Study protocol

Fifty-eight healthy volunteers aged 20-39 years, who had 20/20 or better best-corrected visual acuity, were recruited. The participants had no ophthalmologic disorder, including amblyopia, presbyopia, or corneal or retinal disease and no history of ocular surgery. The participants used a VR device and a smartphone each for 2 hours; the purpose of the latter was to serve as a control. Half of the randomly selected subjects used VR first, and the remaining participants used smartphones first. One experiment (VR and smartphone use) was performed over 2 days with 1-day intervals. Informed consent was obtained from all 58 volunteers who were enrolled in the study. Ethics committee approval was obtained from the Chonnam National University Hospital Institutional Review Board (Gwangju, Korea). The study protocol adhered to the guidelines of the Declaration of Helsinki. We have registered this clinical study in the ISRCTN.

Devices

Samsung Gear VR devices released in 2018 (Gear VR Innovator Edition; Samsung, Suwon, Korea) were used in the study. Headsets were assembled with a smartphone (Galaxy S6; Samsung) with 1440 × 2560 resolution. A fixed-degree convex lens was positioned in front of each eye. The distance between the screen and the front of the subject's eyes was approximately 50 mm to 65 mm. A control wheel at the top of the headset enabled the participants to adjust the inter-pupillary distance.

The participants used the devices while seated on a freely rotating chair. For the VR experiment, the participants freely played a VR game (Lands End, Ustwo Games, UK) for 2 hours that is graded as "comfortable" on a platform provided by Oculus. For the smartphone experiment, the participants used a smartphone with a 5.1-inch light-emitting diode screen from the same manufacturer (Samsung) to play a game (Tetris, Electronic Arts, CA, USA) for 2 hours. If the participants experienced discomfort while using the device, they were allowed a 5-minute rest that was not included in the 2-hours of playtime.

Measurement of refraction and accommodation

Refraction and accommodation were measured using a binocular open-field refractor (Auto Ref/Keratometer WAM-5500, Grand Seiko Co. Ltd, Hiroshima, Japan). Refraction was measured with or without glasses. The spherical equivalent (sphere + 1/2 of the cylinder) was used for the calculation. The accommodative amplitude was calculated by subtracting the refractions obtained, under monocular condition, while viewing a 1 cm × 1 cm E-shaped target at a distance of 20 cm from those obtained while viewing the target at a distance of 5 m. The

accommodative lag was calculated using the value by which the participant's refraction differed from the accommodative stimulus. In this study, the value was calculated by subtracting -5.0 diopter (D) from the refractions obtained with the target at a distance of 20 cm.

Measurements of other visual parameters

Monocular near-point accommodation (NPA) was obtained using Donder's push-up method. A 20/30 single letter on a fixation stick positioned approximately 50 cm from the subject served as the target, and it was moved gradually closer to the subject at a rate of approximately 5.0 cm/s until the subject noticed the blurring of the target.

The near-point of convergence (NPC) was also obtained. The fixation target, the starting point of the examination, and moving velocity of the fixation target were the same as those previously described for the NPA measurement. The first point at which the corneal reflex of the participants began to extend outward was considered the endpoint.

Stereopsis was measured using a near stereopsis vision test (Stereo Fly SO-001 test; Stereo Optical Co., Chicago, IL, USA). Stereopsis of 2500–1200 s of arc, 800–40 s of arc, and 400–100 s of arc was measured using fly photos, graded circle test, and animal test for children, respectively. The test stereogram was held at a distance of 40 cm from the subject during the test. The threshold stereopsis level was recorded in seconds of arc. To facilitate statistical analyses and calculation of means and differences, we used logarithmic transformation of stereopsis, with natural logs.[10]

The presence and magnitude of ocular deviations at far (5 m) and near (33 cm) distances were verified using the cover test and alternating cover test with a prism. A standard set of loose plastic prisms was used for all measurements. The individual prisms increased in power from 1 to 10 prism diopter (PD) in 1-PD increments and from 10-20 PD in 2-PD increments.

Ocular dominance was determined using the hole-in-the-card test, in which the subject was asked to hold a card with a hole at arm's length and to focus, with both eyes, on an object placed 3 m away. The examiner then alternately occluded the eyes to determine the dominant eye, i.e., the eye that was viewing the object through the hole.

All visual parameters were measured, in the order listed above, before and after the participants played games using the VR device or smartphone games. The visual parameters were measured after a 3-minute break with the

eyes closed after the use of the VR or smartphone. All measurements were repeated three times for each tested eye, and the results were reported as mean values. All parameters were examined by a single examiner (HJY).

Choroidal thickness

We used a Heidelberg Spectralis with 870-nm wavelength (Heidelberg Engineering, Heidelberg, Germany) to obtain spectral domain optical coherence tomography images of the posterior segment of the eye. The choroid was imaged using the enhanced depth imaging modality with eye tracking and automated real-time averaging features. The scan through the fovea should have a prominent specular reflex at the bottom of the foveal pit.

Choroidal thickness was measured using the Heidelberg Eye Explorer software (Heidelberg Engineering, Heidelberg, Germany) (Version 1.9.10.0) provided by the instrument manufacturer. We used the semiautomatic segmentation method for choroidal thickness measurement.[11] We manually selected a new line at the choroid–scleral border (CSB). We retained the automatically defined Bruch's membrane (BM) line, and the software calculated the vertical distance between the two segmentation lines. The choroidal thickness was defined as the vertical distance between the BM and CSB. The five targets were divided into 1- and 3-mm zones from the fovea. The choroidal thickness measurements were performed by a single trained examiner masked to the participants' data (HJY).

Evaluation of subjective symptoms

The following 13 symptoms were included in the questionnaire that was based on a computer vision syndrome questionnaire, which was previously reported by Seguí Mdel M et al. [5, 11]: dry eye symptoms (burning, feeling of a foreign body, excessive blinking, tearing, dryness, tingling, and increased sensitivity to light), visual disturbance (blurred vision, double vision, and difficulty focusing for near vision), and neurological symptoms (headache, dizziness, and nausea). The symptom sensation questionnaire included six identical analog scales (0 = none to 6 = too severe to tolerate), and the subject recorded the magnitude of each symptoms compared relative to that at the baseline. After playing the VR and smartphone games, the participants completed the questionnaire.

Statistical analysis

The sample size was calculated using the G*Power software (version 3.1.9.4; Heinrich-Heine University, Germany) with a level of $\alpha = 0.05$, a power of 95%, and effect size of 0.5. Accordingly, a total sample size of 47 patients was found sufficient. Therefore, we recruited a total of 58 participants considering the drop-out rate of

20%. Statistical analysis was performed using SPSS version 18.0 (IBM Corporation, Armonk, NY, USA) for Windows (Microsoft Corporation, Redmond, WA, USA). The distributions of all variables were assessed using the Kolmogorov-Smirnov test. The data are represented as mean ± standard deviation if they were normally distributed; otherwise, they are presented as the median [interquartile range]. If the variables showed normal distribution, they were analyzed using the paired t-test; otherwise, they were analyzed using the Wilcoxon signed rank test. Differences in subjective symptoms between the devices were compared using the Mann-Whitney U test. Spearman's correlation test was used to evaluate bivariate correlation between baseline data (refractive error, accommodative amplitude and lag, NPA, NPC, and ocular deviation) and the changes in these parameters after the use of VR. The variables for a single eye, including refraction, NPA, and accommodative parameters, were solely correlated with those for the corresponding eye. For all tests, $p < 0.05$ was considered statistically significant. If the data were not normally distributed, the Benjamini-Hochberg procedure using a false discovery rate of 0.25 was applied.