EFFECT OF ACUTE HYDROGEN-RICH WATER INTAKE ON INTRAOCULAR PRESSURE IN HEALTHY SUBJECTS

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The authors of the study declare that no conflict of interests exists in the compilation, theme and subsequent publication of this professional article, and that it is not supported by any pharmaceuticals company. The study has not been submitted to in any other journal or published elsewhere, with the exception of congress abstracts and recommended procedures.

Received: April 18, 2023
Accepted: May 17, 2023
Available on-line: July 30, 2023

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SUMMARY

Purposes: The primary aim of the study was to assess the response of intraocular pressure (IOP) to the acute ingestion of hydrogen-rich water (HRW) compared to hydrogen-free water (placebo) in healthy subjects. The effect of HRW intake on central corneal thickness (CCT) was also monitored.
Subjects and Methods: Twenty-four healthy volunteers (5 men, 19 women) aged between 20 and 33 were included in the study, in which one eye of each subject was measured. The study was prospective, randomized and double-blind, with crossover design. Each subject underwent two parts of the experiment, each part on a different day and in random order. In each part of experiment, a total volume of 1260 ml of HRW or placebo was administered over 15 minutes in three doses. IOP and CCT were measured before and during the course of 75 minutes from the start of the HRW or placebo intake.
Results: Administration of both HRW and the placebo caused a significant increase in IOP. The maximum IOP increase was 2.7 mmHg ±2.0 mmHg in minute 25 after the commencement of the experiment (HRW intake), and 1.4 mmHg ±2.0 mmHg in minute 35 (placebo intake). The values of IOP did not differ significantly between both parts, but there were significantly more clinically significant individual IOP increases after HRW intake (58%) compared to the placebo (25%). CCT did not change significantly during the experiment.
Conclusion: The rapid intake of 1260 ml of both HRW and hydrogen-free water causes a statistically significant increase in IOP compared to the baseline in healthy individuals. In the case of HRW, the increase was also clinically significant in most of the subjects. Thus, the results indicate that acute intake of HRW may pose a higher risk than placebo intake in terms of IOP. However, in the case of risk groups such as subjects with glaucoma, ocular hypertension or suspected glaucoma, it is necessary to verify this conclusion by further studies.
Key words: corneal thickness, hydrogen-rich water, intraocular pressure, molecular hydrogen, water

Čes. a slov. Oftal., 79, 2023, No. 4, p. 180–184

INTRODUCTION

For many years, molecular hydrogen (H2) was considered a physiologically inert gas [1]. However, recent studies have highlighted its selective antioxidant, antiapoptotic, antiallergic and anti-inflammatory properties [1-5]. It also has an effect in combating fatigue [3,6-10], and has a stimulating effect on mitochondrial activity [11,12]. In addition, its extensive therapeutic potential has also been demonstrated, including ophthalmological use, without any side effects or toxicity whatsoever [4,5,13-15]. A simple, safe and ever increasingly popular method of intake of H2 is the consumption of hydrogen-rich water (HRW), i.e. water containing dissolved H2.

Consumption of HRW is recommended in particular for persons with an active lifestyle, who may also include persons with glaucoma, with suspected glaucoma, or persons genetically or otherwise predisposed towards the development of glaucoma. Clinically significant parameters that are primarily monitored in association with the diagnosis and treatment of glaucoma include intraocular pressure (IOP) [16]. An increase of IOP, similarly to sharp fluctuations, are risk factors in the progression of glaucoma [17-19]. It is known that IOP may be influenced by a range of different physiological processes, such as changes during the course of the day [20], changes of body or head position [21-23], vigorous physical activity [24-26] or hypoxia [27,28]. Other processes which may have a significant influence on IOP include the drinking of water [29-31] or the consumption of coffee or energy drinks [32-34]. The majority of studies have recorded an increase of IOP following the consumption of water [31-35], in which glaucoma patients appear to be more sensitive in comparison with the ordinary healthy

population [36-38]. However, in the case of HRW the impact on IOP has not been described to date. With reference to the possible increase in the risk of glaucoma changes or with regard to the potential influencing of the results of IOP measurement, as well as the increasing popularity of consumption of HRW, it is important to clarify the effect of HRW on IOP. The primary aim of this study was therefore to evaluate the response of IOP to the consumption of HRW in comparison with normal water (placebo) over the course of 75 minutes from commencement of consumption, in the case of healthy subjects. Since measurement of IOP was significantly influenced by central corneal thickness (CCT) [39,40], the impact of drinking both types of water on CCT was also simultaneously evaluated.

MATERIAL AND METHOD

A total of 29 volunteers took part in the experiment, though the data of only 24 individuals (5 men and 19 women) aged from 20 to 33 years (the mean age was 23 years with a standard deviation of 3 years, average weight 70 kg with a standard deviation of 14 kg) were included in the study. Five subjects were excluded from the original cohort for failure to comply with the conditions stated below. The exclusion criteria for the study were glaucoma, ocular hypertension and other pathologies or abnormalities that could potentially influence IOP such as keratoconus, refractive surgery, high spherical dioptri defect (equal to or greater than 3 D), and corneal astigmatism equal to or greater than 2.5 D. It was also required that the difference in the baseline values of IOP in both parts of the experiments (upon consumption of HRW and consumption of the placebo) was smaller than 3 mmHg, which is a value approximately 1.5 times exceeding the repeatability of measurement of IOP with the equipment in question [41]. The probands were also requested to refrain from consumption of coffee or other caffeinated products, as well as vigorous physical activity, on the day before each measurement. The study was governed by the principles of the Helsinki declaration. Each participant was familiarized in detail with the course of the study before taking part, and signed an informed consent form for participation in the study.

The study took place as a prospective, randomized, double-blind trial with crossover design, in which each of the participants consumed both HRW (Aquastamina HRW, Nutristamina, Ostrava, Czech Republic), and a placebo (Aquastamina H2 free, Nutristamina, Ostrava, Czech Republic), on different days. The median interval between the two parts of the experiment (consumption of HRW, consumption of placebo) was 7 days. The order of the two parts of the experiment was chosen at random. A total of 1260 ml of fluid was consumed in each part of the experiment, specifically in three doses (420 ml) within 15 minutes. Both fluids were served in identical packages, in which one package corresponded to one dose. Since H2 is colorless, and has no taste or aroma, neither the subject nor the examiner was capable of differentiating between HRW and the placebo [28]. HRW and the placebo had the same composition, with the exception of the presence of H2 and the corresponding pH (HRW: pH = 7.8, quantity of H2 0.9 ppm; placebo: pH = 7.6, quantity of H2 0.0 ppm), and had an identical, stable temperature.

IOP and CCT were measured simultaneously with the aid of a Corvis ST tonometer (Oculus, Wetzlar, Germany) in a sitting position, with the measurement conducted by a trained examiner. Only the right eye of each subject was measured. Both parts of the experiment had an identical schema. Immediately after the arrival of the participant, the initial familiarizing measurement of IOP and CCT was conducted – this measurement was not included in the further analysis. The next measurement followed after 10 minutes spent at rest, and was considered the baseline value for the given part of the experiment. The participant was subsequently given three doses of HRW or a placebo, of 420 ml each (total 1260 ml), which he or she was then obligated to drink within 15 minutes (i.e., approximately 5 min. per dose). The time of the experiment was measured from the commencement of consumption of the water. IOP and CCT were measured immediately after the drinking of the entire dose (i.e., at 15 minutes), and subsequently every 10 minutes until the time of 75 minutes from the commencement of consumption.

All the measurements were conducted in the morning hours, for the purpose of eliminating oscillations of IOP during the course of the day [18,20]. During the experiment the participants remained in a sitting position, at rest and with eyes open (with the exception of normal blinking), in the same place with the exception of a slow movement towards the nearby ocular tonometer and back. In case of necessity, participants were allowed to use the toilet. The average air humidity in the laboratory was 43%, and the temperature 24 °C.

The normality of distribution of the measured data was tested by a Shapiro-Wilk test. Whereas the values of CCT always had a normal distribution, IOP recorded significant deviations from the normal distribution. The time course of the observed quantities in the case of normal data distribution (in CCT) was evaluated by a one-factor analysis of variance (ANOVA) for repeated measurements, while in the opposite case (in IOP) a Friedman non-parametric test was used, separately for the part with HRW and with the placebo. In the ANOVA method, in the case that the condition of sphericity of data (Mauchly test) was not met, a Huynh-Feldt correction was used. Post-hoc pair corrections of IOP in the given part of the experiment were conducted by means of a Wilcoxon signed rank test with Bonferroni correction. The congruence between the IOP values following consumption of HRW and the placebo (i.e., between both parts of the experiment) was also tested by means of a Wilcoxon signed rank test with Bonferroni correction, in which the values in the corresponding times were always compared. In addition, the relationship between changes of IOP and body weight (the effect of the given quantity of consumed water may be influenced by the weight of the proband) was evaluated with the aid of the Pearson correlation coefficient r. The level of significance for all the used tests was 0.05. The data are presented in the format of mean ± standard deviation.

The statistical calculations were performed in the program STATISTICA 13.4 (StatSoft, Tulsa, OK, USA).

RESULTS

The mean values and standard deviations of IOP at the individual measurement times in both parts of the experiment are shown in the graphs in Figure 1. From these it is evident that in both cases IOP increased above the baseline value. There was not a significant difference between the baseline values of both parts of the experiment (Wilcoxon signed rank test, $p = 0.08$). Changes of IOP after drinking both HRW and the placebo were also confirmed by a Friedman non-parametric test ($p < 0.0001$ for HRW and $p = 0.0025$ for the placebo). The subsequent Wilcoxon test with Bonferroni correction demonstrated that IOP increased statistically significantly in comparison with the baseline value from minute 15 to minute 55 after the beginning of measurement in the case of HRW, and 25 and 35 minutes after the beginning of measurement in the case of the placebo (indicated with a star or cross in Figure 1). The maximum increase of IOP occurred 25 minutes after the commencement of the experiment (2.7 mmHg ± 2.0 mmHg), following the consumption of HRW, and this change on average was significant also from a clinical perspective (i.e., > 2 mmHg [42]; a clinically significant change took place in 14 eyes out of 24, thus in approximately 58%). In the case of the placebo, IOP reached its peak 35 minutes after the commencement of the experiment (1.4 mmHg ± 2.0 mmHg), from a clinical perspective this increase was insignificant (i.e., ≤ 2 mmHg [42]; a clinically significant change took place in only 6 eyes out of 24, thus in 25%). The changes of IOP as against the baseline value did not demonstrate a significant correlation with the body weight of the subjects in any part of the experiment ($-0.173 < r < +0.388$, $p > 0.061$ for HRW and $-0.121 < r < +0.282$, $p > 0.18$ for the placebo).

A mutual comparison of IOP at the same times after consumption of HRW and the placebo with the aid of a Wilcoxon signed rank test did not demonstrate any statistically significant changes, either with or without Bonferroni correction ($p > 0.12$). A direct comparison of the IOP values therefore did not determine any difference between HRW and the placebo, although from a clinical perspective, significant changes of IOP did occur after consumption of HRW, whereas this did not take place after consumption of the placebo (see above). For this reason, we supplemented the analysis with a chi-square test of independence in a two-way contingency table incorporating two statistical attributes – type of consumed water (HRW, placebo) and clinical significance of deviations of IOP at the time of maximum increase of IOP for the given type of water (for HRW in the 25th minute, 14 out of 24, for the placebo in the 35th minute, 6 out of 24). The significant result ($p = 0.019$) confirmed that in the observed sample a greater number of clinically significant changes occurred after consumption of HRW than after consumption of the placebo. We arrived at the same conclusion also upon a comparison of the number of clinically significant differences across all the points of measurement (47 out of 168 for HRW and 29 out of 168 for the placebo, $p = 0.019$).

In the case of CCT, no statistically significant changes were determined during the course of the experiment, either after consumption of HRW or the placebo (ANOVA

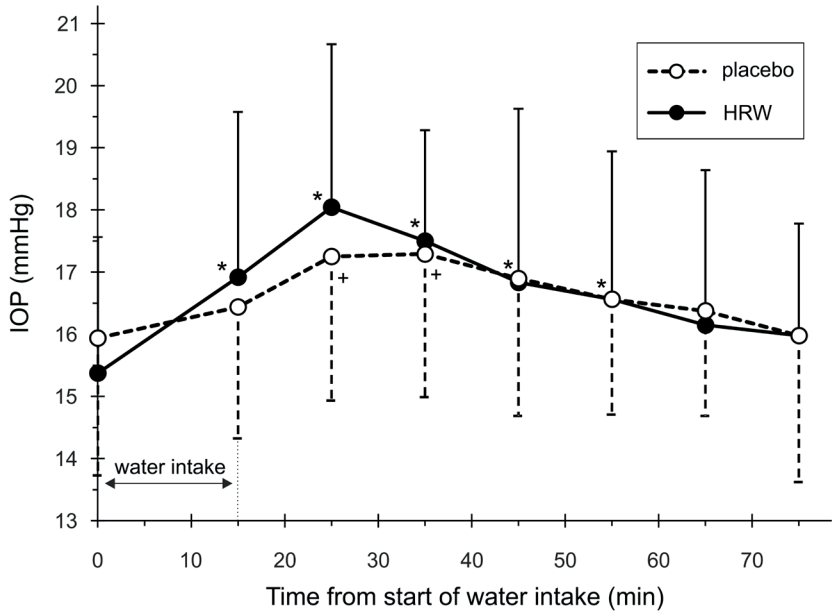

Figure 1. The time course of mean intraocular pressure (IOP) values during experiment; close circles represent mean IOP values for HRW consumption, open circles for placebo consumption; error bars correspond to the IOP standard deviations; significant differences from the baseline are marked by an asterisk or cross for HRW or placebo, respectively

with Huynh-Feldt correction, $F_{5.654;\ 158.30} = 1.610$, $p = 0.15$ and $F_{4.864;\ 136.21} = 1.486$, $p = 0.20$). It is therefore possible to assume that changes of CCT did not significantly influence the measured values of IOP.

DISCUSSION

Consumption of HRW is becoming an ever-increasingly popular resource for better regeneration after sport or for increasing performance [23,6-10], not only for professional sportspeople but also within the ordinary population. However, it is known that rapid consumption of a larger quantity of water triggers an increase of IOP, both in healthy individuals [29-31,35] and in subjects suffering from glaucoma [43-45]. However, knowledge of the influence of HRW on IOP has been lacking up to now.

The existing publications have recorded an influence on IOP upon rapid intake of ordinary water, persisting within the range of tens of minutes. A statistically significant increase was observed from 10 to 15 minutes after consumption of the given quantity [30,31,35,43,45], while the values remained above the baseline values up to 30 [35] or 45 [31,43,45] minutes. These data are in accordance with our results, both in the case of HRW and of the placebo, in which our data indicate a somewhat longer time of influence of HRW in comparison with the placebo. A series of previous studies state an increase of IOP which is significant also from a clinical perspective (i.e., > 2 mmHg [42]). For example, Read & Collins [35] present a mean maximum increase of 2.24 mmHg, and Chen et al. [29] state an increase of 3.5 mmHg, always in healthy subjects upon a comparable quantity of consumed water (1000 ml) as in our own study (1260 ml). In our case, a mean clinically significant increase was determined only after consumption of HRW (2.7 mmHg), while in the case of the placebo the mean values were clinically insignificant (1.4 mmHg), even though a direct comparison of IOP in the case of HRW and the placebo did not confirm any statistically significant differences. However, a supplementary analysis indicated that the consumption of HRW leads to a greater number of clinically significant deviations of IOP than the consumption of a placebo. This discrepancy may be due to the fact that a direct statistical comparison of the values may have been influenced by the difference of several days between both parts of the experiment, despite the fact that participants with a pronounced initial dispersion of IOP were excluded from the study. Even despite the fact that the participants had been instructed, it was not possible to eliminate all the influences that may have had a negative impact on IOP over this several-day period, and which may have thereby increased the undesirable random fluctuations in the values measured on different days. The conducted supplementary analysis of the clinical significance of deviations measured against the specific baseline value on the given day of measurement may therefore limit the impact of these fluctuations.

In the case of ordinary water, according to Chen et al. it is possible to explain the observed increase of IOP by means of the stimulation of the parasympathetic nervous system, which triggers a constriction of the Schlemm's canal, thereby leading to a temporary increase of IOP [29]. However, previous experiments with the consumption of HRW indicate a potential higher stimulation of the sympathetic nervous system as against a placebo, which in comparison with the placebo should limit the increase of IOP [46]. Nevertheless, since the results indicate the opposite, the mechanism of effect of HRW on IOP shall probably be a more complex phenomenon. The influence of the sympathetic nervous system on IOP is described in greater detail e.g., in the publication by Chen et al. [47].

A limiting factor of our study, in addition to the above-discussed time interval between both parts of the experiment, is its focus on healthy eyes. It is known that subjects suffering from glaucoma manifest higher sensitivity of IOP to stress factors, including the consumption of water [43, 45], in comparison with healthy eyes. For example, Kerr & Danesh-Meyer [43] state an increase of 3.3 mmHg following the consumption of 500 ml and 4.9 mmHg after 1000 ml of ordinary water. It is therefore possible to assume that HRW will also have a significant impact upon IOP in subjects suffering from glaucoma, nonetheless in addition to verifying the indicated differences in the effects of HRW and the placebo on IOP it is also necessary to conduct a separate study on this target group.

CONCLUSION

It has been demonstrated that upon a rapid intake of HRW, similarly as with ordinary water, a significant increase of IOP takes place in healthy individuals. The results indicate that from the perspective of clinical significance, the consumption of HRW may have a greater influence on change of IOP than a placebo in the observed healthy individuals. In the case of glaucoma patients, it is also possible to expect a significant increase in IOP following the consumption of HRW, although it is necessary to verify the clinical impact in comparison with a placebo by means of further studies.

Thanks

This study was supported by the projects IGA_PrF_2019_005, IGA_PrF_2020_008 and IGA_PrF_2023_004 of the Faculty of Science, Palacký University Olomouc, Czech Republic.

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