THE WATER DRINKING TEST IN GLAUCOMA – A SURROGATE FOR OUTFLOW FACILITY

Francesca Anna Indiveri

A dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree of Master of Medicine

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DECLARATION

I, Francesca Anna Indiveri, declare that this Dissertation is my own, unaided work. It is being submitted for the Degree of Master of Medicine in Surgery at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination at any other University.

_____

_____day of _____2019 in Johannesburg

PRESENTATIONS ARISING FROM THIS RESEARCH PROJECT

2018 – Ophthalmological Society of South Africa, Paper Presentation

2018 – University of Witwatersrand Faculty of Health Sciences Research Day, Poster Presentation

ABSTRACT

Background: Glaucoma is now the leading cause of irreversible blindness globally, and thus represents a significant public health challenge. The use of efficient diagnostic and prognostic tests has become critical, and one such test that is experiencing revival is the water drinking test (WDT). The importance of the WDT in acting as a surrogate marker for outflow facility has recently been emphasized.

Objectives: To test newfound literature in a local setting by comparing the effect of the WDT in a glaucomatous and non-glaucomatous population and to validate its use as a surrogate marker for outflow facility.

Design and method: A cross-sectional study of two patient populations at St John Eye Hospital, Johannesburg. The case group comprised 50 black South African patients with medically-managed primary open angle glaucoma. An age, race and gender-matched control population was selected. Each group underwent a WDT with intraocular pressure (IOP) measurements at fixed intervals. The peak IOP and IOP range during the WDT were compared between each patient population.

Results: The peak IOP following the WDT was, on average, 9.7mmHg higher in the case than control group ($p<0.00001$). The IOP range during the WDT was, on average, 8mmHg higher in the case than control group ($p<0.0001$).

Conclusion: Patients with glaucoma exhibit significantly greater IOP peaks and range during a WDT when compared to a matched control population.

ACKNOWLEDGEMENTS

This masters project was most definitely a labour of love, and would not have been possible without the passion and enthusiasm of Professor Grant McLaren. Thank you for introducing me to the water drinking test and for your unwavering guidance and support. It has been inspiring to work with you.

Thank you to my family and colleagues for their support, in particular my husband Nic for his constant encouragement.

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LIST OF ABBREVIATIONS

WDT: Water Drinking Test

IOP: Intraocular Pressure

SJEH: St John Eye Hospital

CHBAH: Chris Hani Baragwanath Academic Hospital

GAT: Goldmann Applanation Tonometry

CCT: Central Corneal Thickness

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CHAPTER 1

INTRODUCTION

1.1 Background

Glaucoma is the leading cause of irreversible blindness worldwide and represents a significant public health challenge, as the blindness it causes is irreversible.[1] The use of efficient diagnostic and prognostic tests has thus become even more important, and one such test that is currently experiencing revival is the water drinking test (WDT).[2] The WDT was widely used in the 1960's as a provocative test to diagnose glaucoma,[3] however due to the high rate of false positives and negatives it was soon deemed inadequate.[2,4] Consequently, the importance of the WDT in stressing the capacitance of the trabecular meshwork[4] has recently been emphasized and its role has thus changed. Rather, it has been suggested that the WDT may serve as a potential surrogate marker for outflow facility.[2,4]

According to the Goldmann equation, the intraocular pressure of the eye is determined by the balance of the amount of aqueous humour produced and the ease with which it leaves the eye.[4] Of particular importance is outflow facility, a measure of the compliance of the trabecular meshwork.[5,6] Outflow facility is an important indication of outflow resistance in the ocular drainage pathway.[7] The facility of outflow varies widely in normal eyes; it decreases with age and is affected surgery, trauma, medications and endocrine factors.[8] In glaucoma, decreased pressure-sensitive aqueous outflow through the trabecular meshwork is often present; this impairment is responsible for the large intraocular pressure (IOP) peaks and the significant fluctuations in diurnal IOP that can be found in glaucomatous eyes.

The main risk factor for the establishment of glaucomatous damage is still considered to be high IOP. [9] Post-hoc analysis from the Advanced Glaucoma Intervention Study revealed that fluctuations in IOP were associated with

increased visual field progression, thus corroborating evidence from earlier studies of the role of low IOP in protection against visual field deterioration.[10] Current glaucoma management still relies on static tonometry, which provides 1-point measurements of IOP. As a result, most IOP peaks are missed. Mean IOP, IOP peaks, and IOP fluctuation are important risk factors for glaucoma management but are very difficult to assess in clinical practice. A 24-hour diurnal tension curve would provide a better indication of a patient's IOP profile, as demonstrated by Drance[11] who found that up to one third of patients with single IOP measurements taken at office hours had pressure peaks only detected by a 24-hour tension curve.

24-hour diurnal tension curves are typically not feasible in clinical practice and studies have observed significant correlations between IOP peaks measured during the 24-hour diurnal tension curve and the WDT.[9] This was recently demonstrated in a study by Yassein et al[12] where IOP peaks and fluctuations detected during the WDT were strongly correlated to those observed during the modified diurnal tension curve. In a study by Malerbi et al[9] both the WDT and the modified diurnal tension curve unmasked the existence of IOP peaks, but the frequency of these peaks and greater fluctuation in IOP was more readily demonstrated by the WDT.

It has therefore been suggested that the WDT may be considered a surrogate for detecting IOP peaks not detected during office hours.[13] The WDT entails drinking 1000ml of water (or 10ml/kg body weight) within a set 5-minute period. The subject subsequently undergoes IOP measurements every 15 minutes for 1 hour. Historically, a 6mmHg or 8mmHg rise in IOP was considered abnormal, but newer evidence has shown that it is equally important to look at the overall trend of IOP performance.[2] The WDT may be used to perturb aqueous humour dynamics and, in so doing, the extent to which IOP rises and the rate at which it returns to normal may be assessed.

The WDT is able to accurately detect IOP peaks that may correlate with visual field deterioration. This was shown in a study by Susanna et al[13] where significantly higher mean IOP peak and IOP variation during the WDT were

found in patients with visual field progression compared to those patients who did not show progression. The idea that the WDT may be used as an indirect tool to measure outflow facility is demonstrated in a study by Danesh-Meyer et al which showed that patients controlled with filtering surgery showed decreased fluctuation in IOP as opposed to those patients whose IOP was seemingly controlled with topical medication.[14]

1.2 Aims

As a first of its kind in Southern Africa, this cross-sectional study aims to provide a comparison of the results of the WDT in a glaucomatous population with an age, gender and race-matched control population. It asks if we are able to use the WDT as a reliable surrogate marker for outflow facility in a black South African glaucomatous population.

1.3 Objectives

1. To compare the peaks in IOP in each patient population once a WDT is undertaken.

2. To compare the range of IOP in each patient population following the WDT.

CHAPTER 2

METHODS

2.1. Patient Selection

100 black South African patients from St John Eye Hospital (SJEH), Johannesburg were included in this cross-sectional study – there were two patient populations comprised of 50 patients each. One eye of each patient was included in this study. If data was available for both eyes of a patient, data for one eye was randomly selected. Data collection took place from April to October 2016.

Patients were aged 18 years and older. Patients were gender, race and age-matched (within 1 year) and intraocular surgery was an exclusion criteria in an attempt to negate the differing effects on outflow facility.

All patients underwent IOP measurements via Goldmann applanation tonometry (GAT). Glaucomatous patients had full-threshold automated perimetry performed (Humphrey 24-2 test, Swedish Interactive Thresholding Algorithm, standard). Reliable visual fields were defined as less than 25% of losses in fixation as well as less than 25% false positives and negatives. Glaucomatous patients also had been serially followed up with Zeiss GdX Pro Scanning Laser Polarimeter. Control patients underwent nerve fibre layer imaging using the Heidelberg Spectral-Domain Optical Coherence Tomographer. Central corneal thickness (CCT) measurements were collected retrospectively, and were measured using the Nidek IOL Biometer.

2.1.1 Patient Population 1 (Case)

50 patients known with primary open angle glaucoma, receiving only topical medical therapy, were included in our study. Patients had documented elevated IOP (>21mmHg) prior to treatment initiation. All patients had grade 3 or greater open angles, confirmed on gonioscopy by the investigator. Patients

had documented evidence of visual field damage with a mean deviation (MD) of at least -8dB on reliable Humprey 24-2 visual field testing. All patients had been followed up in the Glaucoma Clinic with serial GDx imaging, and had a Nerve Fibre index (NFI) of greater than 50. Patients in this population were excluded if they had a history of prior intraocular surgery, laser trabeculoplasty or ocular trauma. Patients continued their usual topical medication before the WDT. A baseline IOP of greater than 22mmHg was also an exclusion criterion.

2.1.2 Patient Population 2 (Control)

This population comprised 50 age, race and gender-matched patients. In terms of age, patients were matched within 1 year. All patients had grade 3 or greater open angles, confirmed on gonioscopy by the investigator. All patients had normal retinal nerve fibre analysis measured using Heidelburg Spectral-Domain Optical Coherence Tomography. Patients were excluded if they had a history of prior intraocular surgery or ocular trauma. A baseline IOP of greater than 22mmHg was also an exclusion criterion.

2.2 Data Acquisition

WDTs were performed under standard conditions, consistent with previous studies. All WDTs were performed between 2:00pm and 6:00pm. Patients fasted for 2 hours prior to the WDT taking place. After a baseline measurement of IOP, patients were required to ingest 1000ml of municipal water within a set 5 minute period. IOP was recorded every 15 minutes for 1 hour after completion of water drinking. Study variables included the peak IOP which was defined as the maximum IOP recorded during the 60 minute measurement period, and the IOP range which was calculated as the difference between the peak and baseline IOP. All IOP recorded was measured by the investigator.

2.3 Ethical Approval

Ethical approval was obtained from the University of the Witwatersrand Human Research Ethics Committee with medical clearance number HREC M160260 (Appendix 2) and from Chris Hani Baragwanath Academic Hospital management (Appendix 3).

2.4 Statistical Analysis

The study data was recorded using a data collection sheet, and a separate sheet was used for the case and control populations (Appendix 5.1 and 5.2). Data was then captured into a Microsoft Excel spreadsheet. The full dataset was imported into Statistica^{TM} Version 13.1 and analysed using descriptive statistics. Under consultation with a biostatistician, the paired t-test for continuous data (baseline IOP, outcomes) was used. Continuous variables were summarized by the mean, standard deviation, median and interquartile range; and their distribution illustrated by means of histograms. The 5% significance level was used. Results were documented and displayed by means of tables, graphs and histograms.

CHAPTER 3

RESULTS

Our study included a total of 100 black South African patients. Patients were also gender and age-matched. 56% of patients were male.

The baseline IOP was, on average, 1.6mmHg (SD 3.8mmHg; 95% CI 0.5-2.7mmHg) higher in the case group (glaucomatous patients) than in the control group (p=0.0040). There was no difference in the mean central corneal thickness between the two groups; mean central corneal thickness in the glaucoma group [n=39] 528um; mean central corneal thickness in control group [n=37] 530um (p=0.54).

Table 3.1 Patient Characteristics

	Case Group (n=50)	Control Group (n=50)	P Value
Gender			
Male	28	28	
Female	22	22	
Race			
Black	50	50	
Study Eye			
Right	24	24	
Left	26	26	
Baseline IOP	11.6	10	p=0.004
Mean central corneal thickness*	528	530um	p=0.54

IOP = intraocular pressure
*Collected on retrospective review for the majority of study participants (n=39, glaucoma group; n=37, control group)

96% of the glaucomatous patients in our study were receiving topical prostaglandin therapy as part of their treatment regimen. 14% of these patients were using prostaglandin monotherapy, 23% were using a prostaglandin analogue and a beta-blocker, and the majority (63%) were

using 3 agents; namely a combination of a prostaglandin analogue, beta-receptor blocker and an alpha agonist.

Results of the WDTs are shown in Figure 3.1. Highly significant results between the two groups were observed at all time points. The peak IOP was, on average, 9.7mmHg (SD 5.1mmHg; 95% CI 8.2-11.1mmHg) higher in the case group than in the control group ($p<0.0001$). The IOP range was, on average, 8.00mmHg (SD 3.5mmHg; 95% CI 7.0-9.0mmHg) higher in the case group than in the control group ($p<0.0001$).]

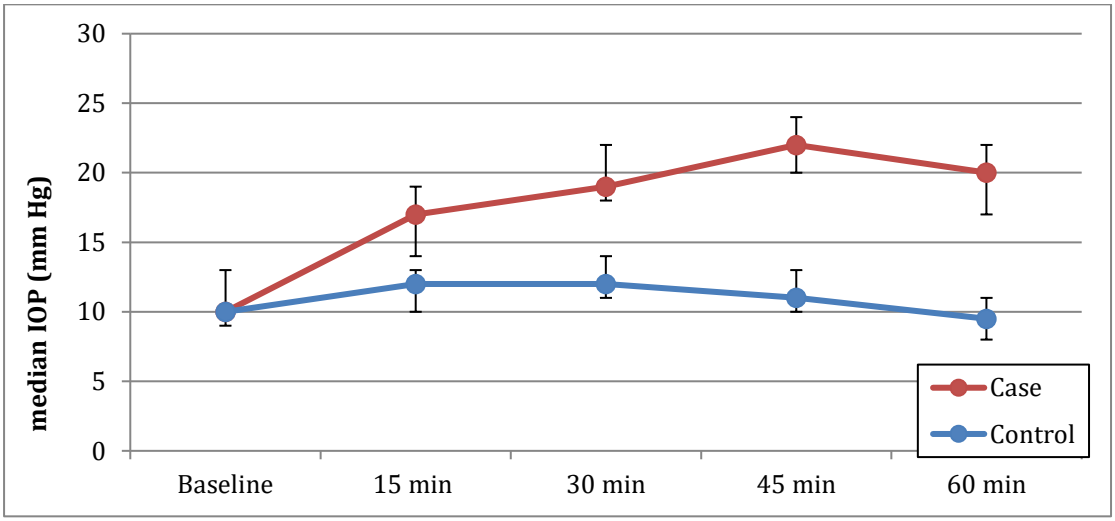

Figure 3.1 Time profile plot of median Intraocular Pressure differences between case and control groups

From the figure above, it is evident that the IOP of glaucoma patients generally peaked at 45 minutes (80%, n=40) whereas the majority of the control patients' IOP peaked at 15 minutes (92%, n=46). It is important to note that not a single glaucoma patient returned to baseline IOP at 60 minutes, whereas all control patients did. 100% of patients in the case group peaked by at least 12mmHg above their baseline IOP, whereas the highest recorded peak in the control group was 4mmHg.

CHAPTER 4

DISCUSSION

4.1 General

It is well known that patients with high-pressure glaucoma have, on average, higher levels of IOP than those without the disease.[15,16] IOP is an important dose-related risk factor.[10,13] Furthermore, greater peaks in IOP have been noted to correspond with faster progression of as well as with the extent of glaucomatous damage.[17,18] It has been shown that progression of glaucoma may occur despite seemingly well controlled IOP.[9,18,19] This may be attributed to the current reliance on static tonometry, which consequently may miss the IOP peaks and range an eye may exhibit.

The WDT was initially widely used as a provocative test in the diagnosis of glaucoma, however due to false negative and positive results in 10 year prospective studies it was deemed inadequate.[20] Since the correlation of this test with the diurnal tension curve[9] its role has changed to it being considered as a stress test to allow for assessment of the capacitance of the trabecular meshwork. It may act as a surrogate marker for outflow facility and, in so doing, has been suggested as an alternative procedure to assess IOP control.

Several studies have explored the ability of the WDT to act as an indirect measurement tool for outflow facility. Susanna and Vessani[13] effectively demonstrated that visual field progression was correlated with greater mean IOP peak and IOP variation during the WDT. In a study by Medeiros and Susanna,[21] the WDT was able to show that IOP fluctuation was lower in patients who had received filtration surgery as opposed to those patients who were solely receiving medical therapy. This study emphasized the fact that surgical management of glaucoma results in blunting of the WDT response, and it is postulated that this occurs due to diversion of aqueous from conventional outflow pathways. It is also important to note that in order for a test to be applicable in a clinical setting, it must produce results that are

reproducible. This is evident in a study by Babic[4] which showed excellent reproducibility of peaks in IOP during the WDT.

As previously stated, multiple prior studies have shown correlations between peak IOP observed during a WDT and peaks in IOP that occur during the day.[9,12] Our study hypothesized that patients with impaired outflow facility would exhibit greater IOP peaks, and a greater variability of IOP. Both of these parameters were shown to be significantly higher in our glaucomatous population with p values of <0.0001. Typically, those eyes with higher IOP peaks are expected to take longer to return to baseline IOP, reflecting the poor outflow status of the eye.[22] No glaucomatous patients in our study returned to baseline IOP at 60 minutes, whereas all control patients did. An intact outflow system should lead to rapid IOP recovery, whereas impaired outflow facility results in sustained IOP elevations as was effectively demonstrated in our study.[23,24]

At present, there is uncertainty regarding the factors that influence time to peak IOP during the WDT, and there is lack of consistency from currently available studies. Regarding glaucomatous eyes, a study by Tran et al[25] found that the IOP peak was highest at 45 minutes after water ingestion whereas Hatanaka et al[26] found the greatest peak to be at 30 minutes. Our study showed that, on average, mean peak IOP was greatest at 45 minutes in a glaucomatous population.

Our study aimed to show that the WDT can be used as a reliable and effective surrogate marker for outflow facility in a black South African glaucomatous population, a population in which the burden of disease is extremely high. Our study effectively demonstrates the ability of the WDT to act as an indirect tool in the measurement of outflow facility in this patient population. This is evidenced by the highly significant IOP peaks and fluctuation shown in the glaucomatous population, as directly opposed to an age, race and gender-matched control population. As a first of its kind study in South Africa, we aimed to effectively demonstrate the efficacy and clinical utility of the WDT.

An article published by Cook[27] attempted to provide an estimate of the size of the burden of glaucoma in sub-Saharan Africa. The predominant subtype was found to be chronic primary open angle glaucoma. Other findings were that glaucoma may occur at an earlier age, may be more rapidly progressive, may present late and may be associated with a higher IOP. In our study, the performance of the WDT is evaluated in a similar patient population and the importance of its findings are highlighted due to the high burden of disease present. The clinical utility of the test is thus emphasized.

4.2 Recommendations

Our study achieved its aim of displaying the efficacy of the WDT as a surrogate marker for outflow facility in black South African patients with high-pressure primary open angle glaucoma. In so doing, the possibilities of its use in clinical practice in this specific population are emphasized. This may include the use of the WDT to assess peak IOP and IOP variation, which in turn allows for identification of patients at high risk of progression. Patients with seemingly normal one-point IOP measurements may be identified as having impaired outflow facility, and this might highlight the need for earlier intervention. The WDT may even allow for the assessment of the efficacy of these interventions.

Brubaker has used the WDT to compare responses of IOP in glaucomatous eyes to differing topical formulations[28] and his study postulated that eyes treated with prostaglandins, which enhance outflow facility, should show reduced IOP variation. This was not noted in our study, but the potential to use the WDT to assess the effects of differing topical agents is emphasized. The difference between the performance of the WDT in medically and surgically managed eyes has been mentioned and, more recently, studies comparing the difference in performance of the WDT in trabeculectomy versus tube surgery have emerged. Of note, an article published in 2017 by Razeghinejad et al[29] found that there was significantly larger IOP fluctuation in the tube group, as opposed to patients who had undergone trabeculectomy. It

is also interesting to note that improved performance of the WDT after selective laser trabeculoplasty has recently been investigated.[30] As evident by this multitude of reinvigorated interest and research surrounding the WDT, its possibilities of use are endless and at the forefront of current glaucoma management.

4.3 Limitations of this study

The most important limitation of this study is the fact that the investigator was not blinded to the two different study populations – all IOP measurements were performed by the principle investigator. The study population depicted reflects one racial group and one subset of glaucoma.

CHAPTER 5

CONCLUSION

In summary, our study effectively demonstrates the ability of the WDT to be used as a low cost and clinically feasible surrogate marker for outflow facility in a black South African population with primary open angle glaucoma. The value of the WDT as a complementary test in clinical practice is emphasized. Having proved the hypothesis that glaucomatous patients will exhibit significantly greater IOP peaks and fluctuation as opposed to a control population, the possibilities of its use in monitoring progression and assessing efficacy of treatment options is displayed. Further studies are required to give a better evaluation of these numerous possibilities.

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APPENDIX 1: Approved Protocol

Title

The water drinking test in glaucoma – a surrogate for outflow facility

Name: Francesca Anna Indiveri
0501443A

Degree: MMed (Wits)

Supervisor: Professor Grant McLaren
Fellow College of Ophthalmologists SA
Consultant Ophthalmologist
St John Eye Hospital
Department of Ophthalmology
University of Witwatersrand
Chris Hani Baragwanath Academic Hospital
Chris Hani Road
Soweto, Johannesburg
South Africa

1. Introduction

Glaucoma is now the second leading cause of blindness globally, after cataracts.[1] Glaucoma, however, presents perhaps an even greater public health challenge than cataracts because the blindness it causes is irreversible. In essence, glaucoma is a disease that exhibits a characteristic optic neuropathy, which may result in visual field loss.[1,4] The most important risk factor is raised intraocular pressure secondary to reduced aqueous outflow through the filtration angle (although its presence or absence does not have a role in the definition of the disease). Glaucoma is thus an entity that we encounter daily and is a huge source of ocular morbidity. The production, circulation, and drainage of aqueous humour into and out of the anterior chamber of the eye maintain the intraocular pressure at a relatively constant level (aqueous humour dynamics).[2,4,5] An understanding of aqueous humour dynamics is integral in appreciating the mechanism of treatment modalities, as well as the use of diagnostic and prognostic tests in glaucoma.

One such test that is currently experiencing revival is the water-drinking test. Previously used indeterminately to diagnose glaucoma, it has since been found that its use in diagnosis is limited.[12] The importance of the water-drinking test in stressing the capacitance of the trabecular meshwork, and thus serving as a surrogate marker for outflow facility, has recently been emphasized and its role has thus changed.[9,12] This study serves to test newfound literature in a local setting by the comparison of the effect of the water-drinking test on a glaucomatous and a non-glaucomatous population, thus illustrating that the water-drinking test can indeed be reliably used as a surrogate marker for outflow facility. With this shown, the possibilities of using the water-drinking test as a prognostic marker, as well as a marker of progression and severity of disease, will be further validated.

2. Literature Review

The rate of formation of aqueous humour is about 1 – 2 ul per minute and the entire volume of aqueous is replaced every 1 – 2 hours (about 1 percent per minute). Using fluorophotometry, diurnal variations have been observed in

aqueous humour turnover rates, reflecting a pattern known as the circadian rhythm of aqueous humour flow in humans. Aqueous humour flow is higher in the morning than at night. Secretion in humans occurs at a rate of 2.6ml/min during the day and falls to 1.0ml/min at night.[2] Aqueous humour is secreted by the ciliary epithelium lining the ciliary processes and enters the posterior chamber. Circulating aqueous humour flows around the lens and through the pupil into the anterior chamber. The aqueous humour leaves the eye by passive flow via two pathways at the anterior chamber angle, anatomically located at the limbus:[2,3,4]

- The **trabecular (conventional) pathway** consists of aqueous humour passing through the trabecular meshwork, across the inner wall of Schlemm's canal, into its lumen, and into draining collector channels. Schlemm's canal is drained by 25 to 30 collector channels, which join the deep scleral venous plexus. The deep scleral venous plexus drains via an intrascleral plexus and an episcleral plexus into the anterior ciliary veins. A few of the collector channels bypass the deep scleral venous plexus and pass directly through the sclera. These channels are known as the aqueous veins, because they contain clear aqueous humour and not blood. The aqueous veins drain into the conjunctival veins close to the corneoscleral junction.

- The **uveoscleral (unconventional) pathway** accounts for a variable proportion (3-20%) of aqueous drainage. Aqueous drains directly into the anterior uvea at the ciliary body immediately posterior to the cornea and thence into the suprachoroidal space. It is then drained by the venous circulation in the ciliary body, choroid and sclera. Uveoscleral drainage is possible because the pressure in the suprachoroid is 2-4 mmHg lower than in the anterior chamber. Uveoscleral outflow is largely pressure-independent and is believed to be influenced by age.

Equilibrium exists between the production and drainage of aqueous humour. Disruption of aqueous outflow, usually through the conventional pathway,

results in elevation of intraocular pressure, which is a major risk factor in the pathogenesis of glaucoma.[4]

The Goldmann Equation and Outflow facility

The original Goldmann equation described the relationship between the intraocular pressure and the components of aqueous humour dynamics. These components include the rate of aqueous formation (F_p, measured in mmHg); uveoscleral outflow (F_u, measured in mmHg), the facility of outflow (C_{trab}, measured in uL/min/mmHg) and episcleral venous pressure (P_v, measured in mmHg).[2,4,5] Since the original equation was written, the importance of uveoscleral outflow has become more apparent and the Goldmann equation was changed accordingly. The Goldmann equation states:

$$F_p = F_u + C_{trab}(IOP - P_v)^4$$

Accurate assessment of aqueous humour dynamics requires the evaluation of each of these variables, most notably episcleral venous pressure and outflow facility.

Episcleral venous pressure

The pioneering work of Lauber in the early 20th century was the first stepping stone towards understanding the role of episcleral venous pressure in aqueous humour dynamics.[4,6,8] This led to Seidel's observation in 1923 that India ink injected in the anterior chamber gained access to episcleral veins, and in 1942 Ascher made the first direct observation of the aqueous veins.[4] Aqueous outflow via the conventional outflow pathway is dependent on the pressure gradient between intraocular pressure and episcleral venous pressure, according to the Goldmann equation. This implies that episcleral venous pressure elevation uncompensated by reduced aqueous inflow or increased aqueous outflow facility will result in increased intraocular pressure. The definite relation between episcleral venous pressure and intraocular pressure, however, is unclear. The normal episcleral venous pressure is 8-10 mm Hg; variability depends on the measurement technique.[6,8] It is thought

that for every mmHg rise in episcleral venous pressure, there is an equal increase in the intraocular pressure;[2,4] although it has been suggested that the magnitude of rise of intraocular pressure can be more.

Causes of elevated episcleral venous pressure may be divided into three different groups:[6]

- Venous obstruction: which includes thyroid ophthalmopathy, retrobulbar tumour, cavernous sinus or orbital vein thrombosis, episcleral or orbital vein vasculitis, and obstruction of the superior vena cava
- Arteriovenous anomalies: including carotid artery-cavernous sinus fistula, orbital varices, dural shunts and Sturge-Weber syndrome
- Idiopathic

Outflow Facility

The trabecular meshwork offers a certain resistance to the outflow of aqueous humour that is needed to maintain a steady-state intraocular pressure. The inverse of this resistance is trabecular outflow facility, a measure of the compliance of the trabecular meshwork.[2,3,4,7] The facility of outflow varies widely in normal eyes. The mean value reported ranges from 0.22 to 0.30 ul/min/mmHg.[5] Outflow facility decreases with age and is affected by surgery, trauma, medications, and endocrine factors.[4] Glaucoma is often characterized by decreased pressure-sensitive aqueous outflow through the trabecular meshwork – this defect in pressure-sensitive aqueous outflow is evident from the low tonographic facility of outflow measured in many patients. The impairment in outflow facility causes the high intraocular pressure and large diurnal intraocular pressure fluctuations often found in glaucoma.[7,8] Pressure-sensitive aqueous outflow helps prevent and dampen pressure spikes; thus, drugs that enhance outflow facility, in particular, may stabilize as well as lower IOP. Outflow facility is an attractive target for glaucoma treatment because enhancing outflow facility tends to restore the self-regulating tendency of intraocular pressure.[7]

The Water drinking test – a surrogate for outflow facility

Mean intraocular pressure, intraocular pressure peaks, and intraocular pressure fluctuation are important risk factors for the progression of glaucoma, but it is very difficult to assess precise intraocular pressure in clinical practice. A shortcoming of current glaucoma management is the reliance on static tonometry, which provides 1-point measurements of intraocular pressure.[7,8,9] Consequently, these techniques miss most intraocular pressure peaks, particularly when they occur outside of office hours. A patient's short-term intraocular pressure profile would be better characterized by a 24-hour diurnal tension; however, the cost and labour involved make the determination of the 24-hour intraocular pressure course difficult and not possible for all patients. Post-hoc analysis of data from the Advanced Glaucoma Intervention Study (AGIS) showed that fluctuations in intraocular pressure were associated with increased progression of visual field defect, thus supporting evidence from earlier studies of a protective role for low intraocular pressure in visual field deterioration.[8] Different strategies have been proposed to estimate the magnitude of peaks in intraocular pressure. Previous studies observed significant correlations between intraocular pressure peaks measured during the 24-hour diurnal tension curve and water-drinking test.

The water-drinking test consists of ingestion of 1000ml of water (or 10ml/kg of body weight) within a 5 minute period. The subject subsequently undergoes intraocular pressure measurements every 15 minutes for 1 hour. After the observation in the 1920's that ingestion of water provoked elevated intraocular pressure, the water-drinking test was widely used as a provocative test to diagnose open angle glaucoma. Due to its high incidence of false positive and false negative results, however, it was deemed inadequate. Recently, the emphasis on the value of this test has changed. It has been used as a surrogate marker for the outflow facility reserve and may indicate the likelihood of disease progression. Dr Remo Susanna Jr. (University of São Paolo, Brazil) has been greatly involved in research surrounding the water-drinking test and has stated that 'the water- drinking test should not be

considered as a provocative test for glaucoma but rather a stress test; we can use the water-drinking test to perturb the aqueous fluid dynamic system, and in so doing, we can learn important things such as the extent to which intraocular pressure rises and the speed with which it recovers'.[9] The reason for performing the water-drinking test has thus changed to it being a stress test to assess the capacitance of the trabecular meshwork. Similarly to other stress tests, the aim is to stress the trabecular meshwork and to observe how high the intraocular pressure rises and how long it takes to return to baseline. Rather than a specific numerical rise in intraocular pressure constituting a positive test, its interpretation depends on each patient's baseline intraocular pressure, level of damage, and rate of progression.[5,7,8]

The exact physiology of the water-drinking test has not been fully elucidated, but several theories have been proposed:

- Susanna et al have proposed that, after drinking water or any hypotonic fluid, there is absorption of water into blood and body tissues, including the eye. This is associated with a consequent rise in intraocular pressure. The ability of the eye to recover from this transient intraocular pressure rise depends on the outflow facility. The rapid inflow of aqueous humour and the low facility of outflow in the glaucomatous eye may lead, at least in part, to larger intraocular pressure fluctuation.[9,12]
- The outflow theory stipulates that water consumption leads to increased episcleral venous pressure, with resulting transient negative aqueous outflow. This would then lead to increased intraocular pressure as a result of the reduced outflow facility from a decreased pressure gradient across the trabecular meshwork.
- The inflow theory postulates that changes in the blood-ocular osmotic pressure gradient could lead to hydration of the vitreous and increased aqueous production, but this has not been confirmed.[7,9]
- Mansouri et al used swept-source optical coherence tomography to measure choroidal thickness and volume before and after the water-drinking test in healthy individuals.[10] They showed that there is a

consistent and statistically significant increase of peripapillary and macular choroidal thickness and volume after the water-drinking test. However, with both the magnitude of the choroidal increase being relatively small and the absence of an association between intraocular pressure rise and choroidal increase, it seems unlikely that changes occurring within the choroid would be the primary mechanism behind the rise in intraocular pressure after this provocative test.

Peer-reviewed literature has shown that intraocular pressure peak detected by the water-drinking test positively correlates with the severity of visual field defects in glaucoma and may be predictive of visual field progression.[8,9,12] It was demonstrated that intraocular pressure peaks during the water-drinking test are correlated and are in agreement with intraocular peaks that normally occur during the day. The water-drinking test has also been used to evaluate the quality of different clinical and surgical treatment options in glaucoma.[11] Here follows a summary of some of the most important current literature and studies that highlight the clinical utility of the water-drinking test.

The importance of intraocular pressure peaks in development of glaucoma progression is illustrated in the study '**The relation between intraocular pressure peak in the water drinking test and visual field progression in glaucoma'**.[9] This study aimed to compare the results of the water-drinking test between glaucomatous eyes with and without visual field progression. It formed a retrospective analysis of 76 eyes of 76 patients with OPEN ANGLE glaucoma subjected to the water-drinking test at the beginning of follow up period. The maximum value of 3 measurements was considered as maximum intraocular pressure during the water-drinking test. Patients were followed up for a mean period of 26 months. All subjects in the study were under clinical therapy (surgery/laser excluded) and all patients had an intraocular pressure < 17mmHg monitored by isolated measurements during the follow-up period. Reliable achromatic automated perimetry tests were performed during study period to characterize visual field progression. The number of eyes that developed visual field progression was determined – the performance of the water-drinking test was confirmed between the eyes that

developed visual field deterioration and those that did not. The results of the study showed that:

- 28 (36.8%) of eyes reached definite visual field progression
- From an overall baseline of 12.7mmHg, a mean difference of 1.9mmHg in the mean intraocular pressure peak was observed between eyes that showed visual field progression and ones that did not (p=0.001)
- A mean percentage of intraocular pressure variation of 16.8% was observed between glaucomatous eyes which showed visual field deterioration and ones that did not progress (p<0.001)

The study concluded that mean intraocular pressure peak and percentage of intraocular pressure variation during the water drinking test were significantly higher in patients with visual field progression compared with patients who did not progress.

The evaluation of the differences in the water-drinking test between medically and surgically controlled glaucoma patients is shown in the study entitled '**Medically controlled glaucoma patients show greater increase in intraocular pressure than surgically controlled patients with the water-drinking test'.**[11] This study aimed to compare the results of the water-drinking test in glaucoma patients who are medically or surgically controlled. The two study populations included 30 glaucoma patients with intraocular pressure controlled by trabeculectomy and mitomycin C and 30 patients with medically treated glaucoma. Patients were matched for level of visual field damage and intraocular pressure at baseline. A baseline intraocular pressure was recorded and intraocular pressure was measured every 15 minutes for 1 hour after water drinking. Intraocular pressure increase was defined as the difference between intraocular pressure peak and baseline, and intraocular pressure range as the difference between the minimum and maximum intraocular pressures measured during the water-drinking test (not including the baseline). The results included:

- A highly significant difference (p<0.001) was observed in mean intraocular pressure between the 2 groups at every 15-minute time point after water ingestion.

- After the water-drinking test, mean intraocular pressures in the surgically and medically treated groups were 10.7±2.3mmHg and 14.6±2.2mmHg.
- The mean maximum intraocular pressure in the surgical group increased by 12.5% from baseline, compared with 56% in the medically treated group ($p<0.001$)
- Ranges of intraocular pressure during the water-drinking test were 2.2±1.3mmHg and 5.6±1.9mmHg in the surgically and medically treated patients, respectively ($p<0.001$)

The study concluded that patients with glaucoma who are medically controlled show greater intraocular pressure elevation and peak intraocular pressure after the water-drinking test than eyes that have undergone trabeculectomy.

The Clinical and Laboratory Standards Institute recommends that in order to be clinically applicable, a test must produce reproducible results. This was illustrated in the study **'Reproducibility of the water-drinking test in treated glaucomatous patients'.**[12] The reproducibility of intraocular pressure peaks and fluctuation elicited during the water-drinking test in treated glaucomatous patients with a long follow-up period was evaluated. It included a retrospective analysis of 34 eyes of 34 patients with primary open angle glaucoma under medical therapy. The water-drinking test performed in two consecutive visits (mean interval between tests was 4.85 months – range 3-6 months) in patients who had no change in therapeutic regimen in this period. Reproducibility of peak (maximum intraocular pressure) and fluctuation (difference between peak and baseline intraocular pressure) during the water-drinking test was assessed using the intraclass correlation coefficient (ICC) test, and the Bland-Altman analysis was applied to assess the agreement of intraocular pressure peaks and fluctuation measured between two consecutive tests. The results showed that there were no significant differences in baseline intraocular pressure values and peaks detected during the water-drinking test between the first and second visits (0.85 ICC, $p<0.001$) and the intraocular pressure fluctuation was not found to be highly

reproducible (0.50 ICC, p<0.001). The results demonstrated excellent reproducibility parameters for intraocular pressure peaks during the water-drinking test; regarding intraocular pressure fluctuation, these parameters were moderate. These results emphasize the test applicability in treatment efficacy assessment in daily practice and in interventional studies. The Advanced Glaucoma Intervention Study showed that patients with a peak intraocular pressure consistently less than 18mmHg had no net progression on visual field analysis.[8] Intraocular pressure peaks are considered the most important intraocular pressure parameter associated with glaucoma progression and thus the importance of observing a better repeatability of intraocular pressure peaks than fluctuation is emphasized.

In conclusion, the water-drinking test is a low cost and feasible test that has a relevant role in the assessment of the effectiveness of treatment and the probability of progression in glaucomatous patients.[7,9,11,12] There is convincing evidence that the water-drinking test can be used as an indirect tool to measure outflow facility and there is an important role for its use in glaucoma management. It thus deserves to be investigated more widely, and further research is needed to better understand its physiology and clinical application.

3. Research Question

Can the water-drinking test be used as a surrogate marker for outflow facility in a glaucomatous population?

4. Hypothesis

Following the water-drinking test, there will be greater peaks in intraocular pressure as well as an increased fluctuation in intraocular pressure observed in the glaucomatous population.

5. Study Aims

This study aims to compare the results of the water-drinking test in a glaucomatous medically-managed population; with an age, gender and race-matched control population (diagnosis of glaucoma excluded).

6. Study Objectives

To compare the **peaks** in intraocular pressure observed in each patient population once a water-drinking test is undertaken, as well as to compare the **difference in fluctuation of intraocular pressure** in each population following the water-drinking test.

7. Research Method

7.1 Design

A prospective, cross-sectional study of two patient populations at Chris Hani Baragwanath Academic Hospital.

7.2 Method

This prospective study will take place at Chris Hani Baragwanath Academic Hospital. Each patient population will be selected (according to stringent inclusion and exclusion criteria) and informed (layman's) consent obtained. Each patient selected will have a fundus examination and GDx test prior to the test. Each patient will undergo a water-drinking test between a set time period (2-6pm). Intraocular pressure will be recorded in each eye prior to the initiation of the test. 1000ml of water will be ingested in a 5-minute period and the patient will subsequently undergo intraocular pressure measurements in both eyes at 15 minutes, 30 minutes, 45 minutes and 60 minutes after ingestion. Intraocular pressure will be measured with a Goldmann applanation tonometer on a slit-lamp biomicroscope.

7.3 Inclusion Criteria

Patient Population 1 (Glaucoma)

- Age greater than 18 years
- Patients with open angles on gonioscopy
- Evidence of structural optic nerve damage as evidenced by:
  Nerve Fibre Index (NFI) on GDx ≥ 50
- Any significant visual field loss
- Patients solely receiving topical medical therapy

Patient Population 2 (Control)

- Age greater than 18 years
- No evidence of structural optic nerve damage:
  Nerve Fibre Index (NFI) on GDx ≤ 30

7.4 Exclusion Criteria

Patient Population 1 (Glaucoma)

- History of intraocular surgery (glaucoma-related or otherwise)
- History of selective laser trabeculoplasty
- History of ocular trauma
- A baseline intraocular pressure >28mmHg

Patient Population 2 (Control)

- History of intraocular surgery
- Previously recorded elevated IOPs
- History of ocular trauma

7.5 Materials and Study Procedures

Patient selection will take place at St John Eye Hospital. Information such as gonioscopy, results of GDx testing and treatment will be recorded from patient files, and control GDx examinations will be performed at St John Eye Hospital. Any information found to be outstanding/incomplete from the patients' records will be completed by the researcher. Intraocular pressure will be recorded using Goldmann applanation tonometry on a single slit lamp biomicroscope at the facility.

7.6 Data Collection

Information collected will include the following (Appendix A, B):

1) Personal Information: Age, gender, race, medications (oral and topical), history of ocular trauma and intraocular pressure
2) Ophthalmic examination and tests: Gonioscopy, GDx findings, Visual field losses

3) Water-drinking test: Baseline intraocular pressure, intraocular pressure at 15/30/45/60 minutes post-test

7.7 Data Management and Statistics

Data analysis will be performed in conjunction with a qualified statistician. Data will be collected in an Excel spreadsheet. The peak intraocular pressure will be determined for each patient. The intraocular pressure fluctuation outcome will be calculated from the peak and baseline measurements of intraocular pressure. Descriptive analysis of the data will be carried out as follows:

- Categorical variables will be summarised by frequency and percentage tabulation, and illustrated by means of bar charts.
- Continuous variables will be summarised by the mean, standard deviation, median and interquartile range, and their distribution illustrated by means of histograms.

Baseline demographic and IOP data will be compared by McNemar's test for paired categorical data, and the paired sample t-test for continuous data. The outcomes (peak intraocular pressure and intraocular pressure fluctuation) will be compared between the two groups using the paired sample t-test. The Wilcoxon matched-pairs test will be used if the assumptions of the paired sample t-test are not met.

Data analysis will be carried out in STATISTICA. The 5% significance level will be used.

7.8 Time Schedule

	Feb 2016	March 2016	April 2016	May 2016	June 2016	July 2016	Aug 2016	Sept 2016	Oct 2016	Nov 2016	Dec 2016
Ethics Submission											
Protocol Approval											
Protocol Amendments											
Ethics Approval											
Data Collection											
Data Analysis											
Report/ Submission											

7.9 Ethical Considerations

The protocol will be submitted to the University of the Witwatersrand Ethical Committee for clearance in order to perform research. Ethical considerations will adhere to the tenants of the Helsinki Declaration. Permission from the Head of Department of St John Eye Hospital, Chris Hani Baragwanath Academic Hospital, has already been granted (Appendix C). No names, hospital numbers or any other patient information that can breach patient confidentiality will be published. A study number will be assigned to each study participant.

8. Reporting Plans

- Submission as Masters in Medicine Dissertation – MMed (OPHTH.)
- Presentation of study findings at the Ophthalmic Society of South Africa annual congress
- Publish in a scientific journal

9. Funding

There will be no external source of funding for this study. All administrative costs will be carried by the researcher.

10. Limitations

- The study will be limited to only one academic hospital in Gauteng and thus will represent a small sample size.
- Data in the glaucomatous population may be skewed due to discompliance.

11. Authorship

1. Dr F. Indiveri: **Principal Researcher**
   Registrar in Ophthalmology
   Chris Hani Baragwanath Academic Hospital
   University of the Witwatersrand

2. Professor G. McLaren: **Research Supervisor**
   Consultant Ophthalmologist
   Head of Department – Chris Hani Baragwanath Academic Hospital
   University of the Witwatersrand

12. References

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surgically controlled patients with the water drinking test. *Ophthalmology*. 2008;**115**:1566-1570.

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APPENDIX 2: Ethics Clearance Certificate

R14/49 Dr Franscesca Indiveri

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160260

NAME: (Principal Investigator)	Dr Franscesca Indiveri
DEPARTMENT:	Ophthalmology Chris Hani Baragwanath Academic Hospital St John Eye Hospital
PROJECT TITLE:	The Water-Drinking Test in Glaucoma - A Surrogate for Outflow Facility
DATE CONSIDERED:	26/02/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Grant McLaren
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	27/07/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/2nd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in February and will therefore be due in the month of February each year.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 3 Permission to Conduct Research (CHBAH)

GAUTENG PROVINCE

REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE
CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 4 July 2016

TITLE OF PROJECT: The water-drinking test in glaucoma – a surrogate for outflow facility

UNIVERSITY: Witwatersrand

Principal Investigator: F Indiveri

Department: Ophthalmology

Supervisor (If relevant): G McLaren

Permission Head Department (where research conducted): Yes

Date of start of proposed study: July 2016
Date of completion of data collection: Dec 2018

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Human Research Ethics Committee of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.

.....
Recommended
(On behalf of the MAC)
Date: 04 July 2016

.....
Approved/Not Approved
Hospital Management
Date: 06/07/16

APPENDIX 4 Permission to Conduct Research (HOD-SJEH)

Consent to Allow for Collection of Data for the Purposes of Research

To whom it may concern,

This document hereby serves as permission for Dr Francesca Indiveri, student number 0501443A, to collect the relevant data needed to complete the research intended under the title:

The Water-Drinking Test in Glaucoma – a Surrogate for Outflow facility

Data will be collected in the Ophthalmology department of St John Eye Hospital, Chris Hani Baragwanath Academic Hospital (CHBAH).

Data that would be needed for this study:

- Each patient's demographic information (race, gender, age) as well as comorbid medical conditions and topical glaucoma medications.
- Clinical examination findings (namely gonioscopy) and relevant tests (GDx, visual fields) as well as multiple intraocular pressure recordings following the water-drinking test.

All data will be collected in a prospective manner as per the submitted protocol, and will remain strictly confidential to the author. All data collection will be performed after approval by the Human Research Ethics Committee of the University of the Witwatersrand.

The intended research will be fully funded by the applicant and will not interfere with the daily running of the hospital or hospital equipment.

Head of Department Ophthalmology CHBAH

Name Q. McKeren

Date 5/2/2016

Signature

APPENDIX 5.1 Datasheet Case Population

Patient Profile – Population 1 (Glaucoma)

Study Number:

Age:

Gender: ☐ **M** ☐ **F**

Race:

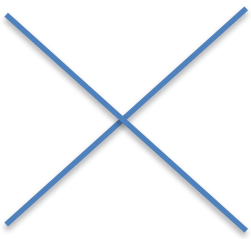
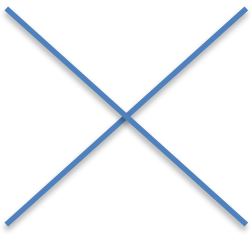
History of Ocular Trauma: ☐ **Y** ☐ **N**

Comorbidities & Medications:

Topical Medication:

Medication	Dosage	Frequency

Examination and Investigations:

	Right Eye	Left Eye
Gonioscopy		
NFI (GDx)		

Water-Drinking Test Performance

Intraocular Pressure Readings (mmHg)

	Right Eye	Left Eye
Baseline		
15 mins		
30 mins		
45 mins		
60 mins		

APPENDIX 5.2 Datasheet Control Population

Patient Profile – Population 2 (Control)

Study Number:

Age:

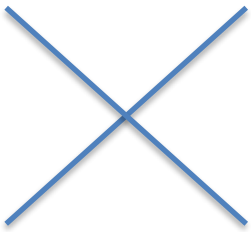
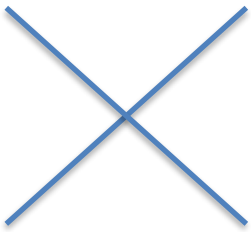
Gender: ☐ **M** ☐ **F**

Race:

History of Ocular Trauma: ☐ **Y** ☐ **N**

Comorbidities & Medications:

Investigations:

	Right Eye	Left Eye
Gonioscopy		
RNFL		

Water-Drinking Test Performance

Intraocular Pressure Readings (mmHg)

	Right Eye	Left Eye
Baseline		
15 mins		

30 mins		
45 mins		
60 mins		

APPENDIX 6.1 Consent Form Case Population

University of the Witwatersrand

CONSENT STATEMENT: Glaucomatous population

TITLE: The Water Drinking Test in Glaucoma – a Surrogate for Outflow Facility

Participant

I have read the research participant information sheet for this study, or someone has explained it to me in a language that I understand. I have been answered all questions I may have, and I am satisfied with the answers I have received. I voluntarily consent to be a participant in this study.

Name of participant:_____

Date:_____

Signature (or fingerprint):_____

Investigator (Person obtaining consent)

I have explained the information in the research participant information sheet to the participant, or had it explained to the participant in a language he/she understands. I have answered all questions to the best of my ability. Consent was given voluntarily by the research participant.

Name of investigator:_____

Date:_____

Signature (or fingerprint):_____

Witness

I have been witness to the explanation of the research participant information sheet, and confirm that the investigator has answered all the participant's questions and that the participant has given voluntary consent.

Name of witness:_____

Date:_____

Signature (or fingerprint):_____

APPENDIX 6.2 Consent Form Control Population

University of the Witwatersrand

CONSENT STATEMENT – control population

TITLE: The Water Drinking Test in Glaucoma – a Surrogate for Outflow Facility

Participant

I have read the control research participant information sheet for this study, or someone has explained it to me in a language that I understand. I have been answered all questions I may have, and I am satisfied with the answers I have received. I voluntarily consent to be a participant in this study.

Name of participant:_____

Date:_____

Signature (or fingerprint):_____

Investigator (Person obtaining consent)

I have explained the information in the research participant information sheet to the participant, or had it explained to the participant in a language he/she understands. I have answered all questions to the best of my ability. Consent was given voluntarily by the research participant.

Name of investigator:_____

Date:_____

Signature (or fingerprint):_____

Witness

I have been witness to the explanation of the research participant information sheet, and confirm that the investigator has answered all the participant's questions and that the participant has given voluntary consent.

Name of witness:_____

Date:_____

Signature (or fingerprint):_____

APPENDIX 7.1 Case Population Information Sheet

University of the Witwatersrand

RESEARCH PARTICIPANT INFORMATION SHEET: Glaucomatous population

TITLE: The Water Drinking Test – a Surrogate for Outflow Facility

Principle Investigator: Dr F. Indiveri
Registrar, Division of Ophthalmology, Department of Neurosciences, WITS
Supervisor: Professor G. McLaren
Head of Department, St John Eye Hospital, Chris Hani Baragwanath Academic Hospital

Dear Sir/Madam

You are being invited to participate in a research study conducted by me, Dr F. Indiveri. I am an eye doctor working at this hospital, and my supervisor is Professor G. McLaren. You are being invited to participate because you are one of the patients being treated for glaucoma at our clinic. This is a masters degree project aimed at learning more about glaucoma and helping the doctor develop research skills.

In order to decide whether or not you would like to be a part of this study, it is important to know what is involved as well as the potential risks and benefits. This form contains all the information you need to know, and will be discussed with you. Once you understand the study, you will be asked to please sign a form if you choose to participate. Please know that you are under no obligation to take part in this study, and there will be no negative consequences if you choose not to participate.

Why are we doing this study?

Glaucoma is a disease that causes damage to the nerve at the back of the eye. One of the ways it does this is by causing high pressure inside the eye. This study will look at patients with and without glaucoma, and will measure the pressure in each participant's eye after an amount of liquid is drank (a 'fluid-challenge').

What is the purpose of this study?

Dr Indiveri will be measuring the pressure inside the eye after one litre of water has been drank in a five minute period. This will be plain municipal water, free from additives and flavourants. It is believed that after drinking this amount of water, the pressure will be much higher, and take much longer to return to normal, in a patient who has glaucoma. In a person who does not have glaucoma, the pressure will not rise as high and will return to normal much quicker. This information will tell us how badly glaucoma has damaged the eye, and will show that drinking water shows a difference between patients with and without glaucoma. It is very important to note that this intake of water will in no way be detrimental to the health of your eye and the progression of glaucoma.

What is your role as a participant in this study?

Each patient's age and gender will be written down. Dr Indiveri will ask you what medication you are using (tablets and drops) and this information will be written down.

Some participants may need to have a GDx test – this is a quick, painless test that measures how healthy the nerve at the back of your eye is. Each participant in this study will have their pressure in each eye measured with an instrument called a Goldmann tonometer . Drops will be put into the eye before this so that no pain is felt. Then one litre of water will need to be drank within five minutes. Following this, the pressure will be recorded four more times (fifteen minutes apart). All these pressure readings will be written down. The test will take one hour of your time.

What are the possible risks to you as a participant?

Measuring the pressure of the eye with the Goldmann tonometer is a routine part of the eye examination, and is done on all patients in our clinic not only those participating in this study. Before taking the pressure, we put drops in the eye that may cause a stinging feeling for a few seconds. This is completely normal and, after receiving these drops, you will not feel pain while the pressure of the eye is measured. It has been shown that measuring the pressure of the eye with the Goldmann instrument is very safe. There is a very small risk that damage to the front of the eye or infection can occur, and if either of these occur they will be treated appropriately with ointment.

What are the benefits of this study?

There will be no direct benefit to you, and there will be no financial compensation. You will help Dr Indiveri with her research expertise and the results of this study may give us important information about the difference between glaucoma and non-glaucoma patients when they are presented with a fluid challenge.

What will happen if you choose NOT to be part of this study?

You are under no obligation to participate in this study and there will be absolutely no negative consequences for you if you choose not to take part. You may end your participation in this study at any time.

Will your information kept private?

Yes. Your name and hospital number will NOT be recorded. Only your gender, age, medications, GDx test result and pressure measurements will be written down.

How many people will participate in this study?

Approximately one hundred (100) people will be part of this study.

Who can I contact if I have an eye problem?

St John Eye Clinic: Office hours (08:00-16:00): 0119339771 Afterhours: 0119338780
Dr F. Indiveri: 0824431303

This study will need to have been reviewed and approved by a Research Assessor Group as well as the Human Research Ethics Committee of the University of the Witwatersrand before commencement.

Date:_____Initial:_____

APPENDIX 7.1 Control Population Information Sheet

University of the Witwatersrand

RESEARCH PARTICIPANT INFORMATION SHEET: control population

TITLE: The Water Drinking Test – a Surrogate for Outflow Facility

Principle Investigator: Dr F. Indiveri
Registrar, Division of Ophthalmology, Department of Neurosciences, WITS
Supervisor: Professor G. McLaren
Head of Department, St John Eye Hospital, Chris Hani Baragwanath Academic Hospital

Dear Sir/Madam

You are being invited to participate in a research study conducted by me, Dr F. Indiveri. I am an eye doctor working at this hospital, and my supervisor is Professor G. McLaren. You are being invited to participate because you do not have glaucoma (high pressure inside the eye), which will allow comparison to those patients who do have glaucoma. This is a masters degree project aimed at learning more about glaucoma and helping the doctor develop research skills.

In order to decide whether or not you would like to be a part of this study, it is important to know what is involved as well as the potential risks and benefits. This form contains all the information you need to know, and will be discussed with you. Once you understand the study, you will be asked to please sign a form if you choose to participate. Please know that you are under no obligation to take part in this study, and there will be no negative consequences if you choose not to participate.

Why are we doing this study?

Glaucoma is a disease that causes damage to the nerve at the back of the eye. One of the ways it does this is by causing high pressure inside the eye. This study will look at patients with and without glaucoma, and will measure the pressure in each participant's eye after an amount of liquid is drank (a 'fluid-challenge').

What is the purpose of this study?

Dr Indiveri will be measuring the pressure inside the eye after one litre of water has been drank in a five minute period. This will be plain municipal water, free from additives and flavourants. It is believed that after drinking this amount of water, the pressure will be much higher, and take much longer to return to normal, in a patient who has glaucoma. In a person who does not have glaucoma, the pressure will not rise as high and will return to normal much quicker. This information will tell us how badly glaucoma has damaged the eye, and will show that drinking water shows a difference between patients with and without glaucoma.

What is your role as a participant in this study?

Each patient's age and gender will be written down. Dr Indiveri will ask you if you are using any medication and this information will be written down. You will need to have an OCT

RNFL test – this is a quick, painless test that measures how healthy the nerve at the back of your eye is. Each participant in this study will have their pressure in each eye measured with an instrument called a Goldmann tonometer . Drops will be put into the eye before this so that no pain is felt. Then one litre of water will need to be drank within five minutes. Following this, the pressure will be recorded four more times (fifteen minutes apart). All these pressure readings will be written down. The test will take one hour of your time.

What are the possible risks to you as a participant?

Measuring the pressure of the eye with the Goldmann tonometer is a routine part of the eye examination, and is done on all patients in our clinic not only those participating in this study. Before taking the pressure, we put drops in the eye that may cause a stinging feeling for a few seconds. This is completely normal and, after receiving these drops, you will not feel pain while the pressure of the eye is measured. It has been shown that measuring the pressure of the eye with the Goldmann instrument is very safe. There is a very small risk that damage to the front of the eye or infection can occur, and if either of these occur they will be treated appropriately with ointment.

What are the benefits of this study?

There will be no direct benefit to you, and there will be no financial compensation. You will help Dr Indiveri with her research expertise and the results of this study may give us important information about the difference between glaucoma and non-glaucoma patients when they are presented with a fluid challenge.

What will happen if you choose NOT to be part of this study?

You are under no obligation to participate in this study and there will be absolutely no negative consequences for you if you choose not to take part. You may end your participation in this study at any time.

Will your information kept private?

Yes. Your name and hospital number will NOT be recorded. Only your gender, age, medications, RNFL test result and pressure measurements will be written down.

How many people will participate in this study?

Approximately one hundred (100) people will be part of this study.

Who can I contact if I have an eye problem?

St John Eye Clinic: Office hours (08:00-16:00): 0119339771 Afterhours: 0119338780
Dr F. Indiveri: 0824431303

This study will need to have been reviewed and approved by a Research Assessor Group as well as the Human Research Ethics Committee of the University of the Witwatersrand before commencement.

Date:_____

Initial:_____

APPENDIX 8 Turnitin Report

Turnitin Originality Report

- Processed on: 08-Oct-2018 6:53 PM SAST
- ID: 1016093309
- Word Count: 3036
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Anna Sophie Mursch-Edlmayr, Nikolaus Luft, Dominika Podkowinski, Michael Ring, Leopold Schmetterer, Matthias Bolz. "Laser speckle flowgraphy derived characteristics of optic nerve head perfusion in normal tension glaucoma and healthy individuals: a Pilot study", Scientific Reports, 2018
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Pearls of Glaucoma Management, 2016.

APPENDIX 9 Plagiarism Form

DEPARTMENT OF NEUROSCIENCES

Neurology, Neurological Surgery, Ophthalmology, Otorhinolaryngology, Psychiatry

School of Clinical Medicine, Faculty of Health Sciences,
7 York Road, Johannesburg 2193, South Africa
Tel: +27 11 717-2774 · Fax: +27 11 717 2775

Plagiarism declaration for written work

I ……. as a postgraduate student registered for a MMed at the

University of the Witwatersrand declare the following:

- I am aware that plagiarism is the use of someone else's work without their permission and or without acknowledging the original source.
- I am aware plagiarism is wrong.
- I confirm that this written work is my own work except where I have stated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or if I have failed to acknowledge the ideas or writing of others.

Signature ……...

Date ……