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Original Article

Factors Affecting ISNT Rule Satisfaction in Normal and Glaucomatous Eyes

Jayoon Moon[1,2], Ki Ho Park[1,2], Dong Myung Kim[1,2], Seok Hwan Kim[1,3]

[1]*Department of Ophthalmology, Seoul National University College of Medicine, Seoul, Korea*
[2]*Department of Ophthalmology, Seoul National University Hospital, Seoul, Korea*
[3]*Department of Ophthalmology, SMG-SNU Boramae Medical Center, Seoul, Korea*

Purpose: To determine the factors that influence the satisfaction of the 'ISNT rule' (neural rim width: inferior ≥ superior ≥ nasal ≥ temporal) in normal and glaucomatous eyes.

Methods: The medical records of patients that visited Boramae Medical Center, Seoul, Korea, were reviewed. Each group of normal and glaucomatous eyes was divided into subgroups based on whether or not they satisfied the ISNT rule. ISNT rule assessment was performed by measuring the rim width with stereoscopic optic disc photographs using ImageJ software. Logistic regression analysis was performed to determine the factors that affect ISNT rule satisfaction.

Results: Seventy-seven normal eyes and 97 glaucomatous eyes were included in the study. The ISNT rule was intact in 59 (76.6%) of the normal eyes and was violated in 71 (73.2%) of the glaucomatous eyes. Logistic regression analysis revealed a significant influence of axial length in violation of the ISNT rule in the normal eye group, while the mean deviation value was a significant factor for violation of the ISNT rule in the glaucomatous eye group.

Conclusions: The ISNT rule should be cautiously applied when evaluating normal eyes with long axial lengths. In addition, the ISNT rule might not be as effective for detecting early glaucoma.

Key Words: Axial length, Glaucoma, Nerve fibers, Optic disk, Optic nerve diseases

Glaucoma is a progressive atrophy of the optic disc that is associated with visual field (VF) defects and is characteristically diagnosed by structural changes of the optic disc [1,2]. Therefore, structural evaluation of the optic disc is a fundamental step in screening for and diagnosing glaucoma [1,3,4]. Although numerous digital imaging technologies have been developed to facilitate structural evaluation of optic disc [5-7], biomicroscopic analysis of the optic disc is still commonly used and is an essential tool in initial glaucoma diagnosis [8].

To differentiate glaucomatous damage, biomicroscopic evaluation of the optic disc includes assessment of cup-to-disc ratio (CDR), change of the optic disc rim, presence of superficial splinter hemorrhage, peripapillary atrophy (PPA), and other parameters [1,3,4,9]. Optic disc rim changes can be detected by the 'ISNT rule,' which was first introduced in 1988 by Jonas et al. [10]. The ISNT rule refers to the normal optic disc rim width, thickest in order of

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Corresponding Author: Seok Hwan Kim, MD, PhD. Department of Ophthalmology, SMG-SNU Boramae Medical Center, #20 Boramae-ro 5-gil, Dongjak-gu, Seoul 07061, Korea. Tel: 82-2-870-2415, Fax: 82-2-831-0714, E-mail: xcski@hanmail.net

inferiorly, superiorly, nasally, temporally [10]. Previous studies have confirmed the effectiveness of the ISNT rule for differentiating glaucomatous optic discs [5,11,12]. However, recent studies have reported results that suggest it has only limited utility [13-15].

Identifying and being aware of the possible factors that limit the utility of the ISNT rule, which are violation of the ISNT rule in normal eyes and satisfaction of the rule in glaucomatous eyes, could lead to improved and more accurate clinical applications and interpretations of the ISNT rule. The purpose of this study was to isolate various factors that affect the ISNT rule satisfaction in normal and glaucomatous eyes.

Materials and Methods

Study design

For this study, 77 eyes of 77 normal subjects and 97 eyes of 97 open angle glaucoma subjects who had visited the cataract and glaucoma clinic of Boramae Medical Center, Seoul, Korea, from June 1, 2016 to July 31, 2016, were consecutively selected, and their medical records were retrospectively reviewed. At the initial work-up, each of the subjects underwent a complete ophthalmologic examination, including a review of medical history, measurement of best-corrected visual acuity, refraction by autorefractor keratometer (KR-8100; Topcon, Tokyo, Japan), slit-lamp biomicroscopy, gonioscopy, intraocular pressure measurement with a Goldmann applanation tonometer, dilated stereoscopic examination of the optic disc, and red-free fundus photography (VX-10; KOWA, Tokyo, Japan). In addition, Humphrey VF examination using the Swedish interactive threshold algorithm standard 30-2 test (HVF C30-2; Humphrey 720i Visual Field Analyzer, Carl Zeiss Meditec, Dublin, CA, USA), optical coherence tomography (Cirrus HD-OCT, Carl Zeiss Meditec), and axial length measurement by immersion ultrasound (Axis II; Quantel Medical, Clermont-Ferrand, France) were performed at the next follow-up. The study was approved by the institutional review board of Boramae Medical Center, Seoul, Korea (16-2017-34), and was conducted with adherence to the Declaration of Helsinki.

Subjects

The normal eye group consisted of patients with no ocular pathology and a normal retinal nerve fiber layer with normal VF and normal intraocular pressure, without any family history of glaucoma. The glaucomatous eye group included patients that presented with retinal nerve fiber layer loss with correlating glaucomatous VF defects, which was defined as a pattern standard deviation (PSD), $p < 0.05$, or glaucoma hemifield test results outside normal limits in consistent patterns in the Bjerrum area on both qualifying VFs. The right eye was selected for the main analysis, but the left eye was analyzed if data for the right eye were insufficient or did not meet the inclusion criteria. The ISNT rule and optic disc evaluation results were entirely exclusive of inclusion criteria from both the normal and glaucomatous eye groups. The exclusion criteria included age younger than 18 years, history of retinal and optic nerve diseases other than glaucoma, previous incisional surgery other than uncomplicated cataract extraction, and hazy media precluding reliable photography or imaging.

Measurements

Digital color fundus photographs centered on the optic disc and macula were obtained with a retinal imaging camera (VX-10) using standard settings. Evaluation of the satisfaction of the ISNT rule, CDR, optic disc tilt ratio, optic disc torsion, and PPA ratio were achieved by measuring and calculating the digital fundus photographs using ImageJ software. The ImageJ software program measurement system uses pixel units, and these pixel units were not converted to absolute measurements because evaluations were performed between the rim widths of the same optic disc, and comparisons between other eyes were assessed by ratios. The optic disc center was defined as the intersection of the longest and shortest axes of the optic disc (Fig. 1). Vertical and horizontal axes were defined as the vertical and horizontal lines that pass through the center point of the optic disc, respectively (Fig. 1). Optic discs that were rotated more than 30 degrees were excluded. No additional adjustments for tilted optic discs were performed in order to maintain ISNT use in simple clinical settings and also to directly evaluate the effects of optic disc tilt on the ISNT rule. The optic disc rim width was measured by assessing the vertical and horizontal optic disc rim widths on the vertical and horizontal axes. The ISNT rule was considered to be satisfied if the inferior rim was the same or wider than the superior rim, the superior rim was the same or wider than the nasal rim, and the nasal rim was the same or wider than the temporal rim (Fig. 1). The CDR was evaluated both horizontally and vertically, and a mean value was also calculated. The optic disc tilt ratio was defined as the ratio of the longest and shortest diameters of the optic disc. The optic disc torsion was defined as the deviation of the long axis of the optic disc from the vertical meridian. The PPA ratio was defined as the ratio of PPA area to disc area. Digital retinal photography evaluation was performed manually with ImageJ software by one blinded ophthalmologist that did not have access to the subjects' data. Disc area was calculated with Cirrus HD-OCT (Carl Zeiss Meditec). No additional adjustments were performed to assess the subject's refractive errors or axial lengths in order to maintain a more realistic clinical setting. Axial length was measured by immersion ultrasound (Axis II). Refraction was measured with an autorefractor keratometer (KR-8100). High myopia was defined as a spherical equivalent less than -6.00 diopters. The mean deviation (MD) and PSD of the HVF C30-2 results were collected.

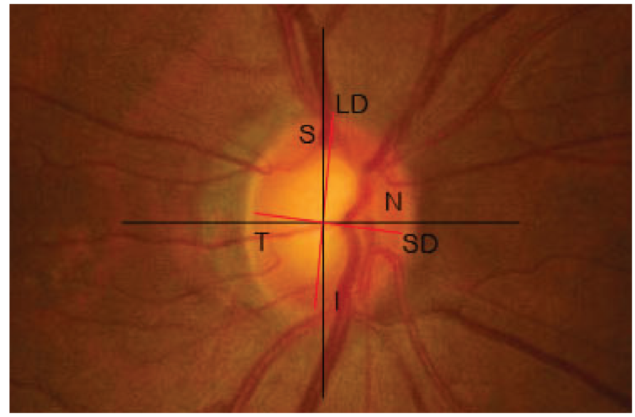

Fig. 1. Clinical assessment of the normal optic disc. Optic disc center was defined as the intersection of the longest diameter (LD) and shortest diameter (SD) of the optic disc. Superior (S) and inferior (I) rims were defined as the vertical line that passes through the optic disc center. Nasal (N) and temporal (T) rims were defined as the horizontal line that passes through the optic disc center.

Statistical analysis

Statistical analysis was performed using IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA). Independent *t*-test and Pearson's chi-square test were used to assess inter-group differences. Logistic regression analysis was performed to determine the influence of various factors on ISNT rule satisfaction after adjusting for covariates. A probability value of $p < 0.05$ was considered statistically significant. The results are presented as mean ± standard deviation unless otherwise indicated.

Results

A total of 174 eyes, comprised of 77 normal eyes and 97 glaucomatous eyes, were evaluated. Among the glaucomatous eye group, 74 (76.29%) and 23 (23.71%) subjects were diagnosed with normal tension glaucoma (NTG) and primary open angle glaucoma, respectively. There were no significant differences between the normal and glaucomatous eye groups in age or gender ($p = 0.828$, paired *t*-test; $p = 0.085$, Pearson's chi-square). The normal eye group had a significantly higher proportion of ISNT rule satisfaction than the glaucomatous eye group ($p < 0.001$, Pearson's chi-square). The MD and PSD of the HVF C30-2, average of CDR, and PPA ratio showed significant differences between the two groups ($p < 0.001$, $p < 0.001$, $p < 0.05$, paired *t*-test). The ISNT rule was satisfied in 59 eyes of the normal eye group (76.6%) and was violated in 71 eyes (73.2%) of the glaucomatous eye group (Table 1).

Ocular parameters were compared between the eyes that satisfied the ISNT rule and the eyes that violated the ISNT rule in the normal eye group. Among the 18 eyes (23.4%) that violated the ISNT rule, axial length was significantly longer than in those that satisfied the ISNT rule ($p < 0.001$, paired *t*-test). In addition, the eyes that violated the ISNT rule showed more optic disc tilt and optic disc torsion and a higher PPA ratio ($p = 0.007$, $p = 0.045$, $p = 0.025$, paired *t*-test) (Table 2).

Subsequently, ocular parameters were compared between the eyes that satisfied the ISNT rule and that violated the rule, in the glaucomatous eye group. Of the 26 eyes (26.8%) that satisfied the ISNT rule, the MD and PSD of the HVF C30-2 were significantly better than those in patients that violated the ISNT rule (both $p < 0.001$, paired *t*-test). Axial length, optic disc torsion, and optic disc tilt did not show any significant differences ($p = 0.241$, $p = 0.098$, $p = 0.659$, respectively, paired *t*-test). The disc area was larger in the eyes that violated the ISNT rule ($p =$

Table 1. Baseline characteristics of normal and glaucomatous eye groups

Characteristics	All patients (n = 174 eyes)	Normal eye group (n = 77 eyes)	Glaucomatous eye group (n = 97 eyes)	*p*-value
Male	82 (47.1)	37 (43.1)	45 (46.4)	0.828*
Female	92 (52.9)	40 (51.9)	52 (53.6)	
Age (average)	52.6954 ± 12.5516	50.8571 ± 12.6155	54.1546 ± 12.3713	0.085†
Analyzed eye (right)	142 (81.6)	61 (79.2)	81 (83.5)	0.469*
Analyzed eye (left)	32 (18.4)	16 (20.8)	16 (16.5)	
ISNT rule(-)	89 (51.1)	18 (23.4)	71 (73.2)	<0.001*
ISNT rule(+)	85 (48.9)	59 (76.6)	26 (26.8)	
High myopia (SE >6.00 D) (+/-)	28/131 (16.1/75.3)	8/61 (79.2/10.4)	20/70 (20.6/72.2)	0.081*
Axial length	24.3645 ± 1.5301	23.9123 ± 1.4696	24.7142 ± 1.4907	0.001†
SE (average)	-2.2374 ± 3.1075	-1.4846 ± 2.8522	-2.8378 ± 3.1876	0.007†
Intraocular pressure (average)	12.9885 ± 2.9680	12.9221 ± 3.1862	13.0412 ± 2.7985	0.796†
Central corneal thickness (average)	0.5402 ± 0.0363	0.5442 ± 0.0398	0.5368 ± 0.0331	0.194†
Mean deviation	-4.2367 ± 5.6160	-0.0650 ± 1.4869	-6.8431 ± 5.9608	<0.001†
Pattern standard deviation	5.7530 ± 5.1449	1.9682 ± 0.9863	8.4645 ± 5.2763	<0.001†
Cup-to-disc ratio (average)	0.6442 ± 0.1141	0.5988 ± 0.0921	0.6802 ± 0.1175	<0.05†
Torsion	11.1931 ± 10.0460	12.6534 ± 11.2003	10.0338 ± 8.9156	0.088†
Tilt	1.2671 ± 0.8389	1.1629 ± 0.1186	1.3497 ± 1.1142	0.145†
Disc area (mm^2, average)	1.9418 ± 0.4462	2.0640 ± 0.4351	1.8448 ± 0.4330	0.001†
Peripapillary atrophy ratio	0.48888 ± 0.5111	0.3391 ± 0.3811	0.6076 ± 0.5688	<0.001†

Values are presented as number (%) or mean ± standard deviation.
SE = spherical equivalent; D = diopter.
*Pearson's chi-square test; †Paired *t*-test.

Table 2. Comparison of normal eye ocular parameters according to satisfaction and violation of the ISNT rule

Normal	ISNT (+)	ISNT (-)	*p*-value
Axial length	23.5429 ± 1.2443	25.1724 ± 1.5135	<0.001*
Mean deviation	0.0228 ± 1.5398	-0.398667 ± 1.2560	0.332*
Pattern standard deviation	1.9556 ± 1.0349	2.0160 ± 0.8039	0.810*
Cup-to-disc ratio (average)	0.5882 ± 0.0894	0.6335 ± 0.0946	0.068*
Torsion	11.2437 ± 9.8986	17.2742 ± 14.0364	0.045*
Tilt	1.1350 ± 0.0858	1.2542 ± 0.1620	0.007*
Disc area (mm^2, average)	2.0712 ± 0.4221	2.0389 ± 0.4873	0.782*
Peripapillary atrophy ratio	0.2601 ± 0.2586	0.5980 ± 0.5733	0.025*

*Paired *t*-test.

0.033, paired *t*-test) (Table 3).

Multivariate logistic regression analysis of the normal eye group revealed a significant association between violation of the ISNT rule and long axial length (odds ratio [OR], 0.548; $p = 0.034$) (Table 4). In the normal eye group, 66.7% of subjects with axial lengths equal or longer than 26.00 mm and 46.2% of subjects with axial lengths between 24.50 and 25.99 mm showed ISNT rule violation (Table 5).

Table 3. Comparison of glaucomatous eye ocular parameters according to satisfaction and violation of the ISNT rule

Glaucomatous	ISNT (-)	ISNT (+)	*p*-value
Axial length	24.6063 ± 1.4946	25.0088 ± 1.4682	0.241*
Mean deviation	-8.7586 ± 5.7527	-1.6123 ± 2.2142	<0.001*
Pattern standard deviation	10.2600 ± 4.8556	3.5615 ± 2.5942	<0.001*
Cup-to-disc ratio (average)	0.7143 ± 0.1099	0.5871 ± 0.0826	<0.001*
Torsion	10.7539 ± 9.7818	8.0673 ± 5.6416	0.098*
Tilt	1.3801 ± 1.3012	1.2667 ± 0.1276	0.659*
Disc area (mm^2, average)	1.9013 ± 0.4277	1.6901 ± 0.4171	0.033*
Peripapillary atrophy ratio	0.6123 ± 0.6246	0.5948 ± 0.3871	0.894*

*Paired *t*-test.

Table 4. Multivariate logistic regression analysis of the factors associated with violation of the ISNT rule in the normal eye group

Covariants	Exp(B)	*p*-value
Axial length	0.548	0.034
Torsion	0.955	0.099
Tilt	0.651	0.144
PPA ratio	0.132	0.182

Exp(B) = the exponentiation of the B coefficient; PPA = peripapillary atrophy.

Table 5. Axial length and ISNT rule violation ratios in the normal eye group

Axial length range (mm)	No. of subjects	Violation ratio (%)
21.00–21.49	13	7.7
21.50–22.99	14	7.1
23.00–24.49	26	11.5
24.50–25.99	13	16.2
≥26.00	9	66.7

Optic disc torsion and optic disc tilt were not significantly associated with the ISNT rule (OR, 0.955; OR, 0.651; p = 0.099, p = 0.144, respectively) (Table 4). Multivariate logistic regression analysis of the glaucomatous eye group revealed a significant effect of the MD on the HVF C30-2 on the ISNT rule (OR, 1.352; p = 0.045), while PSD and optic disc area were not significantly correlated (OR, 0.883; OR, 0.338; p = 0.327, p = 0.463, respectively) (Table 6).

Table 6. Multivariate logistic regression analysis of factors associated with ISNT rule violation in the glaucomatous eye group

Covariants	Exp(B)	*p*-value
Mean deviation	1.352	0.045
Pattern standard deviation	0.883	0.327
Cup-to-disc ratio	0.002	0.107
Disc area	0.338	0.463

Exp(B) = the exponentiation of the B coefficient.

Discussion

The ISNT rule was first introduced by Jonas et al. [10], who measured the rim widths of normal eyes from optic disc photographs and concluded that the indicated rim thickness pattern of the normal optic disc follows the ISNT rule. Thereafter, it was revealed that the ISNT rule was violated in glaucomatous eyes [16]. The ISNT rule has been reported to significantly facilitate clinical differentiation of glaucomatous and normal eyes [11]. However, in other studies, the ISNT rule has shown poor specificity for detecting glaucomatous eyes due to the confounding effects of optic disc size, variability of optic disc tilt degree, and vascular trunk location within the optic disc, and it has been reported that the ISNT rule alone is not sufficient, and that consideration of other variables that affect optic disc topography is essential [14,15]. The clinical application of the ISNT rule can be rendered more effective by determining the additional factors that are associated with the ISNT rule. Thus, this study investigated the factors that influence violation and satisfaction of the ISNT rule in normal and glaucomatous eyes. We concluded that, in normal eyes, long axial length is significantly associated with violation of the ISNT rule, while in glaucomatous eyes, lower MD of the HVF C30-2 is significantly associated with ISNT rule satisfaction, which is not compatible with early glaucoma diagnosis.

Long axial lengths are known to be more prone to be myopic, and highly myopic eyes are usually found to have different optic disc appearances, compared to emmetropic eyes, such as elongated shapes, larger discs, and tilted optic discs [17,18]. Similarly, our study found that normal eyes with long axial lengths were more likely to violate the ISNT rule ($p = 0.028$). Our study also showed that 54.5% of normal subjects with axial lengths equal or over 24.50 mm violated the ISNT rule, while only 9.4% of those with axial lengths less than 24.50 mm violated the ISNT rule. Therefore, when evaluating patients with axial lengths equal or over 24.50 mm, the ISNT rule might show low diagnostic accuracy.

Park et al. [19] reported a high prevalence of optic disc tilt and torsion in Korean NTG patients with myopia. They also found, by univariate and multivariate logistic regression analyses, that optic disc torsion degree was the sole factor correlated with VF defect location. In our study, in the normal eye group, optic disc torsion and tilt were significantly different between eyes that satisfied the ISNT rule and those violating it ($p = 0.045$, $p = 0.007$, respectively). However, multivariate logistic regression analysis of the normal eye group showed that the optic disc torsion and tilt were not associated with the ISNT rule violation, and only axial length was associated with this ($p = 0.099$, $p = 0.144$, respectively). Therefore, we speculated that axial length is associated with optic disc torsion or tilt. In our analysis, axial length was significantly correlated with optic disc tilt (Spearman rho = 0.473, $p < 0.01$, data not shown). In the glaucomatous eye group, optic disc torsion and tilt were not significantly different in eyes that satisfied the ISNT rule and in those that violated the rule ($p = 0.098$, $p = 0.659$, respectively).

The MD of the HVF C30-2 was a significant associative factor based on the multivariate logistic regression analysis of the glaucomatous eye group ($p = 0.045$). Eyes with more progressed glaucoma showed more violation of the ISNT rule. In early glaucoma, disc rim change can be subtle and insufficient to violate the ISNT rule. This finding can be interpreted as an indication that ISNT rule application is perhaps not suitable for diagnosing early glaucoma. Similarly, Sihota et al. [13] reported that neuroretinal rim area ratio alone shows poor diagnostic specificity and sensitivity in differentiating between normal and early glaucoma.

Recently, Law et al. [15] demonstrated that by only evaluating the vertical neural rim widths, both inferior and superior, the specificity of differentiating glaucomatous eyes from normal eyes increased compared with the ISNT rule, and that the specificity was higher among eyes with larger CDRs. In our study, in the normal eye group, CDR was not significantly different between eyes that satisfied the ISNT rule group and those that violated the rule, while these results were different in the glaucomatous eye group ($p = 0.068$, $p < 0.001$, respectively). However, in the multivariate analysis, CDR was not an associative factor of the ISNT rule in the glaucomatous eye group ($p = 0.107$). Subjects with large CDR are more likely to have advanced glaucoma, and large CDR itself can affect the ISNT rule; therefore, satisfaction and violation of the ISNT rule are more frequently associated with glaucoma severity.

Nayak et al. [7] reported that the larger is the disc area, the more likely it is that the ISNT rule will be violated. However, in our current study, disc area was not significantly different in the normal eye group ($p = 0.782$). Although there was a difference in the glaucomatous eye group ($p = 0.033$), the multivariate analysis results did not indicate that it was a significant associative factor of the ISNT rule (OR, 0.338; $p = 0.463$). Correspondingly, Wang et al. [12] found no clear association between disc area and ISNT rule satisfaction among Chinese eyes.

There were some limitations to this study. First, the study population was a small number of eyes, which might not sufficiently represent the normal or glaucoma populations. The glaucomatous eye group consisted of only open angle glaucoma, where the majority were NTG. Therefore, additional studies are needed to evaluate the relationship between type of glaucoma and ISNT rule satisfaction. Additionally, the eyes reviewed were all from one ethnicity, Korean. Race can act as a confounding factor, indicating that our current findings might not be applicable to other ethnic groups. Another limitation of this study was its design, which was based on measurement of the neuroretinal rim width, not area. Therefore, further studies to compare our results with those of a study design based on measurement of sectorial neuroretinal rim areas are recommended. Our study was based on a retrospective medical review of subjects who visited our clinic over a short-term period; therefore, it is uncertain whether normal subjects who have large CDR, whether with or without intact ISNT rule, might develop glaucoma in the future. Though our study showed no significant difference in CDR among normal eye subjects with or without ISNT rule satisfaction (p = 0.068), a prospective study to evaluate the relationship between change in satisfaction of the ISNT rule and CDR and whether glaucoma develops in the future should be conducted in a normal eye group.

In conclusion, when applying the ISNT rule in clinical settings, axial length, especially over 24.50 mm, must be given due consideration, because it is associated with a high probability of ISNT rule violation despite being within a normal range. Finally, the ISNT rule's low detection rate in early glaucoma should also be considered, and improved approaches for diagnostic and treatment modalities are necessary.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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