RESEARCH ARTICLE

Frequency, associated factors and outcome of raised intraocular pressure in live-related renal transplant recipients: A single-centre experience

Fatema Ali Lanewala[1], Akhtar Jamal Khan[2], Mirza Naqi Zafar[3], Tahir Aziz[4]

Abstract

Objective: To investigate the frequency, associated factors and outcomes of elevated intraocular pressure in live-related renal transplant recipients.

Method: The study was conducted at the Department of Ophthalmology, Sindh Institute of Urology and Transplantation, Karachi, in 2023. The data was divided into group A cases having intraocular pressure ≥23mmHg and group B controls having intraocular pressure <23mmHg. The groups were compared for factors such as immunosuppression medications, acute rejection episodes, human leukocyte antigen match, duration of dialysis before transplant, and pre-existing microvascular diseases. Data was analysed using SPSS 22.

Results: Of the 2,738 patients screened, 131(4.8%) exhibited intraocular pressure ≥23mmHg. Intergroup comparison between group A and group B showed no significant relationship of intraocular pressure increase with cyclosporine, tacrolimus and everolimus ($p>0.05$). Azathioprine demonstrated significant association with intraocular pressure elevation at the time of measuring intraocular pressure ($p<0.05$). Mycophenolate mofetil showed an association with IOP only when assessed as initial immunesuppression at the time of transplantation ($p<0.05$). At the time of IOP assessment, MMF was not found to be a significant factor responsible for IOP elevation ($p>0.05$). Patients who had received Antithymocyte globulin (ATG) were found to have remarkable association with raised IOP. No significant link was noted between hypertension, dialysis duration and human leukocyte antigen match ($p>0.05$).

The multivariate analysis showed that Azathioprine was the only factor associated with raised IOP at the time of assessment ($p<0.001$)

Conclusion: There was a potential risk of medication side effects, including secondary glaucoma, among renal transplant recipients.

Keywords: Renal transplant, Steroids, Intraocular pressure, Glaucoma. (JPMA 75: 451; 2025)

DOI: https://doi.org/10.47391/JPMA.21710

Introduction

Renal transplant recipients (RTRs) need lifelong immunosuppression (IS) with low-dose systemic corticosteroids and other immunosuppressants in order to avoid graft rejection.[1] Multiple ocular problems have been reported in literature in such patients, including cataract, elevated intraocular pressure (IOP), opportunistic infections, conjunctival calcium deposits, central serous chorioretinopathy, etc.[2-4]

Among the many reported ocular complications, raised IOP leading to permanent damage to the optic nerve causes irreversible blindness. It is one of the most feared ocular problems, commonly known as glaucoma. The secondary open angle glaucoma, dreaded mainly in the transplant population that remains on systemic steroids for life, shows no warning signs to visit an ophthalmologist. It is usually not associated with pain, redness or sudden loss of vision. Glaucoma is called "the silent thief of sight" due to the painless chronic progressive peripheral loss of vision, later leading to irreversible blindness, preventable with constant monitoring of IOP and timely treatment.[5]

At the Sindh Institute of Urology and Transplantation (SIUT), Karachi, a tertiary care transplant centre, the IOP of RTRs is measured routinely in order to avoid this possible disastrous side-effects of systemic steroids. As routine clinical practice, those diagnosed with glaucoma are treated and followed up regularly. This is necessary due to the known effect of steroids dose and duration on IOP[6] and the chance of glaucoma increasing with advancing age.[7]

The current study was planned to investigate the frequency, associated factors and outcomes of elevated IOP in live-related RTRs.

Materials and Methods

The retrospective case-control study was conducted at the

[1,2]Department of Ophthalmology, Sindh Institute of Urology and Transplantation, Karachi, Pakistan; [3]Department of Chemical Pathology, Sindh Institute of Urology and Transplantation, Karachi, Pakistan; [4]Department of Transplantation, Sindh Institute of Urology and Transplantation, Karachi, Pakistan.

Correspondence: Fatema Ali Lanewala. e-mail: fatemali92.110@gmail.com
ORCID ID: 0000-0002-9024-0475

Submission completed: 12-08-2024 **1st Revision received:** 05-09-2024
Acceptance: 28-12-2024 **Last Revision received:** 27-12-2024

Department of Ophthalmology, SIUT, Karachi, from August to September 2023, and comprised medical records of RTRs screened for IOP between September 2021 and April 2022. The data was divided into group A cases having IOP ≥23mmHg and group B controls having IOP <23mmHg. Patient records were retrieved using convenience sampling technique after approval from the institutional ethics review committee.

Data retrieved from the medical files included post-transplant immunosuppression (cyclosporine, tacrolimus, mycophenolate mofetil (MMF), azathioprine and everolimus), acute rejection episodes receiving antithymocyte globulin (ATG), pre-existing medical conditions, like diabetes mellitus (DM) and hypertension (HTN), and duration of haemodialysis before transplant. These were recorded on a pre-designed proforma. Post-transplant immunosuppression (IS) was evaluated to determine any significant correlation between the medication and the rise in IOP. Post-transplant IS status was analysed at the time of commencement, and then later on at the time of assessing IOP.

Data was analysed using SPSS 22. Data normality was assessed using the Shapiro-Wilk's test. Continuous normally distributed variables were presented as mean +/- standard deviation, while non-normally distributed data was presented as median with interquartile range (IQR). Categorical variables were reported as frequencies and percentages. Intergroup comparison of continuous variables was done using two-sample t-test or Mann-Whitney U test, as appropriate. Chi-square test was used for the comparison of categorical variables. For identification of risk factors, univariate or multivariate logistic regression was performed. P<0.05 was considered statistically significant.

Results

Of the 2,738 patients screened, 131(4.8%) exhibited IOP ≥23mmHg, and glaucoma was identified in 23(0.8%). From among these 131(4.8%) cases, 100(76.3%) were included in group A; 75(75%) males and 25 (25%) females with mean age 36.15±11.17 years. Control group B also had data of 100 patients; 79(79%) males and 21(21%) females with mean age 36.17±11.14 years. The mean time lapse since transplant was 8.02±5.25 years in group A and 8.09±5.23 years in group B (*p*=0.922).

Intergroup comparison showed no significant relationship of IOP increase with cyclosporine, tacrolimus and everolimus, whether analysed at the time of Tx or assessing IOP (*p*>0.05). Azathioprine, MMF and ATG demonstrated significant association with IOP elevation (*p*<0.05). Those receiving Azathioprine at the time of Tx showed a 0.34 times less chance of having raised IOP (*p*=0.019, odds ratio [OR]: 2.916, 95% confidence interval [CI]: 1.160-7.334) while those receiving MMF showed a 2.9 times higher chance of having raised IOP (*p*=0.019, odds ratio [OR]: 2.916, 95% confidence interval [CI]: 1.160-7.334) (Table 1).

Interleukin-2 (IL-2) was prescribed to 4(4%) patients in group A and to 3 in group B only.

At the time of IOP assessment, patients receiving cyclosporine, tacrolimus, MMF and everolimus showed no significant association with IOP elevation, but those taking azathioprine were seen to have 1.97 times likelihood of raised IOP (*p*=0.037, OR: 1.97, 95% CI: 1.035-3.749) (Table 2).

Patients whose initial IS was a combination of cyclosporine, azathioprine, and prednisolone showed less likelihood of raised IOP (*p*=0.027, OR: 0.43, 95% CI: 0.202-0.921) (Table 3).

No substantial association was found between pre-transplant or post-transplant HTN and IOP, but a 2.5 times higher chance was seen in patients who had received ATG

Table-1: Comparison between post-transplant intraocular pressure (IOP) and individual immunosuppression (IS) at time of transplant (Tx).

Variables	Frequency (n)		*p*-value	Unadjusted OR
	Cases n(%)	**Controls** n (%)		**(95% C.I.)**
Cyclosporine	82 (82.0)	88 (88.0)	0.235	0.621 (0.282–1.369)
Tacrolimus	18 (18.0)	12 (12.0)	0.235	1.610 (0.731– .547)
Azathioprine	82 (82.0)	93 (93.0)	0.019	0.343 (0.136-0.862)
MMF	18 (18.0)	7 (7.0)	0.019	2.916 (1.160–7.334)

MMF: Mycophenolate mofetil, OR: Odds ratio, CI: Confidence interval.

Table-2: Comparison between intraocular pressure (IOP) and immunosuppression (IS) at the time of assessment.

Variables	Frequency (n)		*p*-value	Unadjusted OR
	Cases n(%)	**Controls** n (%)		**(95% C.I.)**
Cyclosporine	34 (34.0)	38 (38.0)	0.556	0.841 (0.471 – 1.498)
Tacrolimus	39 (39.0)	29 (29.0)	0.136	1.565 (0.868 – 2.824)
Azathioprine	80 (80.0)	67 (67.0)	0.037	1.970 (1.035 – 3.749)
MMF	16 (16.0)	22 (22.0)	0.279	0.675 (0.331 – 1.379)
Everolimus	6 (6.0)	8 (8.0)	0.579	0.734 (0.245 – 2.198)

MMF: Mycophenolate mofetil, OR: Odds ratio, CI: Confidence interval.

Table-3: Comparison between intraocular pressure (IOP) and post-transplant combination immunosuppression (IS) at time of transplant (Tx).

Variables	Frequency (n)		*p*-value	Unadjusted OR
	Cases n(%)	**Controls** n (%)		**(95% C.I.)**
Tacrolimus+ Azathioprine+Prednisolone	6 (6.0)	5 (5.0)	0.756	1.213 (0.358 – 4.110)
Tacrolimus+ MMF+Prednisolone	12 (12.0)	7 (7.0)	0.228	1.812 (0.682 – 4.811)
Cyclosporin+ Azathioprine+Prednisolone	76 (76.0)	88 (88.0)	0.027	0.432 (.202 - 0.921)

MMF: Mycophenolate mofetil, OR: Odds ratio, CI: Confidence interval.

Table-4: Intergroup comparison for hypertension (HTN), antithymocyte globulin (ATG) and intraocular pressure (IOP).

Variables	Frequency (n)		*p*-value	Unadjusted OR (95% C.I.)
	Cases n(%)	**Controls** n (%)		
Pre-Tx HTN	64 (64.0)	69 (69.0)	0.454	0.799 (0.443 – 1.439)
Post-Tx HTN	75 (75.0)	71 (71.0)	0.524	1.225 (0.655 – 2.291)
ATG	24 (24.0)	11(11.0)	0.016	2.555 (1.175 – 5.554)

Tx: Transplantation.

Table-5: Independent factors associated with intraocular pressure (IOP).

	Sig.	Adjusted OR	95% C.I. for OR	
			Lower	Upper
AZA at Tx (Yes vs No)	0.114	0.273	0.055	1.363
AZA at IOP (Yes vs No)	0.000	4.014	1.883	8.555
Cya AZA Prednisolone (Yes vs No)	0.769	1.246	0.288	5.382
ATG at Tx (Yes vs No)	0.152	2.324	0.733	7.368
Constant	0.767	.819	-	-

Tx: Transplant. AZA: Azathioprine, Cya: Cyclosporine, IOP: Intraocular Pressure; ATG: Antithymocyte globulin.

(*p*=0.016. OR: 2.55, 95% CI: 1.175-5.554) (Table 4).

The multivariate analysis showed that Azathioprine was the only factor that showed 4.014 times higher chance of raised IOP at the time of IOP assessment (*p*<0.001. OR:4.01, 95% CI: 1.883-8.555) (Table 5).

The duration of dialysis before transplant in group A was 10.13±11.77 months and 7.93±10.18 months in group B (*p*=0.922).

Discussion

Renal transplantation is a lifesaving procedure that is on the rise due to its remarkable impact on the quality of life of the recipient. However, the RTRs are required to take multiple medications, including systemic steroids and IS agents in order to make the graft work efficiently. These medications come with their own side effects on the human body.[8]

In addition to the other systemic adverse effects, these medications, especially steroids, can have many harmful effects on the eyes, like cataract, elevated IOP, opportunistic infections, conjunctival calcium deposits, central serous chorioretinopathy, and others.[2-4] The raised IOP can cause optic neuropathy, leading to permanent loss of vision if not diagnosed and controlled in time. In some studies, systemic IS agents have shown to cause a variety of systemic side-effects, but with no ocular involvement identified.[8] In other studies, cyclosporine showed neural and retinal toxicity,[9] while tacrolimus affected optic nerve, visual cortex and macula, leading to visual deterioration.[10,11] MMF has shown variable retinal toxicity in vitro, but no such toxicity has been reported among in vivo subjects.[12]

The current study indicated a remarkable relationship between MMF and the rise in IOP when analysed individually at the time of renal transplant. When individual IS was analysed at the time of IOP assessment, a significant correlation was observed between azathioprine, but no such correlation was seen with MMF.

In combination, cyclosporine, azathioprine and prednisolone showed significantly less likelihood of raising IOP compared to those receiving other IS combinations.

In this study, azathioprine was found to be remarkably related to the rise in IOP, especially when analysed at the time of monitoring IOP at the relevant department. However, azathioprine showed no relationship with IOP when given in combination with tacrolimus. Moreover, tacrolimus showed no association with a rise in IOP at whatever time or with whichever combination it was assessed.

MMF showed a positive relationship with IOP when given as the initial IS at the time of transplant, but no such finding could be established when its effect was analysed at the time of taking IOP or when given in combination with MMF as initial IS post-transplant.

The current data indicated the probability of a positive neuroprotective role of tacrolimus when compared to other IS agents. It may help reduce IOP or keep it under control when given to RTRs. The possible IOP-reducing effect of tacrolimus has been mentioned previously as well.[13]

Prednisolone is a common factor which was given to all the individuals in the current study, including cases and controls. Therefore, the study could not establish its role or the uniqueness of prednisolone.

Earlier studies have established a strong association of systemic steroids and IOP as well as glaucoma, giving it a specific name, "Steroid-induced (secondary) glaucoma."[14] It is a well-known and widely accepted fact that steroids taken through any route, topical, intranasal, oral or intravenous, have a strong role in raising the IOP and leading to glaucoma. However, what remains unclear is the relationship between the duration and dose of steroid and raised IOP leading to secondary glaucoma.[15,16]

In the present study, the correlation between factors other than steroid were explored. These factors included IS agents, which were assessed individually as well as in combination. The study also evaluated any possible role of systemic comorbidities, and acute rejection episodes receiving ATG.

A case study reporting neuroretinopathy secondary to ATG noted that it was not related to high IOP.[17] The current study, to the best of our knowledge, is the first to report the

possibility of ATG having any association with IOP. This rise may have been due to the fact that ATG, when given in cases of acute rejection episodes, is always given in combination with high-dose systemic steroids. As mentioned earlier, this could be an effect of the steroids and not secondary to ATG infusion. This factor needs careful evaluation and exploration in order to confirm any association between ATG and IOP. There is substantial literature over decades to prove the association between systemic HTN and IOP.[18-21] The current study, however, showed no significant relationship between the two factors. A possible explanation for the finding may be the fact that in our setup, systemic HTN is routinely kept under control and managed meticulously during pre- and post-transplantation.

Although literature provides a strong association between DM and IOP,[22] there were not enough participants in the current study to establish the association, which was a limitation. Also, the sample was raised using convenience sampling, which could have influenced the power of the study.

The difference between the duration of dialysis among the two groups was insignificant, therefore, its effect on IOP could not be measured.

The strength of the study is that, to the best of our knowledge, the current study is the first of its kind in Pakistan.

On the basis of the findings, further exploration on a larger scale is recommended for the possible protective role of tacrolimus. A solid evidence-based conclusion about the IOP-lowering role of tacrolimus may help manage post-transplant IS in patients suffering from secondary glaucoma.

Conclusion

Renal transplant recipients require special attention in order to make transplant a success. These individuals are on life-long medications for proper functioning of the allograft. There is potential risk of side-effects of these systemic medications among which secondary glaucoma is a potential ocular side-effect that can lead to permanent loss of vision. Proactive measures and routine ocular examinations are necessary in order to prevent any detrimental effect on the vision, and to improve the quality of life of these individuals.

Acknowledgement: We are grateful to Mr Farid bin Masood, Ms Sualeha Shekhani and Ms Tasneem Ali Lanewala for their help and guidance.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

References

1. Bamgbola O. A Critical Review of Steroid Immunotherapy in Kidney Transplantation. Int J Immunol Immunother 2015;2:006. Doi: 10.23937/2378-3672/1410006
2. Lanzetta P, Monaco P. Major ocular complications after organ transplantation. Indian J Ophthalmol 2004;52:95-7.
3. Kian-Ersi F, Taheri S, Akhlaghi MR. Ocular disorders in renal transplant patients. Saudi J Kidney Dis Transpl 2008;19:751-5.
4. Malerbi FK, Teixeira SH, Hirai LGG, Matsudo NH, Carneiro ABM. Retinal changes in solid organ and bone marrow transplantation patients. Einstein (Sao Paulo) 2017;15:123-9. doi: 10.1590/S1679-45082017AO3992
5. Abdull MM, Chandler C, Gilbert C. Glaucoma, "the silent thief of sight": patients' perspectives and health seeking behaviour in Bauchi, northern Nigeria. BMC Ophthalmol 2016;16:44. doi: 10.1186/s12886-016-0220-6
6. Mandapati JS, Metta AK. Intraocular pressure variation in patients on long-term corticosteroids. Indian Dermatol Online J 2011;2:67-9. doi: 10.4103/2229-5178.85993
7. Hashemi H, Mohammadi M, Zandvakil N, Khabazkhoob M, Emamian MH, Shariati M, et al. Prevalence and risk factors of glaucoma in an adult population from Shahroud, Iran. J Curr Ophthalmol 2018;31:366-72. doi: 10.1016/j.joco.2018.05.003
8. Claeys E, Vermeire K. Immunosuppressive drugs in organ transplantation to prevent allograft rejection: Mode of action and side effects. J Immunological Sci 2019;3:14-21. DOI: 10.29245/2578-3009/2019/4.1178
9. López-Jiménez J, Sánchez A, Fernández CS, Gutiérrez C, Herrera P, Odriozola J. Cyclosporine-induced retinal toxic blindness. Bone Marrow Transplant 1997;20:243-5. doi: 10.1038/sj.bmt.1700878
10. Rasool N, Boudreault K, Lessell S, Prasad S, Cestari DM. Tacrolimus Optic Neuropathy. J Neuroophthalmol 2018;38:160-6. doi: 10.1097/WNO.0000000000000635
11. Santarelli M, Zeppieri M, Salati C. A Case of Tacrolimus Maculopathy. Clin Pract 2022;12:276-83. doi: 10.3390/clinpract12030033
12. M Castillejo Becerra C, Ding Y, Kenol B, Hendershot A, Meara AS. Ocular side effects of antirheumatic medications: a qualitative review. BMJ Open Ophthalmol 2020;5:e000331. doi: 10.1136/bmjophth-2019-000331
13. Kiiski V, Remitz A, Reitamo S, Mandelin J, Kari O. Long-term safety of topical pimecrolimus and topical tacrolimus in atopic blepharoconjunctivitis. JAMA Dermatol 2014;150:571-3. doi: 10.1001/jamadermatol.2013.7016
14. Phulke S, Kaushik S, Kaur S, Pandav SS. Steroid-induced Glaucoma: An Avoidable Irreversible Blindness. J Curr Glaucoma Pract 2017;11:67-72. doi: 10.5005/jp-journals-l0028-1226
15. Mushtaq U, Shaman Ameen B, Nie C, Nechi D, Mazhar IJ, Yasir M, et al. Association Between the Use of Systemic Steroids and Ocular Hypertension as a Side Effect in Pediatric Population: A Systematic Review. Cureus 2023;15:e42112. doi: 10.7759/cureus.42112
16. Wijnants D, Stalmans I, Vandewalle E. The Effects of Intranasal, Inhaled and Systemic Glucocorticoids on Intraocular Pressure: A Literature Review. J Clin Med 2022;11:2007. doi: 10.3390/jcm11072007
17. Munch IC, Traustason S, Olgaard K, Larsen M. Acute macular neuroretinopathy in relation to anti-thymocyte globulin infusion. Acta Ophthalmol 2012;90:e321-2. doi: 10.1111/j.1755-3768.2011.02276.x
18. Mitchell P, Lee AJ, Rochtchina E, Wang JJ. Open-angle glaucoma and

systemic hypertension: the blue mountains eye study. J Glaucoma 2004;13:319-26. doi: 10.1097/00061198-200408000-00010

19. Hennis A, Wu SY, Nemesure B, Leske MC. Hypertension, diabetes, and longitudinal changes in intraocular pressure. Ophthalmology 2003;110:908-14. doi: 10.1016/S0161-6420(03)00075-7
20. Dielemans I, Vingerling JR, Algra D, Hofman A, Grobbee DE, de Jong PT. Primary open-angle glaucoma, intraocular pressure, and systemic blood pressure in the general elderly population. The Rotterdam Study. Ophthalmology 1995;102:54-60. doi: 10.1016/s0161-6420(95)31054-8.
21. Nomura H, Shimokata H, Ando F, Miyake Y, Kuzuya F. Age-related changes in intraocular pressure in a large Japanese population: a cross-sectional and longitudinal study. Ophthalmology 1999;106:2016-22. doi: 10.1016/S0161-6420(99)90417-7
22. Klein BE, Klein R, Jensen SC. Open-angle glaucoma and older-onset diabetes. The Beaver Dam Eye Study. Ophthalmology 1994;101:1173-7. doi: 10.1016/s0161-6420(94)31191-2.

Author Contribution:

FAL: Concept, literature search, design, drafting and review.
AJK: Critical review.
MNZ: Design and data analysis.
TA: Investigation and data acquisition.