



Application of the information-motivation-behavioural skills model to strengthen eye care follow-up amongst glaucoma patients

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Background: Many factors influence glaucoma medication adherence. A better understanding of the relationships between knowledge, attitude and patients' practice problems in using glaucoma medications may reveal opportunities for intervention that could improve patients' clinical outcomes. The challenge of non-adherence to glaucoma follow-up and treatment plans remains a significant global healthcare concern. Non-adherence to medication is a challenge to effective treatment of many chronic diseases, including glaucoma and remains so even with the implementation of strategies aimed at improving adherence. In South Africa, the information-motivation and behavioural skills model (IMBSM) of glaucoma adherence constructs might be useful in describing and predicting adherence behaviours that have not been articulated to people with glaucoma.

Aim: The study applied the IMBSM in strengthening eye care follow-up amongst glaucoma patients in the Limpopo province of South Africa.

Setting: The study was conducted at a selected hospital in the Vhembe District, Limpopo province, South Africa.

Methods: A cross-sectional quantitative descriptive study via questionnaire was conducted on patients who were taking intraocular pressure-lowering medications and subject to follow up at a glaucoma clinic. A total of 429 eligible patients were purposefully selected for data collection using structured questionnaires. Oral informed consent was obtained from all respondents before they completed the questionnaires.

Results: Only 55% of the total sample reported a glaucoma non-adherence rate of less than or equal to 95% compared with 45% who reported glaucoma adherence rate of more than or equal to 95%. Independent predictors of non-adherence were: inadequate glaucoma knowledge (29%), forgetfulness (26%) and patients' beliefs (18%).

Conclusion: The findings revealed the need for on-going glaucoma educational and informational interventions to address the motivation and adherence behavioural skills of patients to strengthen the current levels of glaucoma adherence behaviour. These findings suggest that the application of the IMBSM might improve glaucoma patients' adherence.

Keywords: anti-glaucoma medication; adherence to glaucoma medication; eye care; glaucoma patients; IMBSM.

Introduction

Several studies show that glaucoma is the second leading cause of blindness worldwide, accounting for an approximately 3.12 million cases globally and the leading cause of irreversible blindness. The number of glaucoma patients are expected to rise to about 76.0 million in 2020 and to 111.8 million in the year 2040. The most common risk factor for glaucoma is raised intraocular pressure (IOP). Lowering of IOP is the only proven strategy for preventing the risk of glaucoma progression. Good adherence to ocular hypotensive agents is essential to control the IOP and optic nerve damage.

Medication is often suboptimal for glaucoma and non-adherence is a significant barrier to effective use of medication. An approximately 12-month adherence period is too short for the therapeutic effects in 30% – 50% of patients based on self-reports, pharmacy refills and electronic monitoring. ^{5,6}

Although there are serious consequences such as disease progression and eventual vision loss, non-adherence is common in glaucoma patients.

Appropriate treatment and follow-up care are crucial in preventing vision loss because of glaucoma. Numerous studies estimated non-adherence to follow-up eye appointments to be as high as 43% amongst patients prescribed with eye drops to lower IOP. Lowering IOP is one possible intervention to slow down the disease progression. Adherence is generally defined as the extent to which patients take medications as prescribed by their eye care providers. Generally, glaucoma drug adherence and associated factors are classified into four general groups. These are patient-related, medication-related, provider-related and environmental-related factors. Provider-related and environmental-related factors.

Non-adherence to chronic disease treatment remains a global problem. The World Health Organization estimates that 50% of the developed countries patients fail to adhere to their recommended treatment and the situations are worse in developing countries. The purpose of any prescribed medical intervention is to achieve a certain anticipated outcome in patients. However, despite the best intentions and efforts on the part of healthcare professionals, positive outcomes might not be achievable if patients are non-compliant. The inability to use medications as prescribed can result in decreased treatment effectiveness and outcomes, increased complications and worsened health status. Glaucoma medication non-adherence is a complex matter that might lead to a huge burden on the healthcare system if not adequately addressed. The situation of the same professionals and the same professionals are non-compliant.

Although evidence exists to show that lowering of IOP and medication adherence substantially reduces the risk of vision loss, strategies to strengthen glaucoma eye care service are complicated. These include modifying a range of behaviour related to health such as attending eye clinic appointments and regular use of prescribed eye drops. Researchers recommend different strategies that have been employed in different countries to improve medication adherence and alleviate the effects of the loss to follow-up amongst glaucoma patients. 13,14

However, more research is needed to determine appropriate targets for interventions to increase the uptake rate of glaucoma medication adherence. One basis for the prevention of medication non-adherence is the information-motivation and behavioural skills model (IMBSM). The IMBSM theorises information about a target behaviour, that is, knowledge and motivation to perform behaviour is based on factors such as attitudes and social norms, which lead to the development of relevant behavioural skills such as individuals' objective and perceived abilities to perform the target behaviour.

However, no known study on strategy to strengthen glaucoma eye care follow-up was found for the Limpopo province of South Africa where this study was conducted. Therefore, this study hopes to provide information that will guide hospitals and primary healthcare facilities in addressing specific barriers experienced by glaucoma patients in improving treatment adherence and retention in care in an exclusive cultural setting of the Vhembe District of the Limpopo province. Studies document numerous motivational, cognitive and psychological theories of behavioural change that increase the importance of medication adherence amongst patients on lifelong treatment and management.¹⁶ The researchers analysed a specific theoretical model for improving knowledge, attitude and practices of glaucoma patients as a springboard for strategy development. Therefore, the study investigated how the application of the IMBSM can strengthen eye care follow-up of glaucoma patients in the Limpopo province of South Africa.

Conceptual framework: Information-motivational behavioural skills model

The IMBSM has been widely used in understanding and improving health behaviour in different chronic diseases and populations.¹⁷ The IMBSM has three main constructs, which are as follows: information and knowledge, motivation to perform the behaviour and the behavioural skills necessary to improve health-related behaviours. 18 Each construct can have a direct influence on health-related behaviour. The model proposes that individuals who are well informed and highly motivated and have skills to perform health-related behaviour are more likely to endorse and maintain health-related behaviour. The IMBSM can be also used to identify key factors to implement and maintain the adherence behaviour in patients with chronic diseases.¹⁷ These reasons make the IMBSM relevant for this study. The key constructs and empirical support of the model are discussed here.

The first component information and knowledge refers to the basic knowledge and awareness about one's medical condition such as glaucoma and the efficient strategies to manage it. Studies have reported a significant correlation between medication knowledge and adherence to chronic diseases. ¹⁹ Deeb et al., ²⁰ and Joseph, Ainsworth, Keller and Dodgson²¹ reported that knowledge alone is insufficient to increase healthy eating and physical activity. The IMBSM suggests that knowledge alone may be sufficient to change behaviour if the behaviour is not complicated. According to the IMBSM, knowledge may collaborate with motivations, this collaboration may translate into healthy practices when facilitated by necessary behavioural skills. Also, the IMBSM indicates that knowledge may be more important to certain populations than others. ^{22,23}

The second component of the IMBSM is motivation. Motivation comprises an individual's drives, that is, his or her attitudes and beliefs about engaging or not engaging in a behaviour, and his or her social motivation.^{24,25} Patients with

adequate social support for adherence are likely to adhere to medication. In addition, behavioural skills determine whether a well informed and highly motivated person can adhere to medication. It includes components such as ensuring that the patient has skills, tools and strategies and the confidence or the belief that he or she can achieve the desirable behaviour. Behavioural skills are the individual's ability and willingness to do all the necessary skills that might improve adherence.^{26,27}

Interventions using these constructs can address the patient barriers and help them to remain in care. Kelly, McCarthy and Sahm²⁸ stated that patients' understanding of their conditions and treatment is positively linked to adherence. Similarly, Zullig et al.,10 argued that medication adherence, satisfaction and recall are all related to the amount and type of information given to patients. Sankar et al.,29 also observed that patients who understand the reasons for taking medication adhere more to their treatment than those who do not. In addition, Cook et al.,30 and Ehret et al.,31 argued that the IMBSM suggests that knowledge does affect adherence, along with behavioural skills (including self-efficacy) and treatment motivation. Zhao et al.,32 also reported that older patients with multimorbidities adhere less to their chronic medications because of insufficient knowledge, negative attitude and lack of confidence.

Methods and design

The study employed a cross-sectional survey distribution method. A quantitative study was conducted amongst glaucoma patients who were 18 years and older. The study was conducted at Elim Hospital of Vhembe District, Limpopo province, South Africa. Elim Hospital is the only specialised ophthalmic hospital in the region and the largest referral centre in the Vhembe District. The hospital provides comprehensive eye care services including major surgeries, minor surgeries, glaucoma follow-up, general outpatient and inpatient eye care services for patients coming from different areas of the country. This study employed a nonprobability convenience sampling technique, which was appropriate because of the practical difficulty of using other sampling methods from the target population of interest in the entire district. Moreover, patients happened to be at the right place at the right time at the selected hospital. Preliminary research showed that there was a challenge of loss to follow-up amongst glaucoma patients. A sample of 450 people was reached and this was adequate for yielding reliable results. Only patients diagnosed with glaucoma were purposively sampled and had been under review for at least 3 years. The instrument was developed out of a comprehensive literature review by the first author (see Welge-Lussen et al.33). The developed questionnaire was administered to the participants by trained interviewers. Most study participants were unable to complete the questionnaire on their own as they could not read and write and others had poor vision. Those who were unable to read and write were assisted by the researchers.

To ensure validity, the instrument development was guided by the study objectives and literature. The pre-test ensured that questions were of high quality and clear. The instrument was pre-tested amongst 45 patients who were not part of the main study. Pilot study participants were given 30 min to complete the questionnaire, which helpfully revealed that the time allocated for completion of the questionnaire was inadequate and that some participants could not interpret some questions and these confusing questions were rephrased. Their comments were used to revise the questionnaire and additional time was allocated for completing because some participants were slow because of poor vision. The questionnaire was administered twice to the same participants and then the correlation coefficient calculations were used to compare the first responses with the second responses. For this study, non-adherence was defined as missing at least one dose of medication per week. Participants who had adherence rate <100% were asked to give reasons for their failure to comply with the prescribed medication if any. Adherence rates were defined as good if their score ranged from 95% to 100% and as poor or inadequate if they were less than 95%. Closed-ended questions were used to gather data about patients' demographics, level of glaucoma knowledge, practice regarding glaucoma and factors affecting adherence to medical treatment and motivating factors for adherence. The study used the Morisky Medication Adherence Scale as an instrument to evaluate glaucoma medication adherence. The instrument was developed in the English language and was translated into the local language.

Data analysis

After all the completed questionnaires were scrutinised, data were entered into Microsoft Excel version 2010 and the Statistical Package for Social Sciences (SPSS) version 24.0 for statistical analysis. Level of education was categorised as none (no formal education), primary education (Grades 1–7), secondary education (Grades 8–12) and tertiary education (colleges, technical schools and universities). Patients with tertiary education were grouped with patients with secondary education for data analysis because of the small percentage of participants with tertiary education. Adherence is defined as the degree to which a patient follows the instructions to take a prescribed treatment during a defined period whilst non-adherence describes the failure of a patient to follow health behaviour and treatment advice given by a health provider.¹¹

Ethical considerations

Ethical approval to conduct the study was granted by the University of Venda Research Ethics Committee SHS/18/PH/0111. Using the UHDC's approval and the ethical clearance certificate, the researchers sought permission from the Limpopo Provincial Department of Health and Vhembe District Department of Health. Permission was also obtained from the Hospital managers and CEO of the selected hospital in the Vhembe District.

Results

A total of 450 glaucoma patients were seen during the period of the study. Twenty-one of the patients did not meet the inclusion criteria as they were all newly diagnosed. All participants who met the criteria participated resulting in a response rate of 95% (429). Most study participants (68%, n=294) were females and only 32% were males. A total of 278 (65%) participants were above 65 years. More than half (62%) of the participants claimed to be Christians. Of the 429 participants, 70% had no formal education and only 3% had tertiary education as shown in Table 1.

Information factor

This section assessed how much the participants knew about glaucoma and its treatment adherence (Table 2). Almost half of the participants (46%) did not know the cause of glaucoma whilst 30% attributed it to witchcraft. About 59% of the participants stated that vision lost because of glaucoma could be reversed whilst 41% indicated that it is permanent. A total of 249 participants did not know that

TABLE 1: Socio-demographic characteristics of the study participants.

Variables	Frequencies	Percentages
Gender		
Male	135	32
Female	294	68
Age (years)		
18-24	18	4
25–54	52	12
55-64	81	19
65 and above	278	65
Educational level		
Never attended school	301	70
Primary education	84	20
Secondary education	31	7
College or tertiary	13	3
Employment status		
Employed	86	20
Unemployed	343	80
Religious affiliation		
Christianity	265	62
Non-Christian	164	38

N = 429

TABLE 2: Participants' level of glaucoma knowledge

Variables	Characteristics	Frequencies	%
Perceived cause of glaucoma disease	Hereditary	102	24
	Eye disease that is caused by witchcraft	131	30
	Do not know	196	46
2. Skipping glaucoma treatment can lead to blindness	Yes	194	45
	No	235	55
Knowledge of lifelong glaucoma medication	Yes	180	42
	No	249	58
4. Vision loss because of glaucoma is permanent	Yes	174	41
	No	255	59
5. Most patients with glaucoma have no symptoms	Yes	221	51
	No	208	49
Glaucoma patients may require follow-up care	Yes	189	44
	No	240	56

N = 429.

glaucoma needs lifelong medication whilst 180 said glaucoma needs lifelong medication. A total of 240 patients indicated that a patient with glaucoma disease does not require regular follow-up care. However, 221 participants indicated that glaucoma is asymptomatic.

Motivation factors

This section assessed the personal and social motivation of the patients towards glaucoma adherence (Table 3). Out of the total number of the study participants, 62% said there is no benefit in regular glaucoma medication use. More than half (60%) of the participants disagreed with the idea that glaucoma is a disease that afflicts old people compared with 40% who agreed. About 249 (58%) participants believed that using eye drops can worsen their eye condition (Table 3) whilst 42% did not agree that using eye drops can worsen glaucoma disease. A total of 53% of the participants agreed with the statement that it would frustrate them to think that they would have to instill glaucoma eye drops all their lives. More than half (56%) of the participants agreed that they like to be supported by their family members when taking their medications compared with 44% who said they did not need any support. About 51% participants disagreed with the statement that they are afraid of glaucoma side effects.

Behavioural skills

This section assessed the behavioural skills of the patients regarding glaucoma medication adherence (Table 4).

TABLE 3: Participants' attitude and beliefs towards glaucoma disease.

Statement		Agree		Disagree	
	\overline{f}	%	f	%	
There is no benefit in regular use of glaucoma medication	266	62	163	38	
I do not want people to realise that I use glaucoma medication	219	53	200	46	
I like it when family members give me support during medication refill	241	56	188	44	
I believe that glaucoma is an old people's disease	171	40	258	60	
I dislike using eye drops as it worsens my condition	249	58	180	42	
It is frustrating to take glaucoma medication for life	230	54	199	46	
I am afraid of the glaucoma medication's side effects	179	49	220	51	

N = 429.

f, frequencies.

Table 4: Patients' practice regarding glaucoma medication.

Statement	Practices	Frequencies	%
Number of doses missed per week	None	192	45
	1-2	105	24
	3–5	51	12
	>5	81	19
Level of glaucoma medication compliance	Adherence	192	45
	Non-adherence	237	55
Reasons for non-adherence or non-compliance	Poor knowledge	70	29
	Forgetfulness	61	26
	Religious beliefs	42	18
	Inability to access medication	26	11
	Denial (my eyes are ok)	22	9
	Side effects	16	8

N = 429

TABLE 5: Motivating factors cited by participants to strengthen medication adherence.

Statement	Freque	Frequencies	
	n	%	
Pre-appointment reminder (by phone, SMS or email)			
Yes	191	80	
No	48	20	
More education on the importance of follow-up			
Yes	202	85	
No	35	15	
Understanding the risk of negative effects of non-adherence to glaucoma such as blindness	!		
Yes	197	83	
No	40	17	
Understanding the benefits of regular use of glaucoma medication like halting disease progression			
Yes	170	72	
No	67	28	
Have someone to help with eye drops administration			
Yes	125	53	
No	112	47	
Mobile eye care clinic			
Yes	166	70	
No	71	30	
Forming support groups with others patient with glaucoma	disease		
Yes	93	39	
No	144	61	

A total of 257 (55%) participants had missed their daily doses more than once in a week whilst 45% were classified as 100% adherent according to the study definition. This study evaluated adherence in terms of self-reporting by patients regarding medication use and keeping appointments. Reasons for non-adherence were poor knowledge at 70 (29%), followed by forgetfulness 61 (26%). Medications' side effects were cited as the least reason for non-compliance 18 (8%). Of the 237 patients who were classified as non-adherence, they identified motivating factors that can improve their medication adherence. The most frequently reported motivating factor was getting more education on the importance of follow-up (85%, Table 5), followed by understanding the risk of negative effects of glaucoma treatment non-adherence such as blindness and pre-appointment reminder (by phone, SMS or email) at 83% and 80%, respectively. Almost three quarters (72%) of the participants reported that understanding the benefits of their glaucoma medication motivated them to adhere to their medication regimen. Having mobile eye clinic visit once per month and having someone to help in eye drops administration were the fifth and sixth frequently reported motivating factors for the participants (70% and 53%), respectively. Notably, only one-third (39%) of participants indicated that forming support groups with other patients with glaucoma disease were also an important motivating factor to strengthen adherence (Table 5).

Discussion

The IMBSM was used as a guiding framework to assess factors that influence glaucoma medication adherence in a sample of 429 participants. Most participants were elderly

females (69%) whose age is above 65 years. Almost three quarters (70%) of the participant did not have formal education and were mostly unemployed likely because the study was conducted in a rural setting. Similar findings were reported in Nigeria and South Africa, where the number of female participants without formal education were in the majority.^{2,34}

Participants exposed relatively little or no knowledge about glaucoma. This was revealed when most participants said they did not know what causes glaucoma disease (46%), whilst others believed that it is caused by witchcraft (30%). More than half (59%) of the participants said that vision loss because of the glaucoma disease is temporary. These participants assumed that the effects of the glaucoma disease could be reversed and therefore does not need lifelong medication. Our study concurs with findings obtained in Ghana, Botswana and Southeast Nigeria. 35,36,37 In South Africa, Tshivhase et al.34 also mentioned that 55% of their participants believed that blindness because of glaucoma is reversible. By contrast, Uche et al.2 reported high glaucoma awareness amongst glaucoma patients. Similar results were cited by Abdull et al.³⁸ in Nigeria who stated that there was satisfactory knowledge amongst patients although they did not fully understand the purpose of glaucoma treatment.

In this study, most participants (62%) were not motivated to adhere to glaucoma medication. Participants claimed that there is no benefit in the regular use of glaucoma medication and disliked using eye drops believing that it worsens their eye condition. Moreover, some participants were depressed by the fact that they were expected to use glaucoma medication for the rest of their lives. This suggests that participants should be given adequate and relevant information about glaucoma and its management. This observation is supported by Demirtaş et al.³⁹ who reported that participants in their study were not aware about the importance of regular eye examinations. However, Thompson et al.40 revealed that there are glaucoma patients who believed that it was important to do follow-up even if there was no visible change in their vision. A South African study observed that glaucoma patients were reluctant to go for their routine follow-up care as advised by the health providers.34 Significantly, most participants were motivated to do follow-up when it was explained to them that the glaucoma disease affects all age groups. Sleath et al.41 revealed that younger patients were more likely to report being less adherent than older patients because younger patients perceived a lower risk of diseaserelated morbidity than elderly patients.

In this study, more than half (55%) of the participants had inadequate behavioural skills relevant for glaucoma adherence whilst less than half (45%) were associated with adequate behavioural skills relevant for glaucoma adherence. A total of 237 participants revealed that they had missed their doses more than once in a week. We assessed glaucoma medication adherence using a self-report measure, which asked about the number of days that participants had adhered

to treatment. Just over half (55%) of participants were classified as non-adherent to their glaucoma regimens and 192 (45%) were classified as 100% adherent. The most frequently reported barriers to glaucoma medication adherence in our study sample were lack of knowledge (information barrier), forgetfulness (behavioural skills barrier), religious beliefs (information barrier) and inability to access medication (motivation barriers). This can be explained by the fact that the study had many elderly participants who may be prone to forgetfulness. Other participants stopped taking their glaucoma medication because of their conflicting religious and traditional beliefs. Another contributing factor is that patients are not able to easily access glaucoma clinics because of economic or time factors. Cohen Castel et al. 42 also found that elderly patients who depended on others for help with their glaucoma medications were at greater risk for non-adherence than those who do not depend on others. Our study's findings concur with those by Nayak, Gupta et al.43 and Leung et al.44 who found that glaucoma medication and clinics visits can negatively affect patients because of financial costs. Sleath et al.41 also reported that elderly patients with chronic disease are at risk of glaucoma non-adherence if they have poor support from healthcare providers. Uche et al.² and Tshivhase et al.34 found that glaucoma patients used traditional eye medication (TEM), visited spiritual and traditional healers to try and deal with the disease. These studies indicated that the most common TEM used by glaucoma patients was topical plant extracts. However, some patients still believed in eye drops adherence and making glaucoma follow-up care.⁴⁰

Targeting individual patients' needs to promote their adherence is challenging but important. To achieve adherence and health behaviour change, patients should be given adequate information, motivated to carry out their recommended treament and to have a workable strategy for following recommended treatment.¹¹ Instilling eye drops every day without missing any doses can be challenging. Therefore, when counselling patients, each patient's lifestyle should be considered to promote adherence. Health practitioners should communicate information effectively with patients and their care givers because most of them have poor vision, build trust with the patients, involve patients to participate in decision-making and allow patients to say which methods work better for them. This study found that patients are not motivated to carry out their prescribed medications because they do not believe that they can instill their own eye drops. Therefore, health practictioners should motivate patients to believe in themselves, provide adequate support to patients and their family members during clinic visits, offer emotional support and give necessary skills related to medication adherence, provide patients with pamphlets, listen to them and discuss any negative perception that they might have and help patients to make commitment to adherence. Most patients indicated that they needed someone to remind them to administer their medication. Therefore, community healthcare workers should be involved in providing support and reminding patients about their follow-up dates. Patients

should also be provided with written instruction or reminders; electronic reminders, such as short messages via cell phones and emails and be advised to join support groups.

The most frequently cited motivating factors were related to knowing more about the benefits of medications and understanding the risk of negative effects of non-adherence to glaucoma such as blindness. Most patients believed that being given adequate education about the importance of follow-up visits and having mobile eye care clinics might help them to adhere to their medication. There is also a need to discourage TEM use amongst glaucoma patients. This should be carried out using health education and encouraging good eye care practice.

Limitations

One of the limitation in this study is that 'gold standard' for assessment of adherence does not exist. Therefore, adherence was measured through self-reported assessment measures. Participants in self-report studies tend to overestimate adherence and self-reported adherence measurements are known to increase adherence rates. ⁴⁵ The problem with self-reports of health behaviour is that they may be influenced by a subject's reluctance to report non-adherence to treatment recommendations. Moreover, the study was conducted in one public hospital in the Vhembe District, therefore its results are not generalisable to other districts in the province. In addition, as it is not a longitudinal or a follow-up study, this study's findings are thereby influenced.

Conclusion

Non-adherence limits the potential of successful treatments to improve patients' health and quality of life. Healthcare providers experience substantial frustration over the high propotion of their patients who fail to follow treatment recommendations. The study's findings revealed that nonadherence to glaucoma medication is still a challenge in the study setting. Moreover, the study identified that glaucoma knowledge is low as it is cited as the most contributing factor for glaucoma medication non-adherence. Participants lacked adequate knowledge regarding the importance of glaucoma follow-up. The study showed that information, motivation and behavioural skills are interrelated. Moreover, the study found that glaucoma patients need more information about their condition. Furthermore, it was discovered that strategies such as using cell phone reminders might improve strengthening glaucoma medication adhrence. Therefore, education should focus on improving glaucoma knowledge, improving perceptions of the benefits of glaucoma medication and adoption of good eye practices such as avoiding the use of TEM. It is vital that patients should adequately understand the importance of adherence and the serious consequences of non-adherence. In addition, educating the patients and their caregivers should be a priority.

Recommendations

Recommendations of this study are closely linked to the conclusions drawn from the data: The study found that strategies to improve adherence to glaucoma medication are likely to be effective when they include multiple components such as educating the patient and their family members, educating the community, giving adequate information to patients, providing counselling to patients, providing information about the use of adherence support tools such as using cell phones or email reminders. Health-care providers should provide specific information about health risks and benefits of change and identify reasons for missing doses and address the challenges accordingly in order to improve adherence. The study's findings indicate that a glaucoma clinic should be set up separately from the general outpatient department so that it can operate on weekends.

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S.E.T., L.B.K. and T.G.T. contributed equally to this article.

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