LVPEI Glaucoma Epidemiology and Molecular Genetic Study: teleophthalmology screening for angle-closure disease in an underserved region

Nikhil S. Choudhari¹ · Premanand Chandran¹ · Harsha L. Rao¹ · Ganesh B. Jonnadula^{1,2} · Uday K. Addepalli^{1,2} · Sirisha Senthil¹ · Chandra Sekhar Garudadri¹

Received: 14 March 2019 / Revised: 11 August 2019 / Accepted: 25 September 2019 / Published online: 6 November 2019

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Abstract

Objectives To assess the ability of teleophthalmoscopic grading of peripheral anterior chamber depth (PACD) using the van Herick (vH) technique in detecting gonioscopically occludable angle; and to determine whether combining results from vH grading and ocular biometry can improve the accuracy to diagnose gonioscopically occludable angle

Methods This cross-sectional study was an offshoot of a rural population-based study, Glaucoma Epidemiology and Molecular Genetic Study (GLEAMS). A masked urban ophthalmologist graded digital slit lamp photographs of PACD by vH technique. Sussman four-mirror lens was used to perform dark room indentation gonioscopy. Cutoff values of the tests were, vH technique: grade ≤ 2 , central anterior chamber depth (ACD), as well as axial length: ≤ 25 th percentile and lens thickness ≥ 75 th percentile value of the study population.

Results We studied 1965 eyes of 1029 adult participants. The vH grade was ≤ 2 in 188 (9.5%) eyes. The angle was occludable by gonioscopy in 101 (5.1%) eyes. The performance of the vH test to rule out gonioscopically occludable angle was good [negative predictive value (NPV): 97.3%], despite low sensitivity (52.5%), while its efficacy to rule in the condition was low [positive predictive value (PPV): 28.2%] despite high specificity (92.8%). However, test combination strategy increased the PPV nearly twofold (53.8%). The calculated PPV at 10% prevalence of gonioscopically occludable angle was even higher (70.5%).

Conclusions Van Herick technique can be incorporated into a teleophthalmology program by means of slit lamp photographs of PACD. Combined vH grading and ocular biometry improved the predictability of a gonioscopically occludable angle.

Introduction

Primary angle-closure glaucoma (PACG) is chronic, mostly asymptomatic and often goes undiagnosed. The prevalence of PACG is reported to be highest among people of Asian descent [1]. Besides, the prevalence of blindness due to PACG is higher compared to its counterpart primary open angle glaucoma [2–4]. The prevalence of gonioscopically

occludable angle includes the prevalence of pre-disease states. While the prevalence of PACG varied between 0.6% to 1.1% [5], the regional prevalence of gonioscopically occludable angle varied between 1.5% [6] and 14.5% [7] in Asia. The differences in methodology between the studies may have a significant contribution to the large variation in the prevalence of gonioscopically occludable angle. Nevertheless, the disparity in utilization of health-care between urban and rural areas, and related factors, such as geographic distribution of services, accessibility, and costs involved, compound the problem [2–4].

Several models of teleophthalmology for screening, triage and remote supervision are being applied in resource-constrained or underserved locations. Teleophthalmology can effectively transmit information on intra-ocular pressure (IOP), central corneal thickness (CCT), optic nerve head imaging and visual field examination [8, 9]. However, the

✉ Nikhil S. Choudhari
nkl164@gmail.com
nikhil@lvpei.org

¹ VST Glaucoma Center, L V Prasad Eye Institute, Dr. Kallam Anji Reddy campus, Banjara Hills, Hyderabad, India

² Brien Holden Vision Institute, Sydney, NSW, Australia

technology is significantly limited due to lack of angle assessment.

Gonioscopy is the reference standard for the diagnosis of eyes at risk of angle closure. However, the technique requires training, high skill and experience. Several newer tests are being considered to overcome the limitations in diagnosing angle-closure disease. These include biomicroscope-based techniques, such as the van Herick (vH) technique [10], or newer advanced optical-based systems, like Anterior segment optical coherence tomography (ASOCT) [11–13], Scheimpflug photography [14, 15], and Scanning peripheral anterior chamber depth analyzer (SPAC) [16, 17].

In vH technique, assessment is based on a comparison of the depth of the peripheral anterior chamber to the thickness of the cornea. Compared to the optical-based systems, the vH technique is quick, simple, and does not require expensive and large equipment. Hence, this technique is better suited for resource-constrained or underserved locations [10]. The studies that followed the traditional vH technique, dark room four-mirror indentation gonioscopy and International Society Geographical and Epidemiological Ophthalmology (ISGEO) classification of primary angle-closure disease [18], achieved sensitivity between 79 and 84% and specificity between 89 and 92% [16, 19]. However, as the prevalence of primary angle-closure disease is low, no single diagnostic test is effective for screening.

We incorporated the vH technique into a novel teleophthalmology program. The program linked remote community-based eye care providers to a glaucoma specialist. The primary objective of this study was to evaluate the diagnostic performance of teleophthalmoscopic vH grading for the detection of gonioscopically occludable angle in a southern Indian population. The secondary objective was to combine diagnostic tests to enhance the predictability of a gonioscopically occludable angle.

Materials and methods

This observational, cross-sectional study was part of the L V Prasad Eye Institute's-Glaucoma Epidemiology and Molecular Genetic Study (LVPEI-GLEAMS). The LVPEI-GLEAMS project aims to design models for effective screening of glaucoma at community level. Institutional Review Board approval was obtained. The detailed methodology has been described elsewhere [20]. The study center was a primary eye care center located in a remote village in the Guntur district of the state of Andhra Pradesh, Southern India. The geographic area for the study sample included 16 villages (sub-district Pedanandipadu mandal).

The LVPEI-GLEAMS data was captured between September 2010 and September 2013. Data from subjects who

underwent the study procedures during the first 15 months, i.e., until November 2011, was included in this pilot study. The exclusion criteria comprises of age <40 years; inability to obtain good quality photographs of the peripheral anterior chamber depth (PACD), viz. corneal pathology sufficient to impede visualization of PACD and angle structures; disorganized anterior chamber; manifest strabismus; aphakic or pseudophakic status; and incomplete data collection.

A trained vision technician captured slit lamp photographs of PACD in a dark room setting with a Topcon DC3 slit lamp camera (Topcon, Bauer Drive, Oakland, NJ). A thin-slit beam was focused just within the temporal limbus, offset by 60 degrees. While taking the photograph, the participants were asked to fixate at a distant target and keep their gaze straight. The digital photographs were saved on a compact disc and sent to a masked ophthalmologist (PC) at a tertiary care center for vH grading. A subset of 100 photographs were randomly chosen and re-graded by the same observer on another day to determine intra-observer agreement. The same subset of photographs was also graded by a masked study optometrist (GBJ) at the study center to determine inter-observer agreement in photographic grading of the eyes by the vH technique. The study optometrists (GBJ, UKA) worked in a glaucoma clinic at a tertiary care center for >7 years and have been involved in performing all diagnostic procedures in glaucoma. The eyes were graded into vH grades as follows: Grade 1 was PACD < 1/4 corneal thickness (CT); Grade 2 was PACD equal to 1/4 CT; Grade 3 was PACD 1/4–1/2 CT; and Grade 4 was PACD equal to CT [10]. Eyes having vH grades 2 or less were considered to have narrow angles typical of angle-closure disease and eyes having vH grade 3 and 4 were considered to have open angles.

Gonioscopy was performed on all eyes by one of the two study optometrists using Sussman four-mirror lens under dim illumination, and making sure that the beam does not fall on the pupil. The posterior most structure visible in four quadrants was documented. Indentation was performed in participants with narrow angles, and the presence of blotchy pigments and synechiae were documented. An occludable angle was defined as non-visualization of the posterior trabecular meshwork ≥ 180 degrees under dark room gonioscopy. We followed International Society for Geographical & Epidemiological Ophthalmology (ISGEO) classification to label participants as primary angle-closure suspect (PACS), primary angle closure (PAC), and primary angle-closure glaucoma (PACG) [18].

A trained vision technician measured central anterior chamber depth (ACD), lens thickness (LT), and axial length (AL), using ultrasonic pachymeter AL-1000 (Tomey, Japan). The definition of abnormality for ocular biometry parameters was ≤ 25 th percentile value for the central ACD, as well as AL and ≥ 75 th percentile value for the LT. The

sequence of tests is described in the methodology of the LVPEI-GLEAMS [20].

Statistical analysis

Weighted Kappa was used for intra- and inter-observer variability. Sensitivity, specificity, and positive (PPV) and negative predictive values (NPV) were used to assess the ability of vH technique to detect occludable angles. A multivariate model was used to evaluate the predictive ability of vH technique and ocular biometry. As measurements from both eyes of the same participant are likely to be correlated, bias corrected standard error was calculated during all estimations [21]. The predictive values were also calculated at 10% prevalence of occludable angle. Statistical analyses were performed using statistical software Stata 12.1 (StataCorp, College Station, TX).

Results

A total of 1217 participants underwent examination from September 2010 to November 2011. Incomplete data from 188 participants was excluded. Thus, 1029 participants, 621 (60.3%) female and 408 (39.6%) male, were included in the current study. The median (1st and 3rd quartiles) age of the participants was 50 (45, 60) years. We included both eyes of 936 participants and one eye of 93 participants (total number of eyes: 1965). The reasons for exclusion of fellow eyes of 93 participants were pseudophakia/ aphakia in 59 eyes, pterygium in three eyes, corneal scar in two eyes, phthisis bulbi in one eye, strabismus in one eye, and inadequate quality of slit lamp photograph in 27 eyes.

The kappa value [95% confidence interval (CI)] of the intra- and inter-observer agreement in grading the slit lamp photographs by vH technique was 0.76 (0.65 to 0.87) and 0.56 (0.45 to 0.67), respectively.

The number of eyes categorized into vH grade 1 to 4 were 49 (2.4%), 139 (7%), 908 (46.2%) and 869 (44.2%), respectively. Thus, by vH grading, 188 (9.5%) eyes had

occludable angle and the remaining 1777 (90.4%) eyes had open angle. The angle was occludable by gonioscopy in 101 (5.1%) eyes and was open in 1864 (94.9%) eyes. Among 101 eyes with gonioscopically occludable angle, 56 eyes were PACS, 39 eyes were PAC, and 6 eyes were PACG. The proportion of the study eyes having PACS, PAC and PACG was 2.84, 1.98, and 0.3, respectively.

The median (1st and 3rd quartiles) central ACD was 3.13 (2.89, 3.38) mm; the lens thickness was 4.43 (4.18, 4.67) mm; and axial length was 22.6 (22.08, 23.07) mm.

The sensitivity (95% CI) of vH classification to detect occludable angle was 52.5% (42.3 to 62.5) and specificity was 92.8% (91.5 to 93.9). The positive and negative predictive values (95% CI) at 5.1% prevalence of gonioscopically occludable angle were 28.2% (21.9 to 35.2) and 97.3% (96.4 to 98), respectively.

The correlations were poor between central ACD and LT ($r^2 < 0.01$), central ACD and AL ($r^2 = 0.04$), and LT and AL ($r^2 = 0.01$).

A univariate logistic regression model identified gender, central ACD, LT, AL, and vH grade (excluding age), to be significantly associated with the classification of the angle by gonioscope. This robust model took into account the correlation between two eyes of a participant. In a multivariate regression analysis, which included the significant predictors in univariate analysis, central ACD and LT, along with vH classification were significantly associated with the classification of the angle by gonioscopy (Table 1).

The diagnostic accuracy of the test combination strategy to rule in or rule out gonioscopically occludable angle is shown in Tables 2 and 3, respectively. The diagnostic accuracy measures of vH technique to detect gonioscopically occludable angle were improved by the test combination strategy.

Discussion

The aim of screening for angle-closure disease is to prevent irreversible blindness due to angle-closure glaucoma. This

Table 1 Logistic regression report for diagnosis of gonioscopically occludable angle

Variable	Univariate regression		Multivariate regression	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Age	1.01 (0.98, 1.04)	0.35	-	-
Gender	0.32 (0.15, 0.65)	<0.01	0.64 (0.30, 1.37)	0.25
vH grading	14.14 (8.26, 24.19)	<0.01	6.94 (3.89, 12.37)	<0.01
Central ACD	0.03 (0.00, 0.13)	<0.01	0.10 (0.02, 0.57)	<0.01
Lens thickness	2.21 (1.53, 3.20)	<0.01	1.93 (1.06, 3.50)	0.03
Axial length	0.37 (0.25, 0.53)	<0.01	0.70 (0.43, 1.12)	0.14

CI confidence interval, vH van Herick, ACD anterior chamber depth

Statistically significant $p < 0.01$ values are in bold

Table 2 Diagnostic accuracy of the test combination strategy to rule in gonioscopically occludable angle

Parameter	Specificity	PPV at 5.1% prevalence	PPV at 10% prevalence	LR positive
vH classification	92.8 (91.5, 93.9)	28.2 (21.9, 35.2)	44.6 (38.6, 50.7)	7.25 (5.66, 9.27)
ACD $\leq$ 1st quartile (2.89 mm)	77.9 (75.9, 79.8)	15.2 (12.1, 18.7)	26.9 (24.2, 29.9)	3.31 (2.87, 3.83)
Lens thickness $\geq$ 3rd quartile (4.67 mm)	75.1 (73.1, 77.1)	10.6 (8.0, 13.6)	19.6 (16.7, 22.8)	2.19 (1.80, 2.66)
Combined vH classification OR ACD	97.1 (96.2, 97.8)	44.9 (34.8, 55.3)	62.6 (54.2, 70.2)	15 (10.7, 21.2)
Combined vH classification OR ACD OR lens thickness	98.7 (98.1, 99.2)	53.8 (39.5, 67.8)	70.5 (59, 79.9)	21.5 (13, 35.8)

Data is presented as percentage (95% confidence interval)

PPV positive predictive value, LR likelihood ratio, vH van Herick, ACD anterior chamber depth

Table 3 Diagnostic accuracy of the test combination strategy to rule out gonioscopically occludable angle

Parameter	Sensitivity	NPV at 5.1% prevalence	NPV at 10% prevalence	LR negative
vH Classification	52.5 (42.3, 62.5)	97.3 (96.4, 98)	94.6 (93.5, 95.6)	0.51 (0.41, 0.62)
ACD $\leq$ 1st quartile (2.89 mm)	73.3 (63.5, 81.6)	98.2 (97.4, 98.8)	96.3 (95, 97.3)	0.34 (0.24, 0.47)
Lens thickness $\geq$ 3rd quartile (4.67 mm)	54.5 (44.2, 64.4)	96.8 (95.8, 97.7)	93.7 (92.3, 94.8)	0.60 (0.48, 0.75)
Combined vH classification AND ACD	82.2 (73.3, 89.1)	98.7 (98, 99.2)	97.4 (96.1, 98.3)	0.24 (0.15, 0.36)
Combined vH classification AND ACD AND lens thickness	88.1 (80.2, 93.7)	98.9 (98.1, 99.4)	97.8 (96.3, 98.7)	0.20 (0.11, 0.34)

Data is presented as percentage (95% confidence interval)

NPV negative predictive value, LR likelihood ratio, vH van Herick, ACD anterior chamber depth

requires detecting a gonioscopically occludable angle and offering prophylaxis or treatment, as appropriate. However, a false-positive screening test may lead to inappropriate referral, anxiety to the individual, and unnecessary burden on the health-care system.

Teleophthalmology models typically involve local health-care personnel capturing images and transmitting these to ophthalmologist for assessment. It allows non-ophthalmologists to screen for the disease in a short time, and makes specialist care more accessible at low cost [8, 9]. Glaucoma screening using optic nerve head examination yielded a summary estimate (95% CI) of sensitivity and specificity to be 83% (77, 88) and 79% (66, 87), respectively from a meta-analysis [22]. Intra-ocular pressure measurement, central corneal thickness, ACD, and visual field examination were also incorporated into teleophthalmology [8, 9, 23, 24]. However, teleophthalmic screening for angle-closure glaucoma is mostly limited by angle assessment as gonioscopy cannot be incorporated into the system. On this background, our study reports on the feasibility of incorporating vH grading as an angle assessment tool in teleophthalmology.

Predictive values are useful in determining the value of a test to a clinician but are influenced by the disease prevalence [25]. At the known prevalence of primary angle-closure disease in the general population, no single diagnostic test is effective for screening. At 5.1% prevalence of occludable angle in this study, only about one in three subjects with positive vH test result are likely to be

identified with occludable angle (PPV 28.2%, Table 2). Nevertheless, the test combination strategy shows promise and could increase the PPV nearly twofold. The prediction could be even better at 10% prevalence of gonioscopically occludable angle (PPV 70.5%, Table 2). The test combination approach is better suited and practical for resource-poor or underserved regions than the use of newer anterior segment imaging modalities in glaucoma. However, this approach was used sparingly in the past [26].

Van Herick test has a moderate sensitivity level. One reason could be that vH grades 2 and 3 are not sharply differentiated. A set of standard photographs, as done in modified vH grading might be a solution to this problem [27]. Another reason for moderate sensitivity of the vH test is the clinical pattern of the disease itself. Chronic PACG with asymptomatic nature and relatively deep peripheral anterior chamber is more common than acute or sub-acute symptomatic PACG in our population [2, 3]. Nevertheless, a relatively higher NPV of the vH classification at 97% is attributable to low prevalence of the disease. Thus, vH classification alone might suffice to rule out primary angle-closure disease. The NPV can be improved further by ensuring negative result on central ACD (>1 st quartile of the population) and LT (<3 rd quartile of the population).

The Chennai Glaucoma Study and the Andhra Pradesh Eye Disease Study reported on rural urban differences in the prevalence of angle closure. Both these studies were conducted in urban, as well as rural locations in India [2, 3].

Fig. 1 Flow chart showing our test combination strategy to diagnose gonioscopically occludable angle (vH: van Herick, ACD: anterior chamber depth, LT: lens thickness)

Urban and rural populations might potentially differ in many factors such as the demographic profile, disease pattern, systemic diseases, and access to ophthalmic care. Forty-five percent of the world population and nearly 60% of the African population still reside in rural areas [28]. Our study is the first to demonstrate the utility of teleophthalmology incorporated vH technique in a community setting. Our results show that a gonioscopically occludable angle can be identified most of the time by a combined application of vH technique and ocular biometry. General population-based screening programs have not been cost effective due to low prevalence of glaucoma [29]. Nevertheless, our findings have the potential to develop an opportunistic screening strategy or screening of high-risk groups for angle-closure disease at a community level.

Our study has a few limitations. The intra-observer agreement in grading the slit lamp photographs by vH technique was substantial and was comparable to the reported intra-observer agreement in performing vH technique on patients [30]. However, the inter-observer agreement in grading the slit lamp photographs by vH technique was only moderate. A comparison to the standard photographs while performing the vH technique [27] or automation of photograph-based vH technique are possible solutions. The latter has relevance for the more complex modification of the vH system [27]. Secondly, this study was an offshoot of a major epidemiologic study, and we could not have a single observer to perform gonioscopy of all the study participants. The two study optometrists who performed gonioscopy have over 7-year experience in the glaucoma department of a tertiary eye care center. The agreement between a reference glaucoma specialist and each of the study optometrists for gonioscopy was good on formal testing (weighted kappa 0.92 and 0.84). This was true, even when the optometrists had to categorize the

gonioscopic information into open angle and various subtypes of primary angle-closure disease [31]. We believe that the inter-observer variability is likely to be reduced further with binary gonioscopic classification into “open” versus “occludable” angle as required in the current study.

In conclusion, the vH technique in combination with ocular biometry shows considerable potential for use in population-based or targeted or opportunistic screening for the angle-closure disease. The vH test can be made teleophthalmoscope-friendly by applying it to slit lamp photographs of PACD. A participant should be considered screening positive when vH grading is 2 or less. The remaining participants should undergo ocular biometry and those abnormal on central ACD or LT should also be considered screening positive. The remaining participants are screening negative (Fig. 1). There is 1–2% chance of missing angle-closure disease in those screened negative. Our approach showed analogous results in another study population [32]. This approach offers the advantage of using standard equipment in a primary eye care setting and shows promise for detection of primary angle-closure disease in remote regions.

Summary

What was known before

- Gonioscopy is the reference standard test to assess the angle of the anterior chamber. However, it requires high skill and is subjective.
- Van Herick Technique is a triage test in the detection of primary angle-closure disease.
- Combination of tests could improve the diagnostic accuracy of screening techniques for angle-closure

glaucoma. However, this approach was used sparingly in the past.

What this study adds

- The van Herick (vH) technique can be made teleophthalmoscope-friendly by applying it to slit lamp photographs of peripheral anterior chamber depth.
- The vH technique in combination with ocular biometry showed considerable diagnostic accuracy in the detection of gonioscopically occludable angle.
- The test combination approach is better suited and practical for resource-poor or underserved regions than the use of newer anterior segment imaging modalities and has potential for use in population-based or targeted or opportunistic screening for the angle-closure disease.

Compliance with ethical standards

Conflict of interest HLR: Consultant to Cipla© (Past). CSG: Consultant to Alcon© Allergan© (Past). The other authors declare that they have no conflict of interest.

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