

Ocular disorders in renal transplant patients in Ethiopia.

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Research article

Keywords: Renal transplant, immunosuppressive, ocular complication, end stage renal disease.

Posted Date: March 25th, 2019

DOI: <https://doi.org/10.21203/rs.2.485/v1>

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Abstract

Abstract Background : Renal transplantation has become a very successful and routine procedure of all organ transplant procedures. Visual loss is a rare but potentially devastating ocular complication of organ transplantation. Postoperative therapy with immunosuppressant, steroids and the cause of the end stage renal disease were said to be associated with the development of eye disorders like cataract, high intraocular pressure, ocular surface disorders, opportunistic infections and neurotoxic conditions. Nowadays, Post transplant patients have better survival rates and enjoy improved quality of life so one should look for complications on time and solve them accordingly. The objective of this study is to determine ocular problems in renal transplant recipients in Ethiopian patients. **Methods:** It is a cross sectional study done at Saint Paul's Hospital Millennium Medical College (SPHMMC) from October 2017 to December 2018. All post renal transplant patients who were having follow up at renal transplant unit were taken for the study. Descriptive analysis was done to determine means, frequencies and proportions of the various variables. **Result :** There were a total of 135 renal transplant subjects including 95(70.4%) male and 40(29.6 %) female . The mean age of all the study subjects were 34.4+ 12.1(Range 10 - 69) years. The cause of renal diseases is not known in majority of the study subjects 112(83%). More than 95% of all the study subjects were on multiple immunosuppressant therapy. Of all the individuals examined 128(94.8%) of them have one or more eye problems. The most prevalent ocular abnormality detected were dry eye 76(59.4%), optic neuropathies 10 (7.9%), Cataract 8(6.2%) and retinal pigment abnormality 9(7%). There were no significant sight threatening complications observed in relation to the immunosuppressive therapy or the diseases itself. **Conclusions :** Dry eye is the most commonest eye problem identified among renal transplant patients which is not related to the prolonged use of immunosuppressives or the end stage renal disease. **Key words:** Renal transplant, immunosuppressive, ocular complication, end stage renal disease.

Background

Organ transplantation has evolved over many years. Renal transplantation has become a very successful and routine procedure in now a days. With near optimal rates of transplant patient and allograft survivals, the focus has shifted to the alleviation of complications that can improve outcomes. Advances in surgical technique and development of more effective immunosuppressive agents have rendered kidney transplantation an effective renal replacement therapy. Pharmacologic immunosuppressant like steroids, cyclosporine and tacrolimus has played a major role in the advancement of these transplantation procedures. However, immunosuppressant has been shown to carry the risk of many complications.

Ocular complications following renal transplantation are mainly secondary to age, immunosuppressive therapy (Steroids) and the cause of the underlying renal disease (Diabetes (DM), Hypertension (HPN)) and accumulation of noxious materials (1). There are many studies mentioning that most of the ocular complications following renal transplantation are recognized as secondary to immunosuppressive drugs, especially to the use of corticosteroids (2-5). Steroid induced cataract is a common ocular complication

that occurs in post renal transplant patients. It can be seen in as high as 62.5% of cases(2). There were studies on the relationship between the occurrence of posterior sub-capsular cataract (PSC) and total doses of steroids(4,6,7). The magnitude of PSC cataract and the amount of steroids was statistically significant(55.3% with high-dose steroids, 28.2% in the low-dose steroid group and 6.2% in those who received no steroids). Grading the severity of PSC showed a significant correlation between the degree of PSC and the steroid therapy(6). Increased intraocular pressure was found in 12.5%(2) and 20% (8) of all the renal transplant cases. Dialysis time before transplantation was shown to have a significant influence on ophthalmic complications that happen to occur after transplantation, and the longer the dialysis time before transplantation is the higher rate of glaucoma(1). Anterior segment problems seen in post renal transplant patients were conjunctival degeneration 36.6%, posterior sub-capsular cataracts 24%, pinguecula 17.3%(9). There are also interesting posterior segment findings with different descriptions found in different studies. Pigmentary changes in the choroid and retinal pigment epithelium was seen in transplant cases (4,8,9) as high as 14%(9). This may result in loss of vision caused by serous retinal detachment .

Retinal vein occlusions seen in 3.3%(9), 1.4%(2). Arteriovenous crossing changes in 8.6%, proliferative diabetic retinopathy(PDR) in 6%, central serous chorioretinopathy in 3.3%, and non-proliferative diabetic retinopathy(NPDR), optic nerve atrophy and diabetic macular edema each in 2.7%(9). In another study with different description micro aneurysms, preretinal wrinkling, serous detachments of the retina, hemorrhages and exudates-were observed(8). Renal transplantation stabilized Diabetic retinopathy status in the majority of diabetic patients(60%) though other co-morbid factors such as hypertension, lipid profile, and pre-existing retinopathy status have a significant contribution for the final outcome(10). There are reports that the systemic small vessel disease such as diabetes seen in end-stage renal failure does not normalize after renal transplantation(11).

Cyclosporine is one of the commonly used immunosuppressive drugs used for renal transplant patients. Occipital white matter appears to be uniquely susceptible to the neurotoxic effects of cyclosporine(12). It is also implicated in the development of optic nerve head oedema and in some cases associated with pseudotumour cerebri (13). Bilateral or unilateral sixth nerve palsies and bilateral ptosis were also seen in patients who were on cyclosporine after transplant(14). Some experience visual loss after renal transplantation and cyclosporine therapy(15). Cortical blindness is also mentioned as a cause of visual loss for bone marrow transplant patients who were on cyclosporine (16). Tacrolimus is a relatively new immunosuppressive agent that is particularly indicated in liver transplantation and bone marrow transplantation. It is also used in renal transplant patients these days. It is mentioned as a cause of cataract due to an accumulation of sorbitol in the lens secondary to the diabetogenic effect of the drug. It is supposed that cataract would not develop with tacrolimus if diabetic parameters are under control(17). The other new immunosuppressive agent used and show a promise in graft survival is MMF(mycophenolate mofetil).

Opportunistic infections like cytomegalovirus ocular infection and herpes simplex ocular infections are the other problems detected in these group of patients(18). CMV infections were seen in 2.8% (2), 5%

(5),8%(8) of renal transplant cases and it was attributable to the immunosuppressive drug therapy(5). Blindness and deafness are also reported secondary to other opportunistic infections like meningocerebral cryptococcosis after kidney transplantation.(19) Mucormycosis is an extremely rare complication following kidney transplantation. Augmented immunosuppression, especially with corticosteroids, anti-rejection therapy, older age and PTDM are found to be the main predisposing factors for the infection(20).Saint Paul's Hospital Millennium Medical College is a pioneer in providing major organ transplant like kidney transplant in Ethiopia. Very few patients had the opportunity to receive the service. Even if this is a life changing and exiting addition to the countries health service coverage, its long term outcomes including various complications is not yet assessed. Though visually significant ocular complications such as cataract or increased intraocular pressure observed frequently after renal transplantations, attention to eye check up is uncommon in post transplant patients. Therefore, the aims of this study is to describe ocular findings in renal transplant recipients at St .Paul's Hospital Millennium Medical college.

Methods

The study was a cross sectional study undertaken from October 2017 to December 2018 at St.Paul's Hospital Millennium Medical College(SPHMMC),department of Ophthalmology. The ophthalmology department gives service for more than 16,000 patients and more than 2000 surgeries annually. The kidney transplant centre established almost three years ago in collaboration with University of Michigan, USA. The college has provided treatment for more than 80 people so far. It is the only centre in Ethiopia to give the renal transplant service. All patients who undergo renal transplant surgery (both locally and abroad) and following at the renal transplant unit were included for the study. Patients who are critically sick at the time of data collection were not included in the study. Those subjects who were willing to undergo the eye examination were taken to ophthalmology department for eye examination by an ophthalmologist. After verbal informed consent a complete ocular examination including best corrected snellen visual acuity (BCVA),refraction, ocular motility and external eye examination, slit-lamp biomicroscopy, applanation tonometry and fundoscopy using a non-contact 90 diopter lens following pupil dilation with tropicamide 1% were done. Nephrologic history including underlying disease causing ESRD, post-transplant duration, duration of pre-transplant dialysis and immunosuppressive regimens (types, dose, frequency) used were recorded from the patient's chart. The collected data was checked for completeness immediately after data collection. Incomplete information was corrected immediately before the patient leaves the clinic.

Ethical clearance was obtained from SPHMMC institutional review board(IRB). The director of the renal transplant unit was informed about the study and appropriate permission was secured.

Results

During the study time there were a total of 135 renal transplant subjects including 95(70.4%) male and 40(29.6 %) female . The mean age of all the study subjects were 34.4 ± 12.1 (Range 10 - 69) years. Of all

the patients 92(68%) of them were done the procedure locally in Ethiopia and the rest 43(32%) were patients who follow at the center but done the surgery abroad. All of the study subjects received kidney from live related donors. Most of them 128(94.8%) came from urban area while 7(5.2%) came from semi-urban area. The cause of ESRD is not known in majority of the study subjects 112(83%), and the remaining 23(17%) had a known chronic disease like hypertension, diabetes, obstructive nephropathy and glomerulonephritis constituting 9(6.7%), 7(5.2%), 5(3.7%) and 2(1.5%) respectively (Table 1).

More than half of the study subjects 76(56.3%) did wait for more than a year before undergoing the transplant procedure whereas only 5(3.7%) of the cases undergo the transplant surgery within six months time after the diagnosis of renal failure. Almost all of the study subjects were on dialysis during this time period before surgery. Seventy five(55.6%) of the study subjects passed a year after the transplant surgery while 36(26.7%) of them past six months but not a year and the rest 24(17.8%) were done the transplant before six month.

More than 95% of all the study subjects were on multiple immunosuppressant therapy. The most commonly used immunosuppressant include Mycophenolate mofetil (MMF) (65%), Prednisolone (72%), Cyclosporine (22%) and Tacrolimus (82%). The post-transplant immunosuppressive regimen consisted of triple therapy in 128 (94.8%), single therapy in 1 (0.7%), dual therapy in 6 (4.4%) of study subjects.

In addition to the immunosuppressant therapy, multiple adjuvant treatments (more than three) were given to 107(79.3%) of the transplants while dual adjuvant treatment were taken by 26(19.3%) of the cases. The most commonly used adjuvant treatments include Cotrimoxazole (72%), Pantoprazole (69%) and Amlodipine (70%).

About 18(13.3%) of the study subjects have preexisting medical illness before the transplant and among these diabetes 9(6.7%) and hypertension 6(4.4%) are among the commonest.

Its only 5(3.7%) of the study subjects who undergo eye check up prior to the study. Visual acuity assessment shows, 131(97%) of them have normal visual acuity ($V/A \geq 6/18$) whereas 3(2%) of them have visual impairment ($V/A 6/18-3/60$). No patient had intraocular pressure (IOP) more than 21 mmHg. Refractive error was seen in 78(57.8%) of the study subjects among these presbyopia was seen in 30(22.2%), myopia 19(14.1%), hyperopia in 26(19.3%) and astigmatism in 3(2.2%).

Of all the individuals examined 128(94.8%) of them have one or more of eye problems. The most prevalent ocular abnormality detected was dry eye, seen in 76(59.4%). Cataract (immature) was observed in 8(6.2%) of the subjects. Two of the study subjects already done cataract surgery. Lid problems like blepharitis and conjunctival problems like degeneration was seen in 8(6.2%) and 7(5.5%) of the transplant patients respectively. Nine(7%) of the cases found to have retinal problem and 10 (7.9%) of them have optic neuropathies (Table 2). Most of the retinal problems are retinal pigmentary changes and two of the study subjects had long standing retinal detachment. Among the 10 subjects with optic neuropathy, two of them had glaucomatous optic neuropathy which was first detected during this study.

Treatment in the form of eye drops and eye glass was given for some of the problems mentioned above. Overall treatment provided to 118(87.4%) of the study subjects. Fifty(37%) of them were given both eye drop & eye glass prescription,24(17.8%) of the cases were given an eye drop only and 44(32.6%) were given eye glass prescription only. Follow up link to the department of ophthalmology was facilitated for 12(8.9%) of the cases who need subsequent check up.

Discussion

The cause of the ESRD is known for only 17% of the study subjects and its difficult for us to explain this but there must be strong pathologic investigation for this so that we can work on the prevention of it. In this study most of the study subjects are relatively younger (mean age of 34years) than the average age mentioned in many other similar studies(8,9). The young age of the study subjects may contribute to the fewer cases of sight threatening complications that is observed in this report. Majority of the subjects(70.4%) were males(70.4%) and are residents of town(94.8%) and this could be due to the fact that males and those who live in town have better access to services like medical care than females and those who live in rural areas. The specific causes for the end stage renal disease(ESRD) is not known for the majority(83%) this can be due to limited diagnostic tools and expertise in this area. Similar with other studies(2) the visual acuity is normal ($V/A \geq 6/18$) for most of the study subjects(97%). This could be due to the fewer number of age related eye problems observed as most of the patients are young. Prescription for corrective eye glass were given for most of them (57.8%). On the other hand subnormal visual acuity($V/A < 6/9$) was mentioned as a major functional problem in others(9).

It is known that a rise in intra ocular pressure(IOP) is one of the side effects of corticosteroids (both systemic and topical). Even it was mentioned as a cause for glaucoma according to some reports(5,21). In this study intraocular pressure was found to be normal in all the study subjects but there was a report of high IOP in some literatures 7% (22) and 12.5%(2) among renal transplanted patients. The high IOP level was related to the amount of systemic corticosteroid therapy(3) but we couldn't find this relationship in this study. In an investigation to study the relationship of glaucoma with dialysis time before transplantation ,it was shown that the incidence of glaucoma was related to the dialysis time before kidney transplantation(1). The occurrence of high IOP and glaucoma was related to the change of plasma osmotic pressure. The plasma osmotic pressure decreases after hemato-dialysis and aqueous fluid production intern increase. Similarly urea nitrogen in aqueous fluid during dialysis cannot rapidly decrease with the decrease of urea nitrogen in blood. Thus, osmotic pressure in aqueous fluid and crystalline lens lose the balance, the crystalline lens expand by absorbing the moisture, iris diaphragm of crystalline lens moves forward and the anterior chamber angle narrows, which influence the aqueous fluid draining and make IOP increase. The changes of urea nitrogen in vitreous cavity can also influence the IOP by the similar way(1).

The highest number of cases with dry eyes (76(59.4%)) can be due to the data collection time(dry season) and place (Ethiopia is one of the tropical country). Data was collected in the driest season of the nation that can cause severe dry eyes. Eye lubricants and protective eye glass were given for these

individuals. This much magnitude of dry eye was very high compared to even other extra ocular problems detected in transplanted cases like conjunctival degeneration (36.6%) and pinguecula (17.3%) (9). As an isolated problem, Pinguicula was seen in 5.5% of the transplant cases in this study which is lower when compared to the previously mentioned report(9). This conjunctival degenerative lesions often result from prolonged exposure to ultraviolet radiation(4). In this case it is related to exposure to dry and sunny season during data collection time.

The second most prevalent ocular disorder seen was optic neuropathy, two of the cases were glaucoma suspects and they were linked to glaucoma services and the rest were due to other neuropathies. Optic neuropathies were less frequent problem reported in renal transplant patients.

Retinal pigment abnormalities were seen in 6.7% of the study subjects which is a bit lower than the report from both Iran and US that is 14%(9) and 20%(8) respectively. The cause of this pigmentary changes in the choroid and the retinal pigment epithelium is not known but is related to some change in the haemodynamics of the choroidal circulation(4). Since study subjects in this were relatively young, senile degeneration could not be considered an etiologic factor. Cytomegalovirus retinitis, one of the opportunistic infections is not observed at all in any of the cases in this study but it was mentioned to cause severe visual loss in 5% of all the renal transplants (5) and 8% of transplanted cases with visual compliant(8).

Cataract specifically posterior sub capsular cataract was mentioned as one of the commonly seen disorder in renal transplant cases. It was observed as high as in 62.5%(2),45% (22) and 30%(9),23% (5),34%(7),25.3%(1) which in all case is higher than ours which is 6.2%. Two of our patients undergo cataract surgery after the transplant. Different reports put different reason for this, one of the commonest reason being a dose-dependent relationship between steroid treatment and cataracts(6,5) and the number of days on which the dose exceeded 100 mg(3). We did not find any significant relationship between the use of oral steroids and cataracts. This could be due to careful and monitored use of prednisolone and co administration of other safe immunosuppressive agents like cyclosporine and MMF in this setup.

Conclusions

The occurrence of sight-threatening ocular complications such as cataract in renal transplant patients is relatively low. Dry eye is the most common eye problem detected which is not related to the ESRD or immunosuppressant therapy.

Although most complications are not related to poor vision, routine ophthalmologic evaluation should be done for early detection, better management and improved quality of life of such patients. Though it is not related to the main topic of interest the diagnostic(Pathologic) means to know the cause of ESRD should be improved as most of the time the cause was not known.

Abbreviations

AC = Anterior chamber , BCVA - Best corrected visual acuity ,BP = Blood pressure

CMV = Cytomegalovirus, DR = Diabetic retinopathy, ESRD = End stage renal disease

HIV = Human immunodeficiency virus, HTN=Hypertension, INH = Isoniazide

IOP = Intraocular pressure, MMF = Mycophenolate mofetil, ONH = Optic nerve head

PTDM = post transplant diabetes mellitus, PVD=posterior vitreous detachment

RT = Renal Transplant, SLE = Slit lamp examination, SPHMMC = Saint Paul's hospital

millennium medical college, SPSS = Statistical package for social sciences, TB =Tuberculosis

V/A = Visual acuity

Declarations

Ethics approval and consent to participate

The study was approved by the ethical review board of Saint Paul's hospital millennium medical college. Since this study was non - invasive and most of the study subjects had very low literacy status, there was a problem of reading and understanding the information sheet and consent form. So informed verbal consent was taken from individual patients before participation into this research. The ethics committee already approved the collection of verbal consent.

Consent for publication

Consent for publication from individual patients and approval from ethical review board for publication is not applicable as this study does not contain any personal details, images or videos relating to an individual person.

Availability of data and materials

Data is available if needed.

Funding

This research work was financed by Saint Paul's Hospital millennium medical college. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors' contributions

LT was involved in study conception, data analysis, drafting the manuscript. EG reviewed, edited and approved the manuscript.

Acknowledgment

A special thank goes to all the staff members of transplant unit and optometrists and ophthalmologists involved in the data collection.

The author greatly acknowledge SPHMMC who approved this review concerning the ethical issues and for its financial support.

Competing interests

The author declare that they have no competing interests.

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Tables

Table 1: Causes of end stage renal disease among renal transplant patients following

at Saint Paul's Hospital Millennium Medical College, Addis Ababa,

Nov/2018.

Cause of ESRD	N _o (%)
Unknown	112(83.0%)
Hypertension	9(6.7%)
Diabetes mellitus	7(5.2%)
Obstructive nephropathy	5(3.7%)
Glomerulonephrities	2(1.5%)
Total	135 (100%)

Table 2: Types of ocular problems identified among renal transplanted patients at Saint Paul's

Hospital Millennium Medical College, Addis Ababa, Nov/2018.

Ocular disorders	N _o	% (128)
Dry eyes	76	59.4
Optic neuropathies	10	7.9
Retinal pigmentary changes	9	7.0
Blepharities	8	6.2
Cataract	8	6.2
Conjunctival degenerations	7	5.5
Vitreous opacity and PVD	5	3.9
Others	5	3.9

PVD - posterior vitreous detachment