased significantly during HD compared to pre-HD values.

Conclusion: Although there is no significant change in IOP during HD, the presence or suspicion of glaucoma should be questioned in patients undergoing HD in order to prevent possible optic disc damage due to the decrease in OPP.

Key words: Glaucoma, hemodialysis, intraocular pressure, ocular perfusion pressure.

INTRODUCTION

End-stage renal disease (ESRD) is defined as a glomerular filtration rate less than 15 ml/min/1.73 m^2 requiring either dialysis or kidney transplantation as renal replacement therapy. Hemodialysis (HD) is the primary treatment method used in ESRD patients. HD is needed by these patients to eliminate excess fluid and metabolic waste in the bloodstream and maintain the acid-base and electrolyte balance. HD has been shown to have many effects on the ocular system, including refractive changes, dry eye, corneal and conjunctival epithelial erosions, perilimbal calcium deposits, band keratopathy, intraocular pressure (IOP) fluctuations, posterior subcapsular cataract, ischemic optic neuropathy, choroidal perfusion delay, corneal endothelium alterations, and thickness changes in the central cornea, retinal nerve fiber layer, and choroid .[1,2] Although HD was first shown to impact IOP in 1964, there is still no consensus on the phenomenon.[3]

Glaucoma is a multifactorial optic neuropathy whose etiological mechanism is still poorly understood. The main modifiable factor in its etiology is elevated IOP, which has a direct effect on the optic nerve head (ONH). However, ONH damage continues in some patients despite controlling IOP.[4,5] Various studies have examined vascular risk factors in the pathogenesis of glaucoma, most commonly blood pressure (BP) and ocular perfusion pressure (OPP).[6,7] Ocular blood flow is directly proportional to perfusion pressure and inversely proportional to vascular resistance.[8]

The aim of the present study was to evaluate the effects of HD on IOP, OPP, and BP in patients with ESRD.

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MATERIALS and METHODS

Patients

This prospective study included 106 eyes of 54 patients (32 women and 22 men) who were undergoing HD for ESRD. Two patients were one-eyed due to previous trauma. Therefore, only one eye of these patients was included in the study. The inclusion criteria were a negative history of glaucoma, and a healthy cornea. Patients with a previous history of glaucoma, an ocular surface disorder that would interfere with IOP measurement, and baseline IOP greater than 21 mmHg were not included in the study. This study has been approved by the Research and Ethics Committee of the Adana City Training and Research Hospital (Approval code 63-1038) and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Hemodialysis prescription

All patients had arteriovenous fistulae and were dialyzed for at least 3 months at the Hemodialysis Unit in the Adana City Training and Research Hospital, thrice weekly, for 4 hours per session, using dialysis machine 4008S-Fresenius Medical Care (FMC), equipped with Online Clearance Monitor (OCN®) module and synthetic hollow fiber polynephron dialysis membrane.

Study protocol and pressure assessments

The age, sex, history of diabetes mellitus (DM) and hypertension (HT), filtration volume, and blood glucose levels of the patients were recorded. Blood samples were obtained before and after HD and analyzed for blood urea nitrogen (BUN), creatinine (Cr), and potassium (K) levels.

Systolic blood pressure (SBP), diastolic blood pressure (DBP) and IOP were measured before HD (pre-HD), at the 2nd hour of HD (mid-HD) and at the end of HD (post-HD). Pre-HD BP and IOP measurements were performed after 15 min of rest, before the HD needle was inserted. BP measurement using a sphygmomanometer was always performed before IOP measurement.

IOP was evaluated with a tonometer (TonoPen, model AVIA, Reichert Technologies, Depew, NY, USA) with patients in the supine position. The recorded IOP was the mean of 5 successive measurements.

OPP was estimated by measuring the difference between 2/3 of the mean arterial pressure and the IOP values. Mean arterial pressure measurements, which provide indication of overall circulatory pressure load, were estimated by the formula: diastolic arterial pressure + 1/3 (systolic pressure - diastolic pressure). There was no significant difference in IOP between right and left eyes; therefore, only right eye measurements were used to calculate the OPP.

Statistical analysis

SPSS Statistics version 23.0 software package (IBM Corp., Armonk, NY) was used for statistical analyses. Categorical values were summarized as frequency and percentage; numerical measurements as mean and standard deviation or median and minimum-maximum, as appropriate. For analysis of repeated measures, normality of the data distributions were tested and paired t test was used for normally distributed variables and Wilcoxon test was used for non-normally distributed variables. Correlations between numerical variables were analyzed using Spearman's correlation coefficient. Correlations were interpreted as very strong if $r \geq 0.91$, strong if $0.71 \leq r \leq 0.90$, moderate if $0.70 \leq r \leq 0.51$, weak if $0.50 \leq r \leq 0.31$, and negligible if $r \leq 0.3$. Level of significance was accepted as 0.05 for all tests.

RESULTS

The study included 106 eyes of 54 patients. Twenty-two (40.7%) of the patients were women and 32 (59.3%) were men. The mean age was 53.1±12.6 (range: 27–81) years. Twenty-two patients (40.7%) had DM and 30 patients (55.6%) had a history of HT. None of the patients were using eye drops. The patients' filtration volumes and pre-HD blood glucose levels are shown in Table 1. Comparison of laboratory results before and after HD showed that BUN, Cr, and K levels decreased significantly after HD (p=0.0001) (Table 2).

Repeated measures of IOP at the start (pre-HD), at hour 2 (mid-HD), and at the end of HD (post-HD) in the left and right eyes of the patients showed that IOP increased between pre-HD and mid-HD, then decreased again by post-HD but did not return to the pre-HD level. However,

Table 1: *Filtration volume and blood glucose levels.*

	Mean±SD	Median (Min–Max)
Filtration volume (mL)	2829.6±957.5	2900 (1000–5100)
Blood glucose (mg/dL)	128.0±76.2	96 (59–411)

Table 2: *Blood urea nitrogen, creatinine, and potassium levels.*

	Pre-HD		Post-HD		
	Mean±SD	Median (Min–Max)	Mean±SD	Median (Min–Max)	p
BUN (mg/dL)	112.7±31.9	110 (41–194)	34.8±16.1	30 (9–100)	**0.0001**
Cr (mg/dL)	7.63±2.4	7.49 (2.7–14.8)	2.86±0.9	2.59 (0.98–5.6)	**0.0001**
K (mmol/L)	5.38±0.9	5.24 (3.7–7.1)	3.51±0.4	3.48 (2.1–4.7)	**0.0001**

BUN: Blood urea nitrogen; Cr: Creatinin; K: potassium; HD:Hemodialysis; Pre-HD: at the start of hemodialysis; Post-HD: at the end of hemodialysis.

the changes were not statistically significant (p>0.05) (Table 3, Figure 1).

There was no significant difference in IOP between right and left eyes; therefore, only right eye measurements were used for further analyses (p > 0.05).

Comparison of the patients' systemic BP measurements showed that pre-HD SBP and DBP measurements were significantly higher than mid- and post-HD measurements. SBP tended to decrease during dialysis and there were statistically significant differences between pre-HD and mid-HD (p=0.007) and between pre-HD and post-HD (p=0.019). DBP also decreased during dialysis, with statistically significant differences between pre-HD and mid-HD (p=0.031) and between pre-HD and post-HD (p=0.006). When OPP measurements were examined, significant decreases in OPP were observed from pre-HD to mid-HD (p=0.011) and from pre-HD to post-HD (p=0.014) (Table 4, Figure 2-4).

Table 3: *Intraocular pressure measurements during hemodialysis.*

	n	Pre-HD	Mid-HD	Post-HD	$p_{pre–mid}$	$p_{pre–post}$	$p_{mid–post}$
IOP, right (mmHg)	53	16.9±5.0	18.5±6.7	18.1±6.5	0.234	0.401	0.877
IOP, left (mmHg)	53	16.7±5.1	18.2±6.5	17.6±6.8	0.196	0.579	0.493
IOP (mmHg)	106	16.8±5.0	18.4±6.5	17.8±6.6	0.080	0.328	0.582

IOP R: Intraocular pressure of right eye; IOP L: Intraocular pressure of left eye; HD: Hemodialysis; Pre-HD: at the start of hemodialysis; Mid-HD: 2nd hour of hemodialysis; Post-HD: at the end of hemodialysis.

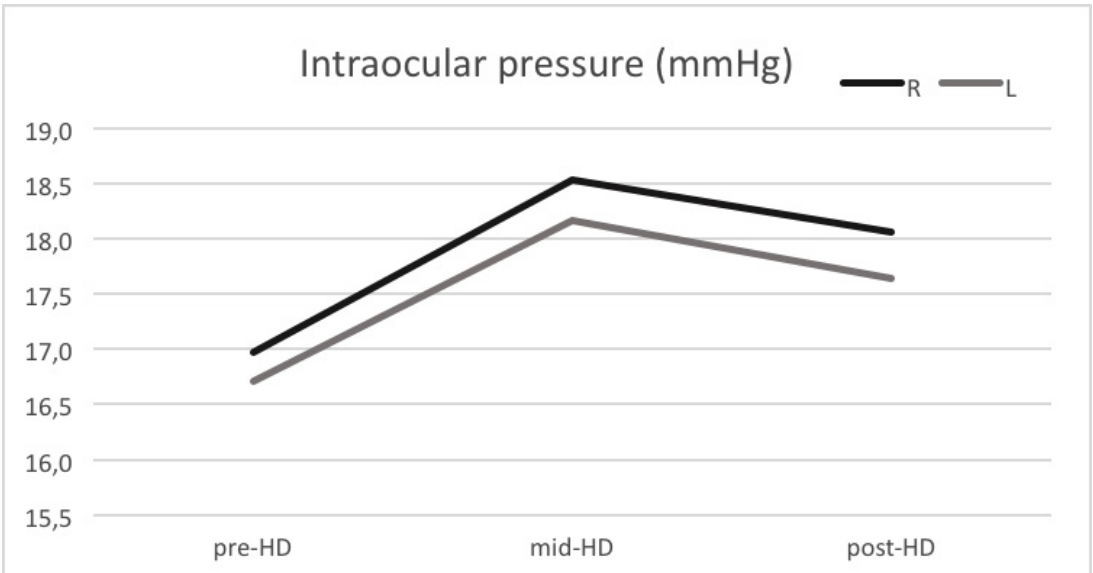

Figure 1: *Changes in intraocular pressure in the right (R) and left (L) eye during hemodialysis. pre-HD: At the start of hemodialysis; mid-HD: After 2 hours of hemodialysis; post-HD: At the end of hemodialysis.*

Table 4: *Ocular perfusion pressure, systolic blood pressure, and diastolic blood pressure measurements during hemodialysis.*

	Pre-HD	Mid-HD	Post-HD	$p_{pre-mid}$	$p_{pre-post}$	$p_{mid-post}$
SBP (mmHg)	130.1±29.8	122.4±26.6	121.4±29.3	**0.007**	**0.019**	0.325
DBP (mmHg)	78.5±18.6	75.9±23.3	73.0±20.7	**0.031**	**0.006**	0.127
OPP (mmHg)	95.7±21.2	91.4±22.2	89.2±21.2	**0.011**	**0.014**	0.387

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; OPP:Ocular perfusion pressure; HD:Hemodialysis; Pre-HD: at the start of hemodialysis; Mid-HD: 2nd hour of hemodialysis; Post-HD: at the end of hemodialysis.

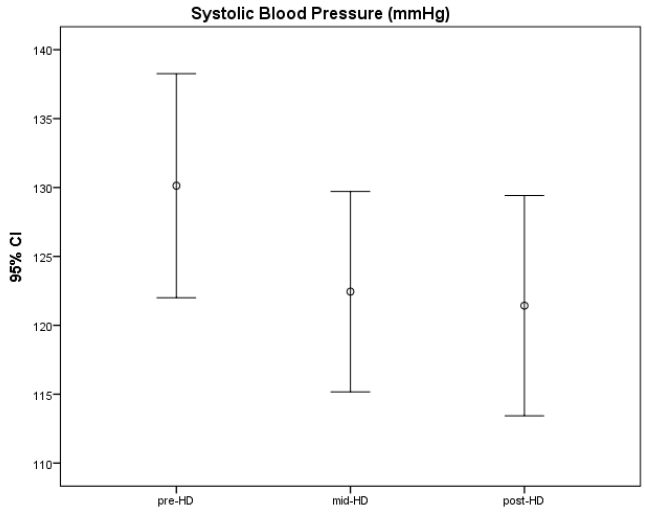

Figure 2: *Variation in systolic blood pressure during hemodialysis. pre-HD: At the start of hemodialysis; mid-HD: After 2 hours of hemodialysis; post-HD: At the end of hemodialysis.*

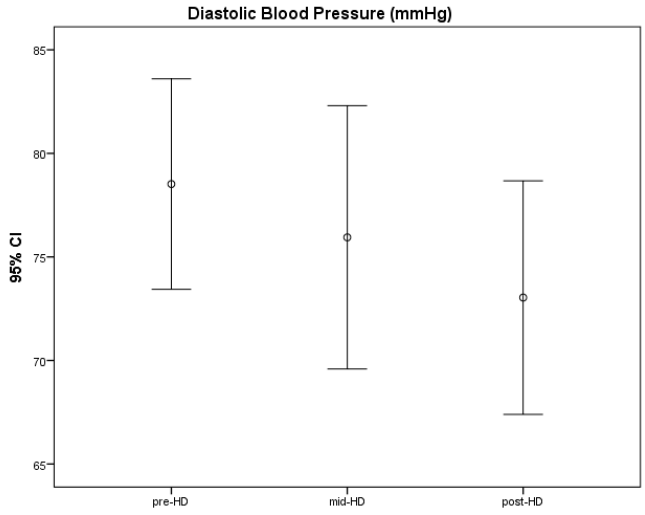

Figure 3: *Variation in diastolic blood pressure during hemodialysis. pre-HD: At the start of hemodialysis; mid-HD: After 2 hours of hemodialysis; post-HD: At the end of hemodialysis.*

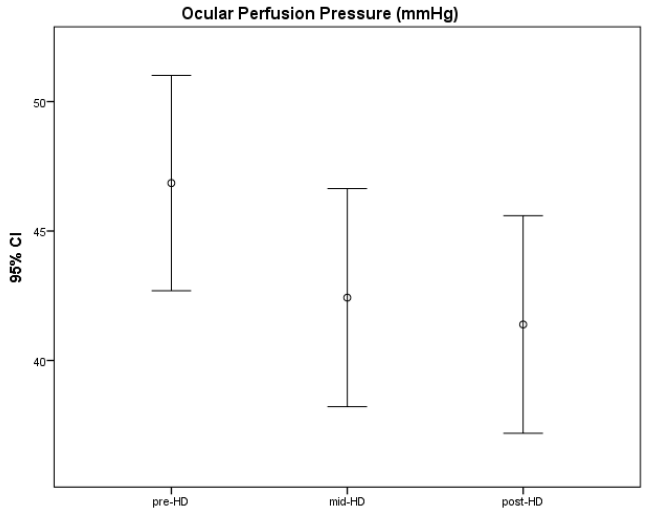

Figure 4: *Variation in ocular perfusion pressure during hemodialysis. pre-HD: At the start of hemodialysis; mid-HD: After 2 hours of hemodialysis; post-HD: At the end of hemodialysis.*

There was no significant correlation between IOP measurements and SBP, DBP, OPP, BUN, Cr, or K ($r \leq 0.3$).

CONCLUSION

Patients with kidney failure undergo HD to eliminate the excess fluid burden and uremic substances in the body. HD especially affects blood glucose, BUN, K, and sodium levels. These changes also alter plasma colloid osmotic pressure. Because differences in osmotic pressure between the aqueous humor and serum can also lead to IOP fluctuation, many studies have investigated the relationship between HD and IOP. Some studies have demonstrated an increase in IOP during HD[3,9-13], while others showed that IOP decreased[14-17] or remained unchanged.[18-22] These differences in results were suggested to result from factors such as study inclusion criteria, IOP measurement techniques, IOP measurement times, and HD procedure or duration.[23] In a recent meta-analysis, the effect of HD on IOP and its potential moderators were examined. Overall data pooling showed no significant rise in intradialytic IOP. Multivariable meta-regression showed only the type

of dialysate factors as a significant moderator. Glaucoma was found to be another significant moderator independent of the dialysate effect in bivariate meta-regression.[24]

In early studies, the increases in IOP during HD were attributed to the rapid decrease in plasma osmolarity and relative increase in urea concentration in the aqueous humor, resulting in the flow of extracellular fluid from the plasma to the anterior chamber.[11] Although only slight IOP elevation occurs in patients with patent aqueous outflow, more pronounced elevation is reported in patients with outflow obstructions such as anterior synechia and closed angle.[25,26] Fluctuations in IOP during HD have also been associated with post-dialysis urea rebound syndrome.[12] During dialysis, the reduction in extracellular urea occurs much earlier than the decrease in intracellular urea concentration. This causes urea to flow from the intracellular space to the extracellular space. The resulting urea concentration gradient causes extracellular fluid to passively infuse into the aqueous humor, thereby causing IOP to increase.

If one examines the commonalities among studies demonstrating a decrease in IOP during HD, it is seen that as HD removes the excess fluid burden, the outflow of fluid from the aqueous humor to the plasma due to the increase in plasma colloid osmotic pressure results in a decrease in IOP in patients without ocular abnormalities.[27] Tokuyama reported that serum osmolarity and IOP decreased with HD but were not correlated. However, they stated that increased colloid osmotic pressure due to ultrafiltration results in a decrease in IOP at the end of dialysis.[14] Similarly, Kılavuzoğlu et al. observed a significant decrease in IOP and serum osmolarity due to HD and attributed this to the fact that increased plasma colloid osmotic pressure has a greater effect on IOP than low serum osmolarity.[16]

HD was reported to have no effect on IOP in studies by Austin et al. using a Schiotz tonometer, Costaglio et al. using a Perkins tonometer, and Pelit et al. using a Goldmann tonometer.[18,19,28] In 2019, Sun et al. reported no significant change in IOP measured using Tonopen in 404 eyes of patients undergoing HD.[21] Also we know that the gold standard tool to measure IOP is represented by the Goldmann tonometer. To the best of our knowledge, comparison among different IOP measurement techniques in patients undergoing HD has not yet been performed. It should also be noted that OPP and IOP measurements might be different than routine upright measurements. Although there is no study showing this difference in HD patients, Costa et al.'s review article mentions differences in IOP and OPP measurements due to upright or supine position.[29] In the present study, IOP increased within the first 2 hours of HD (from 16.8±5 mmHg to 18.4±6.5 mmHg), but this increase was not statistically significant ($p=0.080$). IOP decreased again by the end of HD and although it remained slightly higher than initial levels (16.8±5 mmHg vs. 17.8±6.6 mmHg), this difference was also nonsignificant ($p=0.328$). As expected, blood urea levels decreased significantly from 112.7±31.9 mg/dL before HD to 34.8±16.1 mg/dL after HD ($p=0.0001$). However, we detected no correlation between HD-induced IOP change and pre-HD or post-HD BUN levels ($r \leq 0.3$). Although not statistically significant, the IOP peak seen at hour 2 of HD may be explained by the flow of fluid into the aqueous humor due to the relative urea gradient created by the rapid elimination of urea from the blood during this period. One of the limitations of our study was that we did not measure mid-HD urea concentration. However, the fact that the reduction in BP within the first 2 hours of HD was significantly greater than the decrease in the second half suggests that along with fluid, urea is also rapidly eliminated from the bloodstream in this period.

There is a complicated interplay between IOP, BP and OPP. While some studies demonstrate that systemic HT is a risk factor for glaucoma, others demonstrate that low systemic BP is a risk factor for the development and progression of glaucoma.[30,31] Dysautoregulation of ocular blood flow in patients with high or low BP can decrease OPP and increase the risk of retinal ganglion cell damage.[32] In particular, a strong correlation between low DBP, which causes low OPP, and glaucomatous damage has been reported.[3,33] In their study of 67 eyes, Barbosa et al. detected no significant change in IOP, but OPP and BP also remained unchanged.[34] In our study, we observed reductions in OPP, SBP, and DBP, while IOP did not change significantly. Our findings may be explained by the decrease in mean arterial BP due to the decrease in DBP and the consequent decrease in OPP.

An HD-induced reduction in OPP despite no change in IOP may pose a risk for glaucomatous damage. Patients undergoing HD should first have a comprehensive ophthalmologic examination. This would allow the detection of patients with large IOP fluctuations, high peak pressure, glaucoma, and potential angle obstruction, and thereby increase awareness of the effect of HD on OPP and the optic nerve. Moreover, patients under follow-up for glaucoma who exhibit progression despite IOP lowering should be questioned about a history of dialysis.

This study has certain limitations. The OPP and IOP changes in question were observed in a single HD session. We do not know if these results would be reproduced in other HD sessions. Another limitation was that we could not measure anterior chamber depth, which in previous

studies was shown to decrease[22], increase[35], or remain stable[36]. Studies evaluating parameters such as central corneal thickness, plasma colloid osmotic pressure, and systemic drug use together in larger patient populations are needed.

Our results showed that HD caused reductions in systemic BP and OPP, while IOP did not change significantly. Even if there is no change in IOP, vascular factors in the pathogenesis of glaucoma should be considered and the diagnosis of glaucoma should be questioned in patients who will undergo HD in order to protect the optic disc from possible effects due to the decrease in OPP.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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