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High Ingestion Rate of Iodine from Povidone-Iodine Mouthwash

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Abstract

Iodine-based mouthwash and throat sprays contain povidone iodine (PVP-I) for disinfection. PVP-I mouthwash has been commonly used for decades in Japan and other countries and frequent and/or prolonged use of PVP-I mouthwash can induce transient hypothyroidism. To assess the amount of iodine ingested from an oral rinse, 22 healthy adult volunteers (mean age: 48.1, 29–70 years) were recruited for the study. The subjects were instructed to rinse for 15 s three times with 20 mL of commercially available PVP-I mouthwash diluted into 0.23% or pure water. This method is a standardized method of gargling recommended by the manufacturers. The total iodine in the PVP-I mouthwash was measured with inductively coupled plasma-mass spectrometry. Although the 7% PVP-I mouthwash contains 7 mg of effective iodine/mL, 24.3 mg/mL of iodine was detected in the solution. The median value and ratio of the total iodine ingested were 5.0 mg (range: 2.6–10.8 mg) and 20.5% (range: 10.6–44.5%), respectively. The iodine species released from the PVP-I mouthwash are effective iodine (PVP•nHI_3, I_3^-, and I_2) and I^-; however, the amount and types of iodine actually absorbed into the bloodstream are unknown. PVP-I mouthwash should be used carefully since around 5 mg of iodine could theoretically enter the body with one gargle which exceeds the tolerable upper intake level of iodine for adults. This study was prospectively registered to University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) on March 29, 2021, with the study ID of UMIN000043770.

Keywords Iodine · Povidone iodine (PVP-I) · Gargling · Tolerable upper intake level (UL) · Thyroid dysfunction

Introduction

Iodine is an essential trace element for the production of thyroid hormone; however, adverse effects of excess iodine intake on thyroid function have been reported [1–3]. Iodine-based gargles (mouthwash and throat sprays) contain povidone iodine (PVP-I) for disinfection of the oral cavity [4]. An over-the-counter povidone-iodine oral gargle solution has been commonly used for decades by people in Japan and other countries although the effectiveness of gargling for preventing upper respiratory tract infection among healthy people has not been proven [5]. Thyroid dysfunction due to frequent and/or long-term use of PVP-I gargles is not rare in Japan [6]; however, the amount of iodine ingested by gargling was unclear and the mechanism of PVP-I gargle-induced hypothyroidism is not yet fully understood.

PVP-I is a complex compound consisting of iodine bound to a carrier, polyvinylpyrrolidone (PVP, also called povidone), which maintains an equilibrium state in an aqueous solution and gradually releases iodine as the free iodine concentration in the water decreases. The free iodine (I_2)

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oxidizes water to form H_2OI^+, which is presumed to kill bacteria and viruses by reacting with membrane proteins (-SH group, tyrosine, and histidine) on the surface of bacteria and viruses [7].

The iodine in PVP-I consists of effective iodine and iodine ions (I^-). Effective iodine is mainly present in the form of PVP·nHI_3, I_3^-, and I_2, all of which are brown in color, while an iodine ion (I^-), which has no antibacterial activity, is colorless. The commercially available 7% PVP-I gargle in Japan contains 7 mg of effective iodine in 1 mL of undiluted solution [8, 9]. Some gargle manufacturers in Japan recommend the following dosage and directions for use as the "standard method for gargling" [10, 11]: Dilute 2–4 mL of undiluted solution in 60 mL of water (15–30 times dilution results in 0.23–0.46% of PVP-I solution) [8, 9] and gargle (mouth rinse) once, then rattle (throat rinse) for 15 s twice (more than 30 s in total), several times a day. There are no reports on how much of the iodine contained in PVP-I gargles is absorbed into the body. The purpose of this study is to determine the amount of iodine ingested by the standard gargling method using the PVP-I gargle.

Materials and Method

Subjects

Twenty-two healthy adults, 11 males and 11 females, who were employees of a chemical manufacturing company in Chiba Prefecture were recruited for the study. They had no oral, pharyngeal, or dental disease or dentures and had not received dental treatment at least 2 days before the experiment. They were also asked not to eat or drink for 2 h before the experiment. The mean (SD) age, height, weight, and BMI were 48.1 (12.2) years, 168.6 (7.1) cm, 63.7 (11.6) kg, and 22.3 (2.9) kg/m^2, respectively. The occupational categories were 9 administrative workers, 8 manufacturing workers, 4 testing workers, and 1 other worker. Eleven of the participants gargled habitually, and none of them gargled with PVP-I gargle in the recommended way [10, 11]. The gargle solution used by 10 of the 11 participants was water, while the 11th one used a gargle containing cetylpyridinium chloride for bactericidal action as well as dipotassium glycyrrhizinate for anti-inflammatory action. The frequency of gargling ranged from 1 to 10 times, with a median of 2 times per day, and the duration of gargling varied from 3 to 10 s, with a median of 5 s.

Materials

The PVP-I gargle purchased and used was Isodine® Gargle (serial number 1CA717, expiration date 2023.06) [8, 9] by Shionogi Healthcare Co., Ltd. Osaka, Japan (distributor) and Mundipharma K.K., Tokyo, Japan (manufacturer). Pure water was prepared using a pure water production system for laboratory analysis, Purelight PRO-0100, Organo Corporation, Tokyo, Japan, with a specific resistance value of less than 1 µS/cm. The total iodine concentration in pure water used in this experiment was measured to be 0.041 ppb using inductively coupled plasma-mass spectrometry (ICP-MS), iCAP Q with CASX260, Thermo Fisher Scientific K.K., Tokyo. The gargle solutions were weighed using a precision balance, Shimadzu AP324X, Shimadzu Corporation, Kyoto, Japan, with a minimum weighing value of 200 mg and minimum display of 0.1 mg. The reagents used were 25% tetramethyl ammonium hydroxide solution (TMAH), Wako Pure Chemical Industries, Ltd., Japan; certified reference material for iodine, AS-I9-2Y 1000 µg/mL iodide (Lot No. 4-25I-2Y) SPEX CertiPrep, LLC. NJ, U.S.A.; calibration standard for ICP-MS as internal standard solution, tellurium (Te), 1000 µg/mL and indium (In), 1000 µg/mL, SCP Science, Canada. Since the standard reference material for PVP-I was not commercially available, we used the serum reference materials, QM-S-Q1825 (iodine: 54.5 ppb), QM-S-Q 2007 (iodine: 93.6 ppb) and QM-S-Q 2008 (iodine: 135 ppb), Centre de toxicologie / INSPQ, Canada, for quality control.

Method

The experiment was conducted on an empty stomach from 10:00 to 13:00 on four separate occasions (days) while taking measures to prevent COVID-19 infection.

1. Materials and gargling method

   The PVP-I gargle solution was made by adding 2 mL of 7% PVP-I gargle to pure water up to a volume of 60 mL, i.e., a 30-fold dilution, yielding 0.23% PVP-I solution. The gargle solution used per gargle was 20 mL. According to the recommended standard method [10, 11], the gargle solution should be held in the mouth and gargled for exactly 15 s. After gargling three times with 20 mL of gargle solution, all of the solution was spit out into a separate container together. The amount of gargling liquid and iodine content were measured precisely before and after gargling. The experiment was repeated twice for each participant using pure water and PVP-I gargle solution in this order.
2. Measurement method of gargling liquid volume

   (1) Dispense 20 mL of gargling liquid into three 60 mL paper cups, and measure the total weight (A).
   (2) Measure the weight of the empty 275 mL paper cup (B) used for collecting the gargling liquid that was spit out.

(3) Measure the total weight of the empty 60 mL paper cups (C) and the weight of the 275 mL paper cup containing liquid after gargling (D).
(4) Centrifuge all of the spit-out liquid after gargling at 3000 rpm for 5 min, collect 15 mL of the supernatant, and store it frozen in the dark.
(5) Calculation method for the amount of gargling liquid ingested
    1) Amount of gargling liquid actually used for gargling: A – C
    2) Amount of gargling liquid expelled after gargling: D – B
    3) Amount of gargling liquid that entered into the oral cavity: (A – C) – (D – B)

3. Measurement of saliva secretion

Since saliva secreted during gargling is mixed in the gargling liquid, four subjects (two males, 39 and 70 years old, and two females, 41 and 57 years old) out of the 22 participants were randomly selected to measure the amount of saliva secretion using the Saxon test [12]. The Saxon test is a method of evaluating saliva secretion during stimulation, in which a standardized, specially designed piece of dry gauze is chewed at a constant rate for 2 min, and the weight of saliva absorbed by the gauze is measured to evaluate the saliva secretion. In this study, we cut the gauze into small pieces (dry weight: around 2.1 g), and asked each subject to put it in his/her mouth, chew it for 15 s, and then spit it out. We then measured the weight of each piece of gauze. This was done three times in succession, and the average of the total weight was regarded as the amount of saliva secreted during the experiment.

Analysis

Extraction of iodine in the PVP-I gargle solution before and after gargling was carried out according to "The official method for determining the iodine content of foods" by the Ministry of Health, Labour and Welfare, Japan [13]. One milliliter of sample solution was added to a polypropylene tube (DigiTUBE®, GL Sciences, Tokyo, Japan) up to a volume of 50 mL with 1 mL of 25% TMAH solution and ultrapure water for extraction at 90℃ for 12 h. After cooling to room temperature, the suspension was centrifuged by 3000 rpm for 10 min, then 15 mL of the supernatant was collected, and stored at –25℃ until analysis. Samples were diluted 2550 times and the iodine content was determined at once by using ICP-MS. The limit of detection (LOD) and background equivalent concentration (BEC) of this assay were 0.002 and 0.112 ppb, respectively. The intra-assay coefficient of variation was 2.0–2.6%. All analytical procedures were carried out at the Central Research Laboratory, Tsukuba, Kotobiken Medical Laboratories, Inc.

Statistical Analysis

The results were presented as median and range because the amount of gargle solution and iodine content after gargling was not normally distributed. Differences between two unmatched groups for non-normally distributed data were tested using the Mann–Whitney test. A p-value less than 0.05 was considered significant. All data were processed and statistically analyzed using GraphPad Prism version 8.43 for macOS (GraphPad Software LLC, San Diego, CA, U.S.A.). For conversion to S.I. units: 1 µg/dL = 0.079 µmol/L.

Results

Amount of Total Iodine Ingested from the Gargling Solution

The total iodine value in the PVP-I gargle solution measured by ICP-MS was 23.4–25.3 mg with a median of 24.3 mg before gargling. In the spit-out solution after gargling, the iodine value varied widely from 13.5 to 21.6 mg with a median of 19.6 mg. The median value of total iodine remaining in the oral cavity was estimated to be 5.0 mg and the range was from 2.6 to 10.8 mg. The rate ranged from 10.6 to 44.5% with a median of 20.5% (Table 1). The median value of ingested iodine in female subjects was higher than that in male subjects ($p = 0.0458$).

Table 1 The amount of total iodine from PVP-I mouthwash remaining in the oral cavity

	Total	Male	Female	p*
n	22	11	11	–
Total iodine before gargling (mg)	24.3 (23.4–25.3)	24.3 (23.7–25.1)	24.7 (23.4–25.3)	0.4387
Total iodine after gargling (mg)	19.6 (13.5–21.6)	19.9 (3.5–21.6)	18.2 (15.4–20.5)	0.0759
Total iodine remaining in the oral cavity (mg)	5.0 (2.6–10.8)	4.8 (2.6–10.8)	5.5 (4.2–8.9)	0.0458
Rate (%)	20.5 (10.6–44.5)	19.3 (10.6–44.5)	22.2 (17.5–36.6)	0.0580

Median (range), * male vs. female, for conversion to S.I. units: 1 µg/dL = 0.079 µmol/L

Amount of Ingested Gargle Solution

When gargling with pure water, 2 out of 22 subjects (1 male and 1 female) spit out 0.1–0.2 g of extra fluid. The median amount of water remaining in the oral cavity was 1.3 g (range: –0.2 to 7.6 g), and the median rate was 2.2% (range: –0.3 to 12.6%). With the PVP-I gargle, 11 out of 22 subjects (5 males and 6 females) expelled an extra 0.1–2.5 g. The amount of PVP-I gargle solution remaining in the oral cavity ranged from –2.5 to 2.5 g, and the rate was –4.2 to 4.3% (Table 2). The amount of pure water remaining was more than the PVP-I gargle solution ($p=0.0001$). There was no statistically significant difference in the amount and rate of ingestion of both pure water and PVP-I gargle solution between males and females ($p=0.562$–0.898).

Saliva Secretion

The salivary secretion of the four subjects measured according to the Saxon method for 15 s, three times, ranged from 1.5 to 1.9 g, with a median value of 1.8 g.

Discussion

Iodine Species from PVP-I Solution

The kinetics of PVP-I and iodine in aqueous solution is shown by the following equation [14, 15].

$$\mathrm{PVP \bullet nHI_3} \iff \mathrm{PVP} + \mathrm{nH^+} + \mathrm{nI_3^-}$$
$$\mathrm{I_3^-} \iff \mathrm{I_2} + \mathrm{I^-}$$
$$\mathrm{I_2} + \mathrm{H_2O} \iff \mathrm{HOI} + \mathrm{H^+} + \mathrm{I^-}$$
$$\mathrm{HOI} \iff \mathrm{OI^-} + \mathrm{H^+}$$
$$\mathrm{HOI} + \mathrm{H^+} \iff \mathrm{H_2OI^+}$$
$$\mathrm{3HOI} \iff \mathrm{IO_3} + \mathrm{2I^-} + \mathrm{3H^+}$$

H_2OI^+ produced by the oxidation of water with molecular iodine (I_2) liberated from the PVP-I complex has antibacterial and viral effects. Since it is difficult to measure H_2OI^+ directly, in most cases the concentration of I_2 is used as an indicator of the microbicidal effect of PVP-I solution as well as an effective iodine. The titration method specified in the Japanese Pharmacopoeia is the official method [16] for the determination of free iodine (I_2), and it can also be measured by high-performance liquid chromatography [17]. When PVP-I solution is diluted to 0.1%, the carrier retention becomes the weakest and the iodine stored as PVP-I is released, resulting in the highest concentration of free iodine (25.4 ppm), and the concentration decreases with further dilution [7, 14, 15]. At the same time, the amount of iodine bound to PVP-I decreases.

Iodine Ingested from Gargle Solution

The estimated amount of total iodine remaining in the oral cavity after gargling with 60 mL of 0.23% PVP-I gargle for 45 s was 5.0 mg (range: 2.6–10.8 mg) or 20.5% (range: 10.6–44.5%). To the best of our knowledge, there is no report on the concentration of total iodine, i.e., all iodine species, in PVP-I solution. PVP-I gargles available on the market are ISODINE® GARGLE SOLUTION 7% in Japan or BETADINE® MOUTHWASH & GARGLE outside Japan [18]. According to the package insert of BETADINE®, the concentration of PVP-I is 1%, which is diluted 3 times and used to obtain 0.33%, almost the same as the concentration of ISODINE®. PVP-I contains 9.0–12.0% of effective iodine (PVP-nHI_3, I_3^-, and I_2) and 5% of ineffective iodine ions (I^-) [19]. The ratio of iodine ions to effective iodine is 1:1.8–2.4, and this sum is considered to be the total iodine content. The PVP-I gargle solution used in this experiment was 2 mL of 7% PVP-I stock solution diluted to 60 mL, which contains 14 mg of effective iodine and iodine ions, and theoretically the total iodine content is calculated to be 19.8–21.8 mg. In addition, since iodine is loaded on PVP-I in the form of HI_3 and the iodine detected during analysis is 3 atoms, the total iodine content is 1.5 times higher

Table 2 The amount and rate of mouthwash remaining in the oral cavity

Mouthwash		Total	Male	Female	*p*
n		22	11	11	-
Pure water	Before gargling (g)	58.7 (53.2–60.3)	58.7 (53.2–60.2)	58.7 (55.0–60.3)	0.6063
	After gargling (g)	57.2 (48.7–58.9)	57.5 (48.7–58.9)	56.1 (52.7–58.8)	0.5619
	Amount remaining (g)	1.3 (−0.2 to 7.6)	1.0 (−0.1 to 5.9)	1.6 (−0.2 to 7.6)	0.7477
	Rate (%)	2.2 (−0.3 to 12.6)	1.8 (−0.2 to 9.9)	2.7 (−0.3 to 12.6)	0.7069
PVP-I solution	Before gargling (g)	58.9 (56.3–60.3)	58.9 (58.0–59.9)	58.9 (56.3–60.3)	0.7477
	After gargling (g)	58.7 (56.4–61.3)	58.8 (56.8–61.3)	58.7 (56.4–60.6)	0.8799
	Amount remaining (g)	0.0099 (−2.5 to 2.5)	0.0728 (−2.5 to 2.2)	−0.1184 (−2.2 to 2.5)	0.8977
	Rate (%)	0.015 (−4.2 to 4.3)	0.12 (−4.2 to 3.8)	−0.2 (−3.9 to 4.3)	0.8977

Median (range), * male vs. female

than that of molecular iodine (I_2), which is calculated as 14 mg × 1.5 = 21 mg. In this study the median of the measured value of total iodine including all iodine species was 24.3 (range: 23.4–25.3) mg, which was slightly higher than the theoretical value; however, this value seems to be reliable and acceptable.

Secretion of Saliva and Its Iodine Content During Gargling

According to the original method of the Saxon test, saliva secretion of 2 g or more in 2 min is considered normal, and in this study, the average amount of saliva secretion was 1.8 g in 45 s. Iodine is also secreted into saliva although in small amounts [1]. The average salivary iodine concentration measured using ^{131}I in Japanese adults is 203 (80–450) µg/L [20]. In a Chinese report on salivary iodine concentration in elementary school children measured by ICP-MS, the median value was 106 (67.8–181) µg/L, and the concentration was proportional to the amount of iodine ingested (iodine concentration in urine) [21]. In other words, the concentration of iodine in saliva is 0.1–0.2 µg per gram, which is almost negligible when calculating iodine content in this experiment.

Actual Amount of Iodine Absorbed into the Body

It is clear that the iodine in the PVP-I gargle is absorbed into the bloodstream by oral administration, but there is no data on which type of iodine and how much of it is absorbed from the digestive tract and transferred into the bloodstream. Orally ingested iodine in the form of water-soluble salts is almost 100% absorbed from the gastrointestinal tract, while molecular iodine and iodate are reduced to iodide in the intestine and almost completely absorbed in the small intestine [1]. Although povidone is soluble in water, it is not absorbed from the intestinal tract since it is a high molecular polymer. Therefore, the iodine bound to the remaining povidone that has liberated I_2 may not be absorbed; however, the kinetics of PVP-nHI_3, I_3^-, I_2 and I^- from PVP-I in the intestinal tract are unknown.

The oral cavity contains food residues, saliva, dental plaque, and tongue coating. In addition, the mouth and throat of healthy individuals are inhabited by hundreds of bacteria, fungi, and viruses that colonize and adhere to the different surfaces of the oral and oropharyngeal mucosa [4]. The molecular form of iodine is the only species in topical iodine disinfectants that is able to penetrate into the epidermis, while iodine in the form of iodide and triiodide (I_3^-) cannot. Since the surface of the oral cavity is not protected by a stratum corneum, all species of iodine in a PVP-I gargle can be absorbed [15]. Iodine from PVP-I adhered to oral mucosa may be eventually swallowed, reduced, and absorbed in the stomach and small intestine. In this experiment, the total amount of iodine ingested by the recommended standard gargling method with maximum dilution (30-fold dilution) was 5 mg per gargle, but the actual amount absorbed into the blood is presumably less than this amount.

It has been reported that urinary and blood iodine increase with the use of PVP-I gargle solution [22]. Blood contains organic and inorganic iodine, while urine contains mostly inorganic iodine [1]. Since the circulating iodine includes reused endogenous iodine as well as exogenous iodine, it is difficult to evaluate the amount of iodine absorbed from PVP-I gargle solution with the iodine concentration in blood and urine. The most accurate method might be to look at the distribution and excretion of iodine using PVP-I gargle solution labeled with radioiodine.

Differences in Ingestion of Gargle Solution and Effect on Saliva Secretion

During gargling a considerable amount of saliva was secreted especially when gargling with the PVP-I solution. When gargling with pure water, more solution was ingested than with the PVP-I solution because pure water is easy to swallow due to its low viscosity and non-irritant nature. The method of measuring the amount of liquid before and after gargling makes it difficult to evaluate the exact amount of ingestion due to saliva mixing into the gargling solution.

The Gargling Method and Current Situation of Gargling in the General Population

In previous reports, gargling followed by rinsing of the mouth for 30 s using 10–15 mL of diluted PVP-I mouthwash was suggested in general [4, 5]. In the present study using the recommended standard method [10, 11], three gargles were performed for 15 s each, for a total of 45 s; however, in the standard method of gargling recommended by some companies, there is no set time for the first of the three gargles [8, 9]. We searched for scientific data on the basis of this "standard gargling method," including these companies, but were unable to find any evidence. In this study, half of the 22 participants habitually gargle but none of them gargled according to this method. In a study on gargling practices (44 adults, mean age 65.4 years, Neyagawa City, Japan), many subjects did not follow this "standard gargling method," using a thinner solution (3–6 times), a shorter gargling time (86.4% was less than 45 s), and a larger amount of gargling solution (1.8 times) [23]. In our nationwide survey on iodine nutrition conducted in 2016–2019 (2485 adults, 1435 males and 1050 females, mean age 45.9 years), only 1.9% of the subjects regularly used iodine gargles (unpublished). Since gargling habits and methods vary, it is assumed that the

amount of iodine actually absorbed varies greatly among individuals.

Effect of PVP-I Gargle on Thyroid Function

There are few studies that have observed changes in thyroid function due to gargling with PVP-I [6, 21, 23, 24]. Sato et al. reported overt hypothyroidism in an elderly man who has been gargling with 60–90 mL of undiluted 7% PVP-I gargle solution per month for more than 10 years. The authors also observed urinary iodine excretion increased from 0.66 ± 0.63 to 4.6 ± 2.1 mg/day after gargling with 20 mL of PVP-I mouthwash solution (15-fold dilution of PVP-I stock solution) three times a day in 18 healthy adults [6]. Ader et al. in the USA reported that 46 adults (mean age 28 years) with gingivitis and dental plaque gargled with 10 mL of 5% PVP-I solution for 15–30 s twice a day for 6 months, and serum thyroid function was measured six times every 6 weeks, including before and after the experimental period. Serum iodine and urinary iodine concentrations increased at 6 weeks after the start of the study, but serum thyroid-stimulating hormone (TSH) levels increased slightly within normal limits throughout the entire period, while serum thyroxine and triiodothyronine levels remained unchanged [22]. Ferguson et al. in England observed that serum TSH concentrations increased with prolonged PVP-I treatment for 24 weeks, and TSH returned to baseline levels after 3 weeks of stopping gargling [24]. Murugesan et al. in India treated 47 adult patients with pharyngitis and tonsillitis by having them gargle with 20 mL of PVP-I mouthwash solution (fourfold dilution of PVP-I stock solution of unknown concentration) 3 times a day for 3 weeks, and found a slight increase of serum TSH within normal limits [25]. From these studies, it is clear that long-term gargling with PVP-I solution affects thyroid function. However, the effects of excessive iodine loading on thyroid function in healthy subjects at the individual level are unclear [2, 3]. Large-scale, prospective, and controlled studies are needed to evaluate the safe use of PVP-I gargling.

The UL for Iodine and Iodine Ingestion from PVP-I Gargle

The tolerable upper intake level (UL) is defined as the highest level of nutrient intake, i.e., likely to pose no risk of adverse health effects for almost everyone in the general population. In Japan 3000 µg/day is recommended as the UL for adults by the Ministry of Health, Labour and Welfare [26] while the ULs for iodine in adults established by the European Commission Scientific Committee on Food [27] and the US Institute of Medicine [28] are 600 and 1100 µg/day, respectively. In this study, theoretically, approximately 5 mg of total iodine could enter the body with one gargle which exceeds the UL values although the actual amount of iodine absorbed into the bloodstream is unknown. The daily consumption of iodine in Japan is higher than in most countries and it is also recommended that in Japanese adults, the intermittent occurrence of high iodine intake of up to about 10 mg/day due to the consumption of kelp-based meals is not a problem; however, it should be limited to about 20 mg/day per week [26]. It is not clear that a higher iodine intake results in a high risk of iodine-induced hypothyroidism or autoimmune thyroid disease [2, 3].

The limitations of this study are as follows: (1) The amount of iodine actually absorbed from the intestinal tract cannot be determined from this experiment. (2) Short-term changes in thyroid function were not observed. (3) The effects of age and gender on iodine absorption cannot be evaluated due to the small number of subjects. (4) The method of measurement for total iodine in PVP-I by ICP-MS is not established; however, the theoretical and actual iodine values were almost identical. The advantages were (1) The amount of total iodine ingested by gargling was precisely assessed by measuring iodine in the gargle solution. (2) The total iodine, i.e., all iodine species included in the gargling solution, was measured by ICP-MS. (3) We demonstrated that more iodine than the effective iodine level indicated was detected in the PVP-I gargle solution.

Conclusions

Commercially available PVP-I gargles contain more iodine than indicated, and it is possible that up to approximately 2–10 mg of total iodine remains in the body per gargle if gargling according to the recommended standard method. However, the amount actually absorbed into the blood through the mucous membranes of the oral cavity, pharynx, and intestinal tract is not known, and there are large individual differences in gargling methods. In addition, it is not clear whether the recommended method is widely used. Although this value of ingested iodine theoretically exceeds the UL of iodine for adults, the effects of PVP-I gargle when used as a routine mouthwash on the development of thyroid dysfunction requires careful interpretation and further study.

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Author Contribution The authors contributed to the following aspects of the investigation: Y.F., N.T., M. Y., and Y.I.: designed the research; Y.F.: conducted the research, analyzed and interpreted the data; Y.F.:

wrote the manuscript; Y.F.: was the principal investigator and had primary responsibility.

Data Availability The data that support the findings of this study are not available.

Declarations

Ethics Approval and Consent This study was conducted in accordance with the ethical guidelines contained in the Declaration of Helsinki and Medical Research Involving Human Subjects including epidemiological research, and written informed consent was obtained from all individual participants included in the study. The research plan was approved by the Ethics Committee of the Japanese Red Cross Hokkaido College of Nursing (approval number: 020–366, on February 25, 2021).

Conflict of Interest The authors declare no competing interests.

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