Outcomes of penetrating keratoplasty at a tertiary institution in South Africa.

YM Theron: MBChB (UP), Dip Ophth (SA), FC Ophth (SA); registrar, Groote Schuur Hospital, Department of Ophthalmology, University of Cape Town, South Africa.
https://orcid.org/0009-0004-8635-966X

N du Toit: MBChB (UCT), Dip Ophth (SA), FRCS (Ed), Mmed (UCT), FC Ophth (SA), PhD(UCT), Mauerberger Chair of Ophthalmology and Head of Division of Ophthalmology (Dept of Surgery) Faculty of Health Sciences, University of Cape Town, Groote Schuur Hospital and Red Cross Children's Hospital.
https://orcid.org/0000-0003-1167-2796

M Gajjar: MBChB (UCT); Medical Officer, Potchefstroom Hospital, Division of Ophthalmology.
https://orcid.org/0009-0006-4071-0383

Corresponding Author: Dr Yolande Maryna Theron,
debeeryol@gmail.com

Abstract

Aims: To determine corneal graft survival rates and visual outcomes of penetrating keratoplasty (PKP) in a South African setting.

Methods: A retrospective review of 99 penetrating keratoplasties performed at Groote Schuur Hospital, South Africa over a 3-year period between February 2016 and February 2019.

Results: The mean age of study participants was 38 years (14-85). The study included 60% females and 40% males. The main indications for surgery were keratoconus (58%), corneal scar (21%), regrafts (8%), pseudophakic bullous keratopathy (6%), corneal dystrophies (3%) and pellucid marginal degeneration (1%). The overall graft survival at 1-year follow up was 86%. A higher 1-year graft survival rate of 94% was seen in patients with keratoconus. The total number of patients diagnosed with graft failure at 1 year was 13.The Kaplan-Meier survival analysis was used to assess time to graft failure. The estimate was 11.7 months (mean time to graft failure) with a 95% CI confidence interval from 11.4 to 12 months. In our study, best corrected Snellen acuity in the category of 6/6-6/18 was found in 59.2% of patients one year post-operatively, compared with 1% of patients in the same BCVA group pre-operatively. Patients with a BCVA equal to 3/60 or less reduced from 56% pre-operatively to 20% postoperatively at one year.

Conclusion: Penetrating Keratoplasty is an effective long term treatment option to restore visual acuity in certain corneal disorders in a middle to low-income country. Our results demonstrated a comparable 1-year graft survival rate to high-income countries.

Keywords: penetrating keratoplasty, South Africa, graft failure, cornea, outcomes

Funding: The authors have no proprietary or commercial interest in any of the materials discussed in this article.

Conflicts of interest: There are no conflicts of interest to declare.

Introduction

According to World Health Organisation, corneal opacity is one of leading causes of global blindness and visual impairment.[1,2] . Bilateral blindness affects roughly 45 million people globally. In low-income countries, an estimated 10 million people are affected by corneal blindness[1,2]. Children and young adults are commonly affected by corneal disease resulting in monocular and bilateral blindness. In some areas in Asia and Africa, it has been reported that the incidence of vision loss in children and young adults due to corneal disease is 20 times higher than in other high-income countries.[4]

Corneal transplant surgery, where the diseased host cornea is replaced by healthy donor cornea, can restore visual potential in such patients and is worldwide the most commonly performed transplanted tissue/organ worldwide.[5,6] Different methods of corneal transplant surgery exists, and these includes penetrating keratoplasty (full-thickness corneal transplant) and anterior or posterior lamellar keratoplasty (partial thickness corneal transplant). Lamellar graft surgery has gained popularity during the past 10 years, especially in high-income countries.[6,7]

Low-income countries face many challenges when attempting to resolve the burden of disease associated with corneal blindness. Barriers include amongst others, poor eye bank infrastructure (resulting in shortage of donor tissue), limited number of trained corneal surgeons and socio-economic factors (e.g. poor post-operative follow up). [1;8-11;25]

Long-term graft survival is an important objective in order to improve visual acuity in these patients. [2] Groote Schuur Hospital is a tertiary institution situated in Cape Town, Western Cape Province, which offers general and specialist ophthalmic services. The aim of this study was to evaluate corneal transplant surgery outcomes at Groote Schuur Hospital, to identify causes of graft failure and to subsequently use this data to implement changes where possible to ensure improvements in long-term graft survival in our patients.

Materials and methods

This is a retrospective review of patients who underwent optical penetrating keratoplasty at Groote Schuur Hospital, Cape Town, South Africa between 1 February 2016 and 1 February 2019. All patients older than 13 years who received penetrating keratoplasty surgery during the specific time period were included. During the time period of this study, tectonic penetrating keratoplasty and glycerol graft corneal transplants were excluded. This study was approved by the University

of Cape Town Research Ethics Committee and was in accordance with the tenets of the Declaration of Helsinki.

Data Variables:

Data collected included patient demographics, namely: age, gender and their current area of residence (within 50km of Cape Town or beyond). Pre-operative variables that were recorded were best corrected Snellen visual acuity (pinhole, spectacles or contact lenses), indications for PKP and intraocular pressure (IOP). The different categories for BCVA were based on similar categories used in other studies.[11, 13, 18] The intra-operative data obtained included surgery performed (PKP alone or combined PKP-cataract procedure) and complications encountered. Post-operative data reviewed consisted of BCVA, IOP, graft rejection, graft failure and complications that occurred. Post-operative data was obtained at the 1-month, 6-month and 12-month follow-up visits.

Outcome measures:

The primary outcome measure was graft success. This was defined by evaluating BCVA of 6/6-6/18, the lack of graft rejection and the absence of graft failure at the different time intervals. Secondary outcomes consisted of assessing the complications that were recorded.

Surgical technique:

All patients who underwent penetrating keratoplasty received a general anaesthetic. Donor corneas were obtained from National Medical Supplies (Visionshare) and prepared using a manual trephine. The donor graft was oversized by 0.25-0.5mm compared with the recipient. The corneal donor button was sutured to the host bed with sixteen interrupted 10-0 Nylon sutures. Intracameral cefuroxime as well as subconjunctival betamethasone was given at the end of surgery. All surgeries were performed either by one of the corneal consultants or by a supervised senior registrar. The post-operative regime included prednisolone acetate 1% eye drops six times daily and ofloxacin eye drops 4 times daily for one month. This was then changed to dexamethasone 0.1% eye drops 4 times daily for 6 months and 3 times daily for another 6 months. Loose sutures were removed when encountered and the remainder of sutures were removed at approximately 12-18 months post-op.

Post-operative care:

Patients were seen day 1, week 1, week 2, then 1,3,6 and ,12 months from the date of surgery, and then subsequently at 6-monthly intervals. At each routine follow-up visit, BCVA was measured using a Snellen Chart. IOP was measured using puff tonometry. The graft was evaluated by slit-lamp microscopy for clarity, signs of

rejection or failure and any complication that might have occurred.

Evaluation criteria:

Graft rejection was considered if there was endothelial or epithelial rejection lines and keratic precipitates.[8,9] Early graft rejection was defined as graft rejection occurring at or before 6 months. Graft failure was defined as an existing graft with irreversible loss of clarity as a result of oedema, neovascularization or scarring.[10] Early graft failure was defined as graft failure occurring at or before 6 months.

Statistical Analysis:

IBM SPSS version 28 was used to analyse the data. A *p* value <0.05 was considered as statistically significant. Categorical variables were described using frequency tables and percentages. Continuous variables were summarised using mean and standard deviation. Comparisons between proportions were made using Fisher's exact and Chi- Ssquare tests. Comparisons between two independent means were made using t-tests. Kaplan-Meier survival analysis was used to analyse time to graft rejection. Repeated measures ANOVA was used to compare overall change in IOP over time as well as specific time points.

Results

A total of 112 PKP surgeries were performed during the 3-year study period and data of 99 PKP were included for analysis. Thirteen patients did not attend their 1-year follow up visit and were therefore excluded from the study.

Demographics:

Table 1 summarises the patient's demographics. The mean age was 38 years (range 14-85; SD=20).The majority of patients (85%) lived within 50km radius of the hospital, where they underwent PKP and attended followed-up visits.

Indications:

The main indications for corneal transplant were keratoconus (58%). Refer to Table 2 for other indications.

Visual Outcome:

During the study period, best corrected Snellen acuity (BCVA) was evaluated pre-operatively, at 1 month, 6 month and a year follow up visits. Pre-operatively BCVA of <3/60 was seen in 55 patients (56.1%) in the affected eye. Post-operative BCVA in the operated eye at 1-year in the 6/6-6/18 group was seen in 58 patients (59.2%)

The distribution of BCVA at different time intervals is summarised in Table 3.

Intraocular pressure:

Repeated measures ANOVA was used to compare overall change over time as well as specific time points. IOP increased significantly over the entire time period (Wilk's lambda= 0.792, p=0.004) and also significantly between each time period and the pre-operative value. However, when comparing each time point to the one preceding it, the only statistically significant increase was between pre-op and 1 month.

Figure 1 summarises mean and 95% CI IOP over time.

Graft outcomes:

The Kaplan-Meier survival analysis was used to assess time to graft failure. The estimate was 11.7 months (mean time to graft failure) with a 95% CI from 11.4 to 12 months. The cumulative survival probability at one year was 86%.

The total number of patients diagnosed with graft failure at 1-year was 13. Among these patients, the pre-operative indications included pre-existing corneal scar (46%), keratoconus (23%), regraft (15%) and pseudophakic bullous keratopathy (15%).

Early graft failure (occurring before 6 months) was seen in 30% of patients which had graft failure.

Complications which contributed to graft failure were graft rejection 30% (n=4), persistent central epithelial defect 15% (n=2), infective keratitis 15% (n=2), graft dehiscence 7% (n=1), post-avastin endophthalmitis 7% (n=1) and poor compliance and follow up was seen in 23% (n=3) patients. .

In our study 24% (n=24) of patients experienced at least one episode of graft rejection over a follow-up period of 1-year. Early graft rejection (occurring before 6 months) was detected in 18 patients and 83% (n=15) of these episodes occurred most frequently in the 1 month post-operative time period. The progression to graft failure following an episode of graft rejection was seen in 16% of patients.

Table 4 summarises the complications seen at different follow up visits.

Discussion

The overall graft survival at 1-year was 86% in our study group. This is comparable to studies done in other low-income African countries. Chen et al. in Kenya reported 1-year graft survival rate as 85.8%.[11] Ayalew et al. in Ethiopia and Yorston et al. in Kenya reported the 2-year graft survival as 80% and 87% respectively. [10,13]

In high-income countries a comparable 1-year graft survival rate was reported. The Corneal Transplant follow up study in the UK reported 1-year graft survival as 88% and the Australian Corneal Graft registry reported it as 91%. [19]

The pre-operative indications for PKP greatly influence graft outcomes. Keratoconus most often has a higher graft survival rate as seen in a number of previous studies.[14,15]

In our study group, keratoconus made up the greatest proportion of patients (58%). This is comparable to studies done in other African and high-income Western countries.[15] Khan et al. (2015) reported the commonest indication for PKP in South Africa was keratoconus (64%).[2] Similar reports were noted by Chen et al. indicating the total percentage of patients with keratoconus in their study as 66.1%. [11]

In other low-income countries such as Pakistan and India, studies have reported their main indication for PKP to be corneal scarring. This generally influence graft survival which may explain the lower graft survival rates in these countries.[16,17]. Dandona et al. in India reported graft survival rates at 1-year as 79,6%.[18] Moin-ud-Din in Bangladesh reported the leading indication for PKP to be corneal scarring (41%). [17]

Looking at the different subgroups, the 1-year graft survival rate for keratoconus in our study was 94%. This is comparable to other studies in low-income countries. In Kenya and India the graft survival rates for keratoconus at 1-year was reported as 89,9% and 96,4% respectively. [11,18]

In our study, best corrected Snellen acuity in the category of 6/6-6/18 was seen in 59.2% of patients at 1-year post-operatively. This was much higher compared to the percentage of patients in the same BCVA group pre-operatively.

The overall graft failure rate was 13% in our study group and the majority of these patients had corneal scarring pre-operatively. The causes of corneal scarring were mostly due to infective keratitis, trauma and unspecified reasons respectively. Patients with previous herpes simplex keratitis were not selected for penetrating keratoplasty at Groote Schuur Hospital due to the high risk of graft failure in these patients.

In a multivariate analysis done by Yu et al., the postoperative risk factors strongly associated with graft failure were postoperative glaucoma medication, suture problems, infective keratitis, graft rejection, persistent epithelial defect and retinal surgery. [22]

Graft rejection is one the most common reasons for graft failure.[20] The time period that constitutes the highest risk for graft rejection is 150 days post-operatively as reported by the Corneal Transplant follow up Study.[19] This correlates to findings in our study where the majority of graft episodes occurred within the first 6 months. In

contrast, Perera et al. reported that in their study group, 27% of patients experienced early graft rejection and 73% of patients had late graft rejection episodes.[20]

Rahman et al. in the UK reported that an endothelial graft rejection episode was seen in 21% of patients over a period of 5 years. Of these patients, 7.4% experienced graft failure. [21] In our study a higher percentage of patients (16%) that had a graft rejection episode progressed to graft failure.

In low-income countries, poor follow up and non-compliance with treatment remains a challenge.[23] In our study the non-attendance at 1 month, 6 month and 1-year follow up was 1%,4% and 13% respectively. Twenty three percent of graft failure cases failed to attend the 6 month follow up visit and therefore poor compliance and non-attendance were contributing factors. A study done in Kenya reported that 33% of patients that underwent PKP did not attend the 1-year follow up visit and financial barriers were the main reason for non-attendance in 42% of these patients.[24] Dandona et al. reported that patients in poor socio-economic circumstances had a higher chance of graft failure - the relative risk was 1.28.[1]

It is important to note that good outcomes with penetrating keratoplasty were achievable despite using imported corneas travelling long distances from the USA.

Limitations to our study were the small number of patients included and the relative short follow up time. This was also a retrospective study based on the review of medical records and the information provided in patient's folders determined the quality of data.

Conclusion

In this study, the overall graft survival rate at 1-year was 86%, with 59,2% of patients having BCVA of 6/6-6/18. Therefore, penetrating keratoplasty remains an effective long term treatment option to restore visual acuity in certain corneal disorders. This is comparable to other studies done in low-income and high-income countries. In South Africa, the lack of resources such as a shortage of donor corneas greatly impacts the number of PKP that can be performed. [2,25] Socio-economic challenges also influence the post-operative care. Despite these hurdles in our system, our study reports that an effective corneal graft outcome can be achieved. Although we didn't assess donor corneal graft availability, efforts in increasing the number of graft tissue remains a high priority to address the burden of corneal blindness. Further prospective studies are required to give more information on outcomes of penetrating keratoplasty in South Africa.

Tables and illustrations:

Table 1: Patient's demographics

		Count	%
Sex	Male	40	40.4%

	Female	59	59.6%
	Total	99	100.0%
Residence : Local or country	C	14	14.1%
	L	85	85.9%
	Total	99	100.0%
Age (years)	Mean (SD)	38 (20)	

C = Country ; L = Local ; SD = Standard variation

Table 2: Indications for PKP

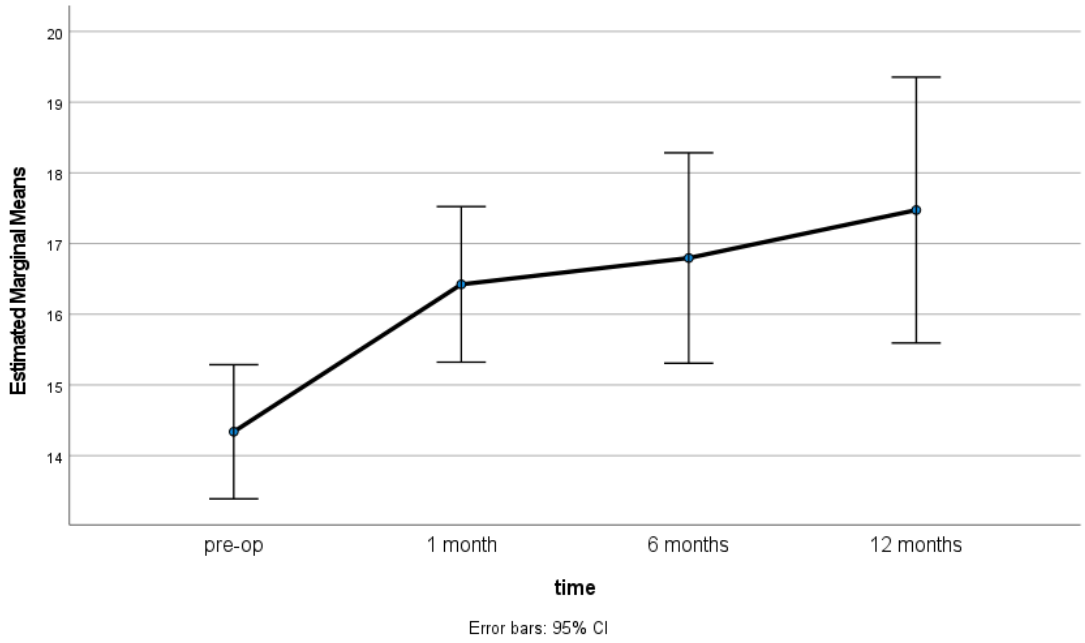
			Count	Column %
Indications	Bullous keratopathy		6	6.1%
	Corneal dystrophy	Lattice	1	1.0%
		Fuch's	4	4.0%
	Corneal scar	Trauma	6	6.1%
		IK	13	13.1%
		Unspecified	2	2.0%
	Failed graft		8	8.1%
	Keratoconus		58	58.6%
	Pellucid marginal degeneration		1	1.0%
	Total		99	100.0%

IK = Infective keratitis

Table 3: Best corrected visual acuity outcomes

	Pre-op		1 month		6 months		1 year	
BCVA category	n	%	n	%	n	%	n	%
6/6 – 6/18	1	1.0%	34	35.4%	47	50.0%	58	59.2%
<6/18 - 6/36	26	26.5%	34	35.4%	25	26.6%	17	17.3%
<6/36 - 6/60	16	16.3%	6	6.3%	4	4.3%	3	3.1%
<6/60 - 3/60	0	0.0%	0	0.0%	0	0.0%	0	0.0%
<3/60	55	56.1%	22	22.9%	18	19.1%	20	20.4%

Figure 1 : Mean and 95% CI IOP over time



IOP = Intraocular pressure; CI = Confidence interval

Table 4: Complications at various time intervals

		Count	Column %
Intra-op complications	Aqueous misdirection	2	2.0%
	Hyphaema	1	1.0%
	Leucoma adherens	1	1.0%
	None	88	88.8%
	Suture tract leak	2	2.0%
	Thin peripheral host corneal tissue	5	5.1%
	Total	99	100.0%

	1 month		6 months		1 year	
	Count	%	Count	%	Count	%
Non attendance	1	1.0%	4	4.0%		
Descemet folds	2	2.0%				
Graft dehiscence	3	3.0%				
Graft failure			4	4.0%	13	13.1%
Graft rejection	15	15.2%	4	4.0%	6	6.1%
Graft rupture: trauma	1	1.0%	3	3.0%	1	1.0%
Infective keratitis	1	1.0%	1	1.0%		
Loose sutures	1	1.0%	1	1.0%	1	1.0%
Non compliance	3	3.0%	1	1.0%		
None	65	65.7%	64	64.6%	68	68.7%
Ocular surface	1	1.0%	2	2.0%		

disease						
Other			4	4.0%	5	5.1%
Persistent CED	2	2.0%	2	2.0%		
Steroid induced ocular hypertension	4	4.0%	9	9.1%	6	6.1%
Total	99	100.0%	99	100.0%	99	100.0%

CED = Central epithelilal defect

Acknowledgements:

The authors would like to thank Prof Tonya Esterhuizen for statistical support.

References

1. Pineda R. Corneal Transplantation in the Developing World: Lessons Learned and Meeting the Challenge. Cornea. 2015;34:35-40.

2. Khan M, Visser L, Mahomed S. Penetrating keratoplasty in eThekwini Health District 2011–2014. Afr Vision Eye Health. 2015;74:1-4.

3. Flaxman SR, Bourne RRA, Resnikoff S et al. Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. Lancet Glob Health. 2017;5:1221-1234.

4. Whitcher JP, Srinivasan M, Upadhyah. Corneal blindness: a global perspective. Bulletin of the World Health Organization. 2001;79:214-221.

5. Gain P, Julienne R, He Z et al. Global Survey of Corneal Transplantation and Eye Banking. JAMA Ophthalmol. 2016;134:167-173.

6. Omar N, Bou Chacra CT, Tabbara KF. Outcome of corneal transplantation in a private institution in Saudi Arabia. Clinical Ophthalmology. 2013;7:1311-1318.

7. Quigley, C., McElnea, E. Fahy, G. Trends in corneal transplant surgery in Ireland: indications and outcomes of corneal transplant surgery and intraocular lens opacification following Descemet's stripping automated endothelial keratoplasty. Ir J Med Sci (2018) 187: 231.

8. Pan Q, Li X, Gu Y et al. Indications and outcomes of penetrating keratoplasty in a tertiary hospital in the developing world. Clinical and Experimental Ophthalmology. 2012;40:232-238.

9. Raj A, Gupta N, Dhusmana R et al. Indications and Visual Outcome of Penetrating Keratoplasty in Tertiary Eye Care Institute in Uttarakhand. Journal of Clinical and Diagnostic Research. 2016;10:1-4.

10. Ayalew M, Tilahun Y, Holsclaw D et al. Penetrating Keratoplasty at a Tertiary Referral Center in Ethiopia: Indications and Outcomes. Cornea. 2017;36:665-668.

11. Chen MC, Kunselman AR, Stetter CM et al. Corneal transplantation at Tenwek Hospital, Kenya, East Africa: Analysis of outcomes and associated patient socioeconomic characteristics. PLoS One. 2017 Oct 27;12(10):e0187026. doi: 10.1371/journal.pone.0187026. eCollection 2017.

12. Vanathi M, Tandon R, Panda A et al. Challenges of eye banking in the developing world. Expert review of Ophthalmology. 2007;2:923-932.

13. Yorston D, Wood M, Foster A. Penetrating keratoplasty in Africa: graft survival and visual outcome. Br J Ophthalmol. 1996;80:890-894.

14.Reinprayoon U, Srihatrai P, Satitpitakul V et al. Survival Outcome and Prognostic Factors of Corneal Transplantation: A 15 year retrospective Cohort study at King Chulalongkorn Memorial Hospital. Clinical Ophthalmology. 2021;15:4189-4199.

15. Thompson RW, O.Price M, Bowers PJ. Long-term Graft Survival after Penetrating Keratoplasty. Ophthalmology. 2003;110:1396-1402.

16. Al-Sharif E, Alkharashi M. Indications, surgical procedures and outcomes of keratoplasty at a Tertiary University-based hospital: a review of 10 years' experience. Int Ophthalmol. 2021;41:957-972.

17. Moin-ud-Din ASM, Sultana C, Shahid MAM et al. Indications and Outcomes of Penetrating Keratoplasty at a Tertiary Hospital in Bangladesh. Pak J Ophthalmol. 2020;36:440-444.

18. Dandona L, Naduvilath TJ, Janarthanan M et al. Survival analysis and visual outcome in a large series of corneal transplants in India. Br J Ophthalmol. 1991;81:726-731.

19. Vail A, Gore SM, Bradley BA et al. Conclusions of the corneal transplant follow up study. Br J Ophthalmol. 1997;81:631-636.

20. Perera C, Jhanji V, Lamoureux E et al. Clinical presentation, risk factors and treatment outcomes of first allograft rejection after penetrating keratoplasty in early and late postoperative period. Eye. 2012;26:711-717.

21. Rahman I, Carley F, Hillarby C et al. Penetrating keratoplasty: indications, outcomes, and complications. Eye. 2009;23:1288-1294.

22. Yu AL, Kaiser M, Schaumberger M et al. Clinical Ophthalmology. 2014;8: 1641-1647.

23. Pineda R. Corneal Transplantation in the Developing World: Lessons Learned and Meeting the Challenge. Cornea. 2015;34:S35-S40.

24. Ikpoh BI, Kunselman A, Stetter C et al. Lost to follow-up: reasons and chararacteristics of patients undergoing corneal transplantation at Tenwek Hospital in Kenya, East Africa. Pan African Medical Journal. 2020;36:95. doi: 10.11604/pamj.2020.36.95.19993. PMID:32774654; PMCID: PMC7392857.

25. York NJ, Tinley C. Corneal donations in South Africa: A 15-year review. South African Medical Journal. 2017;107(8):697-701.

DECLARATION

I, ……., hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: ……

Date: ……..