A Pilot Study to Develop a New Method of Assisting Children in Taking Their Medication by Using Immersive Virtual Reality

Kazuyuki Niki,*a,b Maki Yasui,a Maika Iguchi,a Tomomi Isono,a Hiroto Kageyama,a and Mikiko Ueda

*a Department of Clinical Pharmacy Research and Education, Osaka University Graduate School of Pharmaceutical Sciences; 1–6 Yamadaoka, Suita, Osaka 565–8871, Japan; and b Department of Pharmacy, Ashiya Municipal Hospital; 39–1 Asahigaoka-cho, Ashiya, Hyogo 659–8502, Japan.

Received August 14, 2020; accepted November 8, 2020

Taking bitter-tasting drugs can be stressful for children who have underdeveloped swallowing skills and do not understand the meaning of medication. Furthermore, the senses of vision and smell are known to majorly influence taste. This pilot study was aimed at determining the effect of visual stimulation by immersive virtual reality (iVR) on taste and the safety of this approach for developing a new method to assist children with taking medication. Ten subjects participated in this study, and their mean (standard deviation (S.D.)) age was 21.8 (0.8) years. The subjects tasted the bitter aqueous solution (quinine 0.00375%) while viewing two different VR images (strawberry sponge cake and orange juice) alternately and received sensory tests immediately after the tasting and again 30 s later. In addition, nausea was assessed 30 s after tasting for each VR image. The primary endpoint was the difference in sensory test scores immediately after the tasting and 30 s later, between the two images. There were no significant differences in the sensory test scores between the placebo and either strawberry sponge cake or orange juice immediately after tasting. However, 30 s after tasting, the scores changed significantly to a tendency to perceive sweetness from the strawberry sponge cake and orange juice images compared with the placebo. No subject experienced nausea. Therefore, the findings of this study suggest that displaying images of sweet foods by using iVR to stimulate visual perception could safely reduce the sense of bitterness.

Key words medication support; immersive virtual reality; child; vision; taste

INTRODUCTION

The bitter taste of medicines inconveniences patients and could reduce treatment effectiveness by worsening adherence.1) In particular, children who have underdeveloped swallowing skills and do not understand the meaning of medication may find it stressful to take medicines that are too bitter, which could be a burden to the family. Medication instructions are given to resolve the problem, such as taking drugs with other foods or drinks. However, the bitterness of the drugs may be enhanced by their dissolution in food and drink or may cause negative psychological effects, such as a dislike of foods that are mixed with the drugs. Furthermore, many parents have misconceptions about how to ensure that their children take medications, and current medication instructions do not sometimes improve adherence for children who are already struggling with medication.2) Therefore, it is necessary to develop a new medication method that can solve this problem.

Vision and smell are known to majorly influence the sense of taste in humans3,4) and, a project to change the taste of food by using virtual reality (VR) and an aroma diffuser has been recently launched5); however, recreating the texture of food is a major challenge. On the other hand, many children are prescribed powdered medicine because the drug dosage is adjusted according to their weight. Thus, we hypothesized that the texture of the powders is less likely to affect subjects’ sense of taste compared to food. Therefore, this study was aimed at determining the effect of visual stimulation by immersive VR on taste and safety, as a pilot study for the development of a new method of assisting children in taking medications.

MATERIALS AND METHODS

Subjects Men and women aged 18 years or higher, who were fully informed about the study, and who provided their written consent for study participation with the full understanding of the study were considered eligible for participation. Patients with visual impairment, prone to motion sickness, and considered to have a taste disorder (diagnosed by a doctor or who did not meet the following taste screening criteria) were excluded. Subjects were screened for taste by the whole oral method using taste test reagents (Tastedisk®, SANWA KAGAKU KENKYUSHO CO., LTD., Nagoya, Japan). Each of the four standard reagents in the kit (sweetness [refined white sugar solution], saltiness [sodium chloride solution], sourness [tartaric acid solution], and bitterness [quinine hydrochloride solution]) has five concentration levels. The subjects were blinded to the tastes, and 0.5 mL of the test solution was poured into their mouth, starting with the lowest concentration. The subjects then responded by selecting the taste they thought was applicable from among four tastes (sweet, salty, sour, and bitter). If the subjects could not answer correctly, the concentration of the test solution was increased by one step, and 0.5 mL of the solution was poured into the mouth again. The test was repeated until the subjects answered correctly, and based on the attached document6) of Tastedisk®, no taste abnormality was judged if the answer was correct within 3 steps from the lowest concentration of the test
solution. When changing the taste, the subjects were asked to rinse their mouth with water and the following evaluations were performed after 5 min. Subjects were recruited from February 4, 2019, to March 31, 2019, and this study was conducted in April 2019. Ten people applied to participate in this study and all of them met the criteria for participation.

Preparation of VR Images for Visual Stimulation
Strawberry sponge cake and orange juice from the top five food and drink items that were highly preferred by 4- and 5-year-old children in common were selected as images that could help mask bitterness, based on a previous study. Both strawberry sponge cake and orange juice were purchased commercially (Fig. 1). To capture 180-degree images, a 360-degree camera (Galaxy Gear 360, Samsung Electronics Co., Ltd., Suwon, Korea) was used. A smartphone (Galaxy S7 edge, Samsung Electronics Co., Ltd.) and VR goggles (Zeiss VR ONE Plus, Carl-Zeiss AG, Oberkochen, Germany) were used to view the VR images.

Assessment Methods
Bitterness and sweetness were rated on the following structured scale by using a sensory test method based on a previous study: −3, very bitter; −2, quite bitter; −1, slightly bitter; 0, neither; +1, slightly sweet; +2, quite sweet; and +3, very sweet. Nausea was assessed using the Numerical Rating Scale (NRS). The NRS is used to rate the degree of physical and other symptoms on a scale of 0 to 10, which in this study was defined as follows: 0, no nausea at all and 10, most severe nausea imaginable.

Viewing VR Images and Evaluations
(A) Presentation of the Reference Taste in the Sensory Test
Using Tastedisk® standard solutions as references for the sensory test, a 20% aqueous solution of refined white sugar was defined as +3 (very sweet) and quinine 0.1% aqueous solution was defined as −3 (very bitter). Subjects tasted the 0.5 mL of 20% aqueous solution of refined white sugar and the 0.5 mL of 0.1% aqueous solution of quinine, in that order, and recognized the sweet and bitter tastes. They were asked to rinse their mouth with water and a 5-min interval was maintained between each taste change.

(B) Bitterness Evaluation
Subjects first tasted the 0.5 mL of quinine 0.00375% aqueous solution blindfolded and then received sensory tests immediately after tasting and 30 s later. This tasting condition was defined as a placebo. The quinine 0.00375% aqueous solution was prepared by diluting the quinine 0.02% aqueous solution from the Tastedisk® standard solution with distilled water. Subjects were asked to wear VR goggles (Fig. 2) and exposed to two different 180-degree images (strawberry sponge cake and orange juice) randomly selected by the researcher by using the lottery method. While viewing the VR images, they tasted the 0.5 mL of quinine 0.00375% aqueous solution; the subjects received the sensory tests immediately after the tasting and 30 s later. Then, the subjects received the test again and were asked to rate again while viewing the other VR images. Furthermore, nausea was assessed after 30 s of tasting with each VR image. The subjects were asked to rinse their mouth with water for 5 min before changing the VR images. It took approximately 60 min per subject from taste screening to completion of the entire assessments.

Primary and Secondary Endpoints
The primary endpoint was the difference between images for sensory test scores immediately after the tasting and 30 s later. The secondary endpoint was the difference between images in the NRS scores for nausea 30 s after tasting.

Statistical Analysis
Steel’s multiple comparison test was used to evaluate the primary and secondary endpoints; the control groups were treated with the placebo. Wilcoxon’s signed-rank test was used to compare sensory test scores immediately after the tasting and 30 s later in the same image condition. Statistical analyses were performed using BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan), and a p-value < 0.05 was considered statistically significant.
**Ethical Considerations** This study was conducted according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects and approved by the Clinical Research Ethics Review Committee of the Osaka University Graduate School of Pharmaceutical Sciences and the School of Pharmaceutical Sciences (Approval Number: Yakuohito 30-16).

**RESULTS**

Ten subjects (3 male and 7 female subjects) participated in this study; the mean subject age (mean ± standard deviation (S.D.)) was 21.8 ± 0.8 years. The results of the sensory test are shown in Table 1. There was no significant difference between the placebo and strawberry sponge cake or orange juice immediately after tasting (0s). However, 30s after tasting, the scores changed significantly to a tendency to perceive sweetness for the strawberry sponge cake and orange juice compared to the placebo.

Regarding the time elapsed after the tasting, there was a significant change in scores for the tendency to perceive sweetness at 30s after viewing VR images of strawberry sponge cake and orange juice compared to immediately after the tasting; however, there was no change in the placebo group. The NRS score for nausea was 0 at 30s after tasting for all images, with no significant difference among the images (Table 2).

**DISCUSSION**

This study suggests that visual stimulation by displaying images reminiscent of sweetness via immersive VR may reduce bitterness and shorten the duration for which bitterness is tasted. Previous studies investigating the relationship between vision and taste have used two-dimensional (2D) images, such as monitor images and photographs, and little has been done to examine the impact of immersive VR images on taste. However, Kono et al. recently found that immersive VR images caused subjects to perceive tastes significantly more often than 2D images displayed on a monitor did, suggesting that immersive VR may have a greater impact on taste. However, they did not examine the effect of the type of image on specific tastes. Thus, this is the first study to reveal the effect of immersive VR images that evoke sweetness on bitterness. Sensory test results showed no significant difference among strawberry sponge cake, orange juice, and placebo immediately after tasting. After 30s of tasting, there was no reduction in bitterness with the placebo. However, there was a significant difference between the placebo and strawberry sponge cake. The bitterness significantly reduced when viewing VR images of strawberry sponge cake and orange juice compared to that in the immediate post-tasting period. Therefore, because it is conceivable that it may take several seconds for the bitterness to reduce upon visual stimulation, it is speculated that the present approach may be effective for powdered medicines with persistent or delayed bitterness. For example, Zithromax® fine granules, a typical powdered medicine considered bitter for children, is characterized by delayed bitterness due to a coating to mask the bitterness. Therefore, future studies should account for the elution time of each drug. Furthermore, although nausea is the most worrisome adverse effect of VR, the NRS score for nausea was 0 with all images. This finding is consistent with those of multiple studies that have shown that recent immersive VR did not cause severe nausea.

There are multiple limitations. First, this was a pilot study with a small sample size. Future studies are needed to determine a sample size based on the findings of this study. Second, because the results were obtained solely from the subjective evaluation, individual preferences for food and drink may have influenced the results. In addition, depending on the part of the image that subjects focus on, the taste they recall may change, in particular, children have fewer food experiences than the subjects in this study. Therefore, it is necessary to evaluate objective indices such as variations in pupil diameter and eye movements. Third, the subject were not children. Because the VR goggle cover the subjects’ vision, we worried about the risk of aspiration was high in children with underdeveloped swallowing function, thus, the subjects were limited to people aged 18 years or higher. Considering ways to prevent aspiration is needed. However, since this study used selected images of foods and drinks that are highly preferred by children, we expect to obtain similar results if the study subjects are children. Fourth, we did not use images that could evoke other tastes than sweetness. Since the sensitivity to taste is enhanced when the taste and the image match, we guess the image that evokes bitterness will not diminish the

**Table 1. Sensory Test of Taste**

| Time (s) | Placebo | Strawberry sponge cake | Orange juice | p-Value |
|---------|---------|------------------------|-------------|---------|
| 0       | −1.0 (0.5) | −1.0 (0.3)             | −1.0 (0.3)  | Placebo vs. strawberry sponge cake: 0.1924 |
|         |         |                        |             | Placebo vs. orange juice: 0.4979 |
| 30      | −1.0 (0.2) | 0.0 (0.3)              | 0.0 (0.3)   | Placebo vs. strawberry sponge cake: 0.0264 |
|         |         |                        |             | Placebo vs. orange juice: 0.0264 |
| p-Value | 0.72    | 0.04                   | 0.02        |         |

Data are shown as median (95% CI) values. Abbreviation: CI, confidence interval.

**Table 2. Evaluation of Nausea**

| Time (s) | Placebo | Strawberry sponge cake | Orange juice | p-Value |
|---------|---------|------------------------|-------------|---------|
| 30      | 0.0 (0.42)| 0.0 (0.39)          | 0.0 (0.39)  | Placebo vs. strawberry sponge cake: 0.8493 |
|         |         |                        |             | Placebo vs. orange juice: 0.8493 |

Data are shown as median (95% CI) values. Abbreviation: CI, confidence interval.
taste, but the effect of other tastes (saltiness, umami, and sourness) on masking bitterness is unknown. Finally, this study was only conducted using taste test reagents.

However, this study suggests that displaying images reminiscent of sweetness as immersive VR to stimulate visual perception could safely reduce bitterness. We will examine the effect on taste when VR images and odors are presented simultaneously in the future because scent has been shown to affect taste.4,14–16

Acknowledgments We thank all the subjects and colleagues at Osaka University.

Conflict of Interest The authors declare no conflict of interest.

REFERENCES

1) Ishiguro T. Approach to patient-friendly preparations—Masking bitter and disgusting taste of drugs with cyclodextrins. Oleosciences, 15, 423–430 (2015).
2) Mizutani K, Noda Y, Kobayashi T, Andoh H, Nabeshima T. Survey of administration methods for powdered medicines and effectiveness of medication instruction in improving compliance in pediatric patients. Jpn. J. Pharm. Health Care Sci., 31, 151–157 (2005).
3) Sakai N, Morikawa S. The pictures of fruits affect flavor perception of fruit juice. The Japanese Journal of Taste and Smell Research, 13, 463–466 (2006).
4) Sakai N, Kobayakawa T, Gotow N, Saito S, Imada S. Enhancement of sweetness ratings of aspartame by a vanilla odor presented either by orthonasal or retronasal routes. Percept. Mot. Skills, 92, 1002–1008 (2001).
5) Project Nourished. https://www.youtube.com/watch?v=1bpPJnhhB-A, accessed 24 July, 2020.
6) A package insert of Tastedisk®: https://med.skk-net.com/diagnostics/products/item/20031_atta.pdf, accessed 24 July, 2020.
7) Muto S, Fujikura J, Ikeda H, Segawa Y, Surasak B. Comparison study of food preference of school children in Thailand and Japan. 38th Conference of Asia-Pacific Consortium for Public Health 2006 (Bangkok, Thailand), pp. 127–128 (2006).
8) Kobayashi M, Watanabe K, Arumugam S, Nishimura R, Hasegawa N, Goto T, Ueno K. Relationship between dissolution behavior and sensory evaluation of film-coated metformin hydrochloride preparations. Japanese Journal of Generic Medicines, 10, 82–86 (2016).
9) Kono H, Takenaga T, Taki K, Etio S. Sensory change effects and applicability of virtual reality with head mounted displays. Bulletin of Karume Institute of Technology, 41, 92–100 (2018).
10) Niki K, Okamoto Y, Maeda I, Mori I, Ishii R, Matsuda Y, Takagi T, Uejima E. A novel palliative care approach using virtual reality for improving various symptoms of terminal cancer patients: a preliminary prospective, multicenter study. J. Palliat. Med., 22, 702–707 (2019).
11) Jones T, Moore T, Choo J. The impact of virtual reality on chronic pain. PLoS ONE, 11, e0167523 (2016).
12) Ferguson C, Shade MY, Blaskewicz Boron J, Lyden E, Manley NA. Virtual reality for therapeutic recreation in dementia hospice care: a feasibility study. Am. J. Hosp. Palliat. Care., 37, 809–815 (2020).
13) Bradley MM, Miccoli L, Escrig MA, Lang PJ. The pupil as a measure of emotional arousal and autonomic activation. Psychophysiology, 45, 602–607 (2008).
14) Schifferstein HNJ, Verlegh PWJ. The role of congruency and pleasantness in odor-induced taste enhancement. Acta Psychol. (Amst), 94, 87–105 (1996).
15) Stevenson RJ, Prescott J, Boakes RA. Confusing tastes and smells: How odors can influence the perception of sweet and sour tastes. Chem. Senses, 24, 627–635 (1999).
16) Stevenson RJ, Case TI. Preexposure to the stimulus elements, but not training to detect them, retards human odour-taste learning. Behav. Processes, 61, 13–25 (2003).