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Effect of Optimization of Hemodialysis on Ophthalmological Variables in Patients with End Stage Renal Disease

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Abstract

Background: Conventional hemodialysis (HD) used in treating end stage renal disease (ESRD) can result in multiorgan insult including the eye-owing to the resultant reperfusion after the ischemic event. Optimization of HD can be done using a process called remote ischemia which includes applying cycles of brief, nonlethal ischemia followed by reperfusion to one limb. This method sends signal to the end organs to prepare themselves for the upcoming ischemia thus preventing their injury. Aim: To evaluate the effect of remote ischemia preconditioning in HD on ophthalmological variables. Patients and Methods: A pre-post interventional analytical study conducted on patients receiving hemodialysis. Remote ischemia preconditioning was done before each HD session incorporating 3 cycles of alternating ischemia and reperfusion (5 minutes each) performed in the upper limb using sphygmomanometer cuff. Ophthalmic examination was done at baseline and 3 months after HD optimization. Assessment was done half to one hour pre- and post-session for visual acuity, corneal, conjunctival deposits, tear break up time (TBUT), anterior chamber depth and central macular thickness. Results: The study included 50 eyes of 25 patients with almost equal gender distribution and mean age of 37.52 ± 9.824 years. They were maintained on hemodialysis for median 10 years (range 3 - 25 years). The commonest cause of ESRD was hypertension. The studied ocular parameters showed insignificant change after pre-conditioned HD except for TBUT that was statistically longer (p = 0.018). Conclusion: Optimization of hemodialysis using remote ischemia does not seem to have significant ocular effect apart from prolonged TBUT.

Keywords

Hemodialysis, Optimization, Tear Break Up Time, Ophthalmology

1. Introduction

Chronic kidney disease (CKD) is a common public health problem, which occurs in many countries with an increasing prevalence. Hemodialysis (HD) is the most popular modality for renal replacement therapy, with HD, lots of alterations occur in patients' haemostasias and metabolic parameters [1].

The fluid dynamic changes after HD can also affect ocular tissues that receive a high volume of blood flow. Ocular effects of HD can vary significantly, ranging from dry eye, corneal erosion, band keratopathy, perilimbal calcium deposits, posterior subcapsular cataract, intraocular pressure (IOP) changes, thickness changes in the central cornea (CCT), retinal nerve fiber layer, and choroid to retinal hemorrhage, retinal detachment, and macular edema. Best corrected visual acuity (BCVA) increases following a single HD session [2] [3] [4].

Conventional hemodialysis besides being associated with endothelial injury, oxidative stress, and high inflammatory activity, can induce microcirculation injury with consequent critical ischemia and tissue damage during the procedure [5]. Moreover, tear meniscus area, tear meniscus height, and tear meniscus depth were reported to be significantly lower in patients with ESRD [6].

The retina is an extension of the brain tissue and is the highest oxygen-consuming organ in the body, with high sensitivity to ischemia. Retinal ischemia can lead to functional and morphological changes culminating in blindness. Several ophthalmic diseases are related to retinal ischemia, including glaucoma, obstructive retinopathy, ischemic optic neuropathy, carotid artery occlusive disease, and diabetic retinopathy. Thus far, retinal ischemic injury is still an issue for treatment [7].

The target of optimization is to find better options or solutions for hemodialysis complications to improve overall quality of life [8]. Several points had been discussed in previous studies regarding methods of optimization as remote ischemia preconditioning [9]. Remote ischemia includes applying cycles of brief, nonlethal ischemia followed by reperfusion to one limb. This method sends signals to the end organs to prepare themselves for the upcoming ischemia thus preventing their injury [10].

Renal failure patients undergoing HD may be at increased risk of developing vision-threatening complications, and both physicians of the hemodialysis unit and ophthalmologists should be aware of this risk. The current study was conducted to evaluate the effect of remote ischemia preconditioning as a method of optimization in HD on different ophthalmological variables.

2. Patients and Methods

2.1. Ophthalmic Data Gathering

A pre-post-interventional and analytical study conducted on ESRD patients receiving hemodialysis in Mansoura Urology and Nephrology Center. Ophthalmological evaluation was done in Mansoura Ophthalmic Center; Mansoura University; Egypt. Patients with ESRD on HD of both genders and aged over 18 years were included in the study if not on waiting list for kidney transplantation. Patients with glaucoma, ocular pathology, previous ocular surgery and eyes with hazy media obscuring the visualization were excluded.

The study adhered to the Declaration of Helsinki and was approved by the institutional Review Board (IRB), Faculty of Medicine, Mansoura University under protocol No. (MS.20.06.1156). written informed consent was obtained from all the patients before being enrolled in the study.

Detailed history was obtained from all participants for data as age, gender, body mass index (BMI), height, cause of ESRD, duration of hemodialysis, vascular access type and site, maintenance medications and history of ocular diseases.

2.2. Optimization Technique (Remote Ischemia Preconditioning)

Remote ischemia was done for three months. Before each HD session, a 9-cm blood pressure cuff was been placed around the arm that did not have vascular access, usually the right arm. Three cycles of ischemia were performed for five minutes followed by reperfusion for five minutes. To induce ischemia; the cuff of a standard blood-pressure-manometer (Boso, Jungingen, Germany) was inflated above systolic blood pressure for 5 minutes before every session. Efficacy was assessed clinically by pulselessness of radial artery and acrocyanosis followed by reactive hyperemia. The correct cuff inflation was verified by the disappearance of a pulsatile signal on a pulse oximeter placed on the ipsilateral index finger. All participants received 4-hour, three weekly hemodialysis sessions using Gambro AK 96 HD machines. Glucose free-, calcium: 1. 5 mmol/L, low potassium (2 mEq/L) dialysate was used. Bicarbonate was used as acid-buffer. Temperature was maintained on 36.4˚C.

2.3. Ophthalmic Evaluation

Evaluation was done twice; first time before application of the method for optimization; the second time, after 3 months of optimization. Assessment was done ½ to 1-hour pre- and post-session. Ophthalmic evaluation included of visual acuity testing using Landolt's broken ring chart then transformed to Log MAR for statistical analysis, refraction measured by auto refractometer (Canon, Japan), full slit lamp examination (Topcon SL-7F Slit Lamp - Alternup Medical, France), tear break up time (TBUT) and intraocular pressure measurement (IOP) using Goldmann applanation tonometer and dilated fundus examination using slit lamp examination with Volk lens 90D. Ultrasound A-scan was used to measure anterior chamber depth (ACD) and Lens thickness. Optical coherence tomography (OCT) using swept Source OCT (Topcon, DRI Triton, Tokyo 190-0016. Japan) was used to measure central macular thickness (CMT) and retinal nerve fiber layer (RNFL) thickness.

3. Statistical Analysis

The collected data were coded, processed, and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Quantitative data were expressed as mean ± SD (Standard deviation). Paired samples t-test was used to assess the difference between two dependent groups of normally distributed variables (parametric data) while Mann Whitney test was used to assess the difference between two dependent groups of abnormally distributed variables (non-parametric data).

4. Results

The study was conducted on 50 eyes of 25 patients with ESRD on hemodialysis. The age of studied sample ranged from 19 years to 62 years with mean 37.52 ± 9.824 years including 13 (52%) males and 12 (48%) females. The patients were dialyzed for median 10 years (range 3 - 25 years). The most common cause of dialysis in the studied sample was hypertension accounting for 28% of cases followed by renal atrophy and vesico-ureteric reflux in 12% of cases, SLE in 8.0% and amyloidosis in 4% cases (**Table 1**).

Table 1. Demographics and hemodialysis characteristics.

Parameter	Total (n = 50 eyes)
Age (years) Mean ± SD	37.52 ± 9.824
Gender No. (%):	
- Male	13 (52%)
- Female	12 (48%)
Disease duration (years) Median (IQR)	10 (4 - 13)
Dry body weight (Kg) Mean ± SD	63.90 ± 12.986
Height (m) Mean ± SD	1.68 ± 0.117
Original kidney disease No. (%):	
- Amyloidosis	1 (4.0%)
- Atrophy	3 (12.0%)
- Hypertension	7 (28.0%)
- SLE	2 (8.0%)
- Vesicoureteral reflux	3 (12.0%)
- Others	9 (36.0%)

SD = standard deviation; SLE = systemic lupus erythmatosis.

Baseline ocular examination showed that uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA) ranged from 0 to 1 with median 0.2 remained almost the same after HD. Cataract was the most common finding before optimization detected in 58% of the cases. Conjunctival calcification was detected in one more eye after 3 months (28 eyes versus 27 eyes at baseline) and corneal degeneration was no more evident in two eyes after 3 months (24 versus 26 eyes) without statistical significance difference in both findings. On fundus examination, the majority of the cases (44%) had hypertensive retinopathy, 8% had age-related macular degeneration (ARMD), 18% had vasculitis and 6% had retinal degeneration. Fundus was normal in 24% of cases. Results of posterior segment examination remain unchanged after 3 months.

Tear break up time increased significantly after optimization from 7.69 ± 1.24 to 8.01 ± 1.25 sec ($p = 0.018$). There were no statistically significant differences between the 2 time-points regarding refraction, intra-ocular pressure, anterior chamber depth, lens thickness, central macular thickness, and retinal nerve fiber layer thickness (Table 2).

Table 2. Comparison of ophthalmic examination between pre- and post-optimization.

Parameter	Pre-optimization	Post-optimization	p value
UCVA Median (min, max)	0.2 (0, 1)	0.3 (0, 1)	0.06
BCVA Median (min, max)	0.2 (0, 1)	0.2 (0, 0.6)	0.22
Refraction (D) Median (min, max)	−0.5 (−3.5, 1.5)	−0.06 (−3.75, 2.13)	0.114
IOP (mmHg) Mean ± SD	12.93 ± 4.246	12.63 ± 3.247	0.600
ACD (mm) Mean ± SD	3.18 ± 0.351	3.17 ± 0.324	0.724
Lens thickness (mm) Mean ± SD	4.39 ± 0.415	4.47 ± 0.566	0.212
CMT (um) Mean ± SD	178.20 ± 26.087	175.26 ± 12.222	0.376
RNFL thickness (um) Mean ± SD	108.76 ± 27.343	102.58 ± 14.089	0.145
TBUT (seconds) Mean ± SD	7.69 ± 1.241	8.01 ± 1.253	0.018
Corneal degeneration No. (%)	26 (52%)	24 (48%)	0.317
Conjunctival calcification No. (%)	27 (54%)	28 (56%)	0.564
Cataract No. (%)	29 (58%)	29 (58%)	1
Fundus examination No. (%)			
- Normal	12 (24%)	12 (24%)	1
- ARMD	4 (8%)	4 (8%)	
- Hypertensive retinopathy	22 (44%)	22 (44%)	
- Vasculitis	9 (18%)	9 (18%)	
- Retinal degeneration	3 (6%)	3 (6%)	

(UVCA) uncorrected visual acuity; (BCVA) best corrected visual acuity; (IOP) Intra-ocular pressure; (ACD) Anterior chamber depth; (CMT): Central macular thickness; (RNFL) Retinal nerve fiber layer thickness; (TBUT) Tear break up time. Test used: Paired samples t-test. Significance at $p < 0.05$ written in **bold**.

5. Discussion

Earlier studies reported significant decline in the systolic and diastolic flow velocity of the central retinal artery after HD. These findings had driven researchers to believe that optic blood vessels provide relatively insufficient blood supply after HD. Hence, physicians should pay special attention to the prevention and treatment of ocular ischemic diseases [11]. Optimization methods of hemodialysis are ways to improve dialysis outcomes, a trend toward improving quality of life and decreasing inflammatory process [12].

Yet, few studies evaluated the ocular effects of remote ischemia on patients with other diseases. The aim of the current study was to evaluate the effect of optimization of hemodialysis in ESRD patients on ophthalmological variables including ACD, lens thickness, central foveal thickness, RNFL thickness, and IOP measurement.

As HD is a process of clearing excess water and metabolic waste from the body; the fluid volume as well as the solute concentration usually drops after HD sessions. As tears are part of body fluids; the TBUT and Schirmer's test results were reported to significantly decrease during HD with resultant exacerbation of dry eye symptoms that can be perceived instantly after a single HD session [13].

Using remote ischemia method in our patients, a significant improvement of tear break-up time test was reported. Possibly due to the fluid dynamic changes after remote ischemia that can also affect ocular tissues as they receive a high volume of blood flow including meibomian glands in lids, so increase secretion of lipid layer in tear film that retard evaporation.

Another potential consequence of the decrease in body fluids during HD is reduction of the anterior chamber depth (ACD). This shallowness might lead to elevation in the IOP and even prompt an acute attack of angle-closure glaucoma in predisposed eyes with occludable angles. Thus in those patients who are at high risk of angle closure, preventative measures should be taken before HD [14]. In our study ACD did not change significantly after the remote ischemia preconditioning.

Till now, there is no solid consensus regarding the effect of HD on the IOP. Studies suggest that changes in the measured IOP might be related to the measurement method used, anterior chamber depth, as well as the blood pressure [2]. The IOP in the current cohort did not vary significantly from the baseline measured values.

Previous published studies reported statistically insignificant differences before and after HD regarding the macular thickness [15] or the retinal nerve fiber layer [16]. Our results showed insignificant decrease in CMT and RNFL. In contrast to these results, Chen *et al.*, [2] in their study noticed statistically significant increase in the previous parameters and presumed that reduction in the plasma crystal osmotic pressure during HD drives the fluids into the retinal layers along the concentration gradient causing retinal edema. In a study by Manaviat *et al.*, [17] remote ischemia was performed for 40 diabetic patients with macular edema before receiving standard treatment and were compared to 40 control patients. He did not report significant differences between both groups after treatment regarding macular thickness and visual acuity. Harman *et al.*, [18] evaluated the effect of retinal ischemia in adult rats and he concluded that parental hypoxia provides functional protection against retinal ischemia in adult offspring. Another experimental study found that remote ischemia in rats is protective against traumatic optic neuropathy as it significantly increased the survival of retinal ganglion cells by inhibiting oxidative stress and inflammatory process [19].

El Dabagh *et al.*, [20] went through the effect of remote ischemia in diabetic patients on the baseline diameter and contraction of peripheral arterioles and he found that the baseline diameter and contraction during isometric exercise in peripheral retinal arterioles are reduced immediately after remote ischemic conditioning (RIC), whereas the diameter responses in macular arterioles are unaffected by this intervention. In diabetic patients, the corresponding diameter responses are reduced and are unaffected by RIC. The reactivity of peripheral retinal arterioles after transient ischemia in the arm might be a marker of vascular dysfunction in diabetic patients. Another study by Zhu *et al.*, [7] evaluated the protective role of limb remote ischemia against retinal injury induced by increased IOP in mice. He concluded that remote ischemia protected high IOP-induced retinal injury via antioxidant and endoplasmic reticulum (ER) stress inhibition. Reduced monocyte infiltration and microglia activation may have played an important role in this protection.

No observable change in either UCVA or BCVA occurred in our studied patients. These results were in consistence to the previous research which concluded that HD cannot directly affect visual acuity [21]. Zhao *et al.*, [22] proposed that HD can improve BCVA. Other researchers studied the correlation between the visual acuity and the initial cause of ESRD and found that visual acuity in diabetic patients was significantly worse than in patients with other etiologies both before and after HD [2].

The main advantage of the current study is the novelty as according to our knowledge, this is the first study to go through effect of hemodialysis optimization generally on ocular manifestations and the effect of remote ischemia specifically. The sample size of the current study was adequate in comparison to previous studies and guarantees generalizability.

The study had some limitations as absence of control group specifically with same intervention. Also, we did not compare our findings to normal healthy non-dialysis control group.

6. Conclusion

In conclusion, the present study was unable to detect significant effect of hemodialysis optimization on different ocular parameters apart from significant improvement in TBUT.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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