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Prevention of Upper Respiratory Tract Infections by Gargling

A Randomized Trial

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Background: Gargling to wash the throat is commonly performed in Japan, and people believe that such hygienic routine, especially with gargle medicine, prevents upper respiratory tract infections (URTIs). Its effectiveness, however, has not been established by clinical trials.

Design: Randomized controlled trial carried out in 2002–2003 winter season and analyzed in 2003 and 2004.

Participants: Healthy volunteers (387) aged 18 to 65 years.

Intervention: Participants were randomly assigned to water gargling, povidone-iodine gargling, and usual care (control). Subjects in the two gargling groups were requested to gargle with water or diluted povidone-iodine at least three times a day. Participants were followed for 60 days.

Main Outcome Measures: The primary outcome measure was first URTI incidence. Severity of URTI symptoms among incident cases was also evaluated. Both outcomes were assessed with a self-administered symptom record. Analyses were performed on an intention-to-treat basis.

Results: A total of 130 participants contracted URTIs. The incidence rate of first URTI was 0.26 episodes/30 person-days among control subjects. The rate decreased to 0.17 episodes/30 person-days in the water gargling group, and 0.24 episodes/30 person-days in the povidone-iodine gargling group. Respective incidence rate ratios against controls were 0.64 (95% confidence interval [CI]=0.41–0.99) and 0.89 (95% CI=0.60–1.33). A Cox regression (proportional hazard model) revealed the efficacy of water gargling (hazard ratio=0.60, 95% CI=0.39–0.95). Even when a URTI occurred, water gargling tended to attenuate bronchial symptoms ($p=0.055$).

Conclusions: Simple water gargling was effective to prevent URTIs among healthy people. This virtually cost-free modality would appreciably benefit the general population.
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Introduction

Upper respiratory tract infection (URTI) is one of the most common medical problems in the daily lives of otherwise healthy people. In the United States, people experienced 2.5 episodes, on average, every

year.^{1,2} However, corroborative evidence for URTI prevention is quite scarce. People, therefore, take measures on the basis of their own experience or preferences.

Gargling is generally accepted and strongly recommended as a preventive modality against URTI in Japan. A lot of people use gargle medicines such as povidone-iodine expecting virucidal effects.^{3,4} Some simple questionnaire survey and nonrandomized studies suggested that frequent gargling with diluted povidone-iodine would reduce the incidence of URTI or influenza and the following absenteeism from schools or workplaces.^{5–8} However, there have been no controlled trials, and it remained unresolved as to whether gargling was really effective.

To answer this simple question, a randomized controlled trial was conducted in community healthcare settings all over Japan.

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Methods

Study Associates and Participants

In September 2002, authors invited applications for study associates through several relevant mailing lists from the Internet. Eighteen healthcare professionals who agreed with the purpose and protocol of the study were appointed local administrators. From December 2002 through January 2003, healthy adult volunteers were recruited for the study in the local administrators' areas. The inclusion criteria were both genders, aged 18 to 65 years, and subjectively healthy. The exclusion criteria were (1) having a habit of frequent gargling; (2) almost never infected with URTI over the years; (3) in a low immune state (e.g., poorly controlled diabetics or steroid users); and (4) not eligible for the use of povidone-iodine (e.g., patients with thyroid disease). After careful explanation, written consent was obtained from each participant.

By an individual drawing of sealed opaque envelopes, subjects were randomly assigned to the following three groups: water gargling, povidone-iodine gargling, and control. Group assignment was based on simple computer-generated random digits; allocation was completely concealed from study administrators. To prevent post hoc exchange of the envelopes, local administrators wrote down both the name of each subject and the number on the envelope he/she drew before breaking the seal.

Baseline characteristics of the participants were collected by the self-administered questionnaire, including gender, birth year, occupation, smoking status (current/former/never smoker), anti-influenza vaccination in the pre-season (yes/no), and frequency of URTIs in the preceding year (never/one to two times/three or more times).

Itagaki et al.⁶ reported that the cumulative incidence of URTI and influenza among school children was 61.8% when gargling with povidone-iodine and 85.8% when not gargling. Consequently, the sample size was calculated as 70 for each group at the power level of 0.90, and the significance level of 0.05. With the expectation of dropouts, we set the total sample size at 300.

Intervention

Local administrators instructed the subjects of the water gargling group to gargle with approximately 20 mL of water for about 15 seconds three times consecutively, and to carry out this treatment at least three times a day. The subjects of the povidone-iodine gargling group were told to gargle with approximately 20 mL of 15 to 30 times diluted 7% povidone-iodine (as indicated by the manufacturer) in the same way as water gargling. When povidone-iodine caused serious discomfort or was not available, subjects of this group were allowed to gargle with water instead of diluted povidone-iodine. Control group members were instructed to retain their previous gargling habits. All subjects were asked to keep up their hand-washing routine, not to change other hygienic habits, and not to take any cold remedies during the intervention period.

All subjects were requested to fill in the prescribed form (gargling diary) every day. This form included the frequency of gargling and hand-washing, and various URTI complaints such as nasal symptoms (rhinorrhea and sneezing), pharyngeal symptoms (soreness and scratchiness), bronchial symp-

toms (cough and phlegm), and general symptoms (feverishness, arthralgia, and malaise). Each symptom was classified into four grades, that is, none, mild, moderate, and severe, according to the Jackson method.⁹ "Mild" was defined as when a subject was unaware of the symptom when he/she was busy; "moderate" as when one always felt discomfort; and "severe" as when one experienced difficulties in activities of daily life. Even when a subject contracted a URTI based on subjective feeling, he/she was asked to continue filling in the gargling diary for 1 week after its onset to confirm the incidence and severity of URTI.

During the follow-up period, local administrators monitored participants' hygienic actions and health condition, and encouraged them to keep up their assigned intervention every week.

Statistical Analysis

One-way analysis of variance was used for group comparisons of numerical variables, and the chi-square test was used for those of categorical data. A trend test was performed using the Mantel extension method. Tukey's correction was applied for multiple comparisons.

The primary endpoint was the first URTI incidence. It was defined as all of the following conditions: (1) both nasal and pharyngeal symptoms, (2) severity of at least one symptom increased by two grades or more, and (3) worsening of a symptom of one increment or more for ≥ 3 days. Because of the difference in the mode of transmission, we excluded influenza-like diseases featured by moderate or severe fever and arthralgia, and treated them separately. Disease incidence was determined by one study physician who was not informed of the results of assignment.

The incident rate of first URTI was evaluated, and the rate ratio and its 95% confidence interval (CI) were calculated. Incidence curves were drawn by the Kaplan-Meier method, and the differences between groups were verified by the log rank test. To examine the independent contribution of each background factor to the incidence, a multivariate analysis was performed using the Cox proportional hazard model. The hazard ratio and its 95% CI were computed for each item.

As the secondary endpoint, the severity of URTI of the incident cases was assessed. Severity grades of each symptom during the initial 7 days after the onset of URTI were replaced with numeric scores: none=0, mild=1, moderate=2, and severe=3. Peak and total scores for 7 days were compared between groups by the Kruskal-Wallis test.

Statistical analysis was carried out in 2003 and 2004 using SPSS software (version 10.0J, SPSS, Inc., 1999). All statistical tests were two-sided and regarded as significant at $p < 0.05$. All analyses were performed on an intention-to-treat basis.

Results

Figure 1 is the flowchart of this study. A total of 387 subjects participated in the study at 18 sites (four in northern Japan, nine in the central region, and five in the western region; two to 52 persons per site) and were randomized. The follow-up period was 60 days between December 2002 and March 2003. Excluded from analysis were two subjects who already suffered from URTI on the first day of intervention, and one subject who

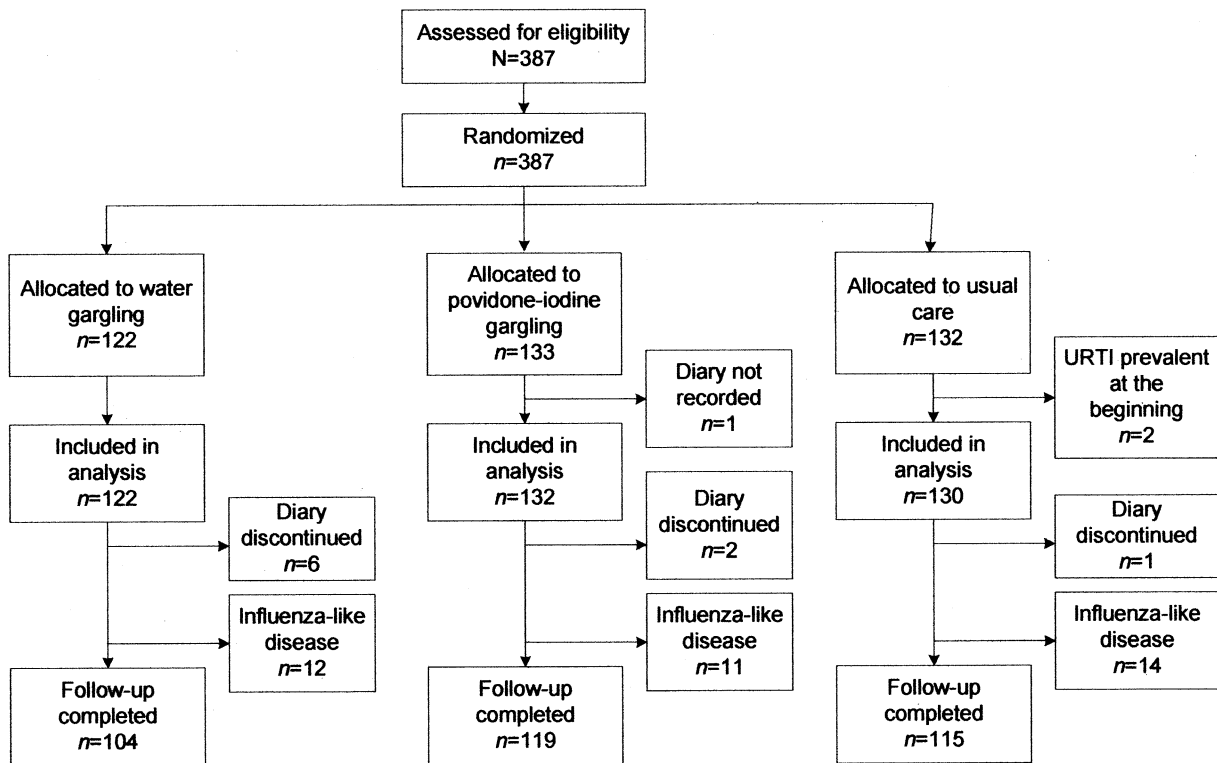


Figure 1. Flowchart of the study. URTI, upper respiratory tract infection.

did not write in the diary at all (follow-up 99%). Two subjects assigned to the povidone-iodine gargling group found that povidone-iodine did not agree with them and gargled with water instead. However, they were analyzed as povidone-iodine gargling group members (intention-to-treat analysis). Among all subjects, nine did not complete the diary. Most of them had contracted URTI subjectively, but their symptoms did not meet the study criteria. Twelve other subjects in the water gargling, 11 in the povidone-iodine gargling, and 14 in the control group succumbed to influenza-like diseases ($p=0.78$). Both kinds of affected subjects were treated as censored cases at the onset of their symptoms.

Baseline characteristics of the three groups are shown in Table 1. Gender, age, region of residence, occupation, smoking habits, anti-influenza vaccination,

and frequency of URTIs in the preceding year were similar, and randomization was unbiased. Actual frequency of gargling and hand-washing of the participants during the intervention period were examined. On an average, each person gargled with water 3.6, 0.8, and 0.9 times per day in the water gargling, povidone-iodine gargling, and control group, respectively ($p<0.001$), and gargled with povidone-iodine <0.1 , 2.9, and 0.2 times per day in each respective group ($p<0.001$). None of the two gargling groups skipped gargling, while 36 (28%) among the control subjects did not gargle at all. Thus, participants were generally compliant with their group assignment. Frequency of hand-washing was 6.5, 6.1, and 6.2 times per day in the water gargling, povidone-iodine gargling, and control group, respectively ($p=0.67$).

Table 1. Baseline characteristics of study subjects

	Water gargling (n=122)	Povidone-iodine gargling (n=132)	Controls (n=130)	p value
Gender (male/female)	39/83	34/98	43/87	0.38
Age (mean)	34.7	35.6	36.2	0.64
Residence (northern/central/western Japan)	28/64/30	28/81/23	37/65/28	0.31
Occupation (employed/not employed)	69/53	72/60	77/53	0.99
Smoking habits (current smoker)	8.3%	9.2%	11.5%	0.69
Anti-influenza vaccination (yes)	14.3%	23.8%	19.2%	0.16
Frequency of URTIs in preceding year (0, 1-2, ≥ 3 times) ^a	14/71/36	14/81/34	16/78/36	0.99

^aData missing for four participants.
URT, upper respiratory tract infection.

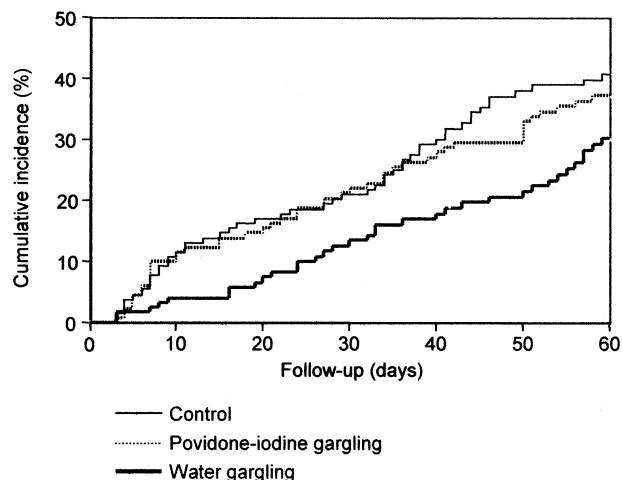


Figure 2. Kaplan-Meier incidence curves of first upper respiratory tract infections according to intervention.

During the intervention period, URTI was diagnosed in 130 subjects. Incidence rate of first URTI varied with background factors. The rate was as high as 0.32 episode/30 person-days for those aged ≤ 29 , with a decreasing trend of 0.23 for those aged 30 to 39, 0.16 for those aged 40 to 49, and 0.10 for those aged ≥ 50 (trend $p < 0.001$). Compared with subjects who lived in central Japan (Kanto, Tokai, and Kinki districts: 0.19 URTI episode/30 person-days), those in northern (snowy) areas of Japan (Hokkaido, Tohoku, and Hokuriku districts: 0.33 URTI episode/30 person-days) were more likely to contract URTI (rate ratio=1.70, 95% CI=1.16–2.51), while those living in western Japan (Chugoku, Shikoku, and Kyushu districts) were quite similar in susceptibility (rate ratio=0.98, 95% CI=0.61–1.59). URTI occurrence was less frequent among workers than nonworkers (0.19 vs 0.28 episode/30 person-days; rate ratio=0.68, 95% CI=0.48–0.96). The rate was only 0.08 episode/30 person-days among participants who were almost free from URTIs in the preceding year, but it increased to 0.21 and 0.33 episode/30 person-days among those who contracted URTIs one to two times and three or more times, respectively (trend $p < 0.001$).

On the other hand, the incidence rate was not significantly different between men and women (0.20 vs

0.23 episode/30 person-days; rate ratio=0.88, 95% CI=0.61–1.29), or among current smokers, former smokers, and never-smokers (0.19, 0.17, 0.23 episode/30 person-days, respectively; rate ratio for current vs never-smokers=0.83, 95% CI=0.45–1.55). Morbidity was almost identical between those vaccinated/not vaccinated against influenza (0.23 vs 0.22 episode/30 person-days; rate ratio=1.04, 95% CI=0.68–1.62).

Figure 2 demonstrates the first URTI incidence curves of the three intervention groups. Compared to 50 subjects (40.8% by the Kaplan-Meier estimation) in the control group, 34 (30.1%) in the water gargling group ($p=0.044$) and 46 (37.2%) in the povidone-iodine gargling group ($p=0.59$) became infected until day 60. Incident rates were lower in the water gargling subjects (0.17 episode/30 person-days) and in the povidone-iodine gargling subjects (0.24 episode/30 person-days) than in controls (0.26 episode/30 person-days). Their respective rate ratios were 0.64 (95% CI=0.42–0.99) and 0.89 (95% CI=0.60–1.33). When a multivariate analysis was performed using Cox's proportional hazard model including other baseline factors, the results were essentially unaltered: the hazard ratios were 0.60 (95% CI=0.38–0.93) for water gargling and 0.88 (95% CI=0.58–1.34) for povidone-iodine gargling.

Symptoms of URTI were compared among incident cases of the three intervention groups (Table 2). The mean peak score in bronchial symptoms was somewhat lower in the water gargling group (0.97) than in the povidone-iodine gargling group (1.41) and the control group (1.40); the difference was marginally significant ($p=0.055$). Other symptoms were not significantly different between groups. The results of 7-day summed scores were almost identical to those of peak scores. No adverse events were observed during the 60-day intervention period.

Discussion

To our knowledge, this is the first randomized controlled trial to evaluate the effectiveness of gargling for the prevention of URTIs among healthy people. Authors found that simple water gargling would reduce the incidence rate of URTIs during 60 days in the

Table 2. Severity of upper respiratory tract infection (peak score in 7 days after onset)

	Water gargling (n=122)		Povidone-iodine gargling (n=132)		Controls (n=130)		p value
	M	SD	M	SD	M	SD	
Nasal symptoms	1.56	(0.79)	1.83	(0.90)	1.84	(0.84)	0.250
Pharyngeal symptoms	1.79	(0.81)	1.65	(0.79)	1.82	(0.69)	0.505
Bronchial symptoms	0.97	(0.76)	1.41	(0.98)	1.40	(0.86)	0.055
Feverishness	0.82	(0.90)	0.96	(1.03)	1.02	(1.15)	0.876
Total	5.12	(1.85)	5.80	(2.25)	6.06	(2.32)	0.185

M, mean; SD, standard deviation.

Gargling is not popular in the Western world, but has been strongly recommended in Japan to prevent upper respiratory tract infections (URTIs).

This randomized controlled trial indicates a 36% decrease in incidence of URTIs among apparently healthy adults by tap water gargling, and also only trifling preventive effects of gargling with diluted povidone-iodine solution.

This simple modality may substantially reduce the physical and economical burden caused by URTIs.

prevalent season by 36%. Water gargling might also decrease supervening bronchial symptoms even if one contracted a URTI.

Whirling water is deemed to wash out pathogens from the pharynx and oral cavity. The incubation time of rhinovirus, a representative microbe of URTI, is 8 to 12 hours,¹⁰ and even intermittent gargling could disrupt its propagation. Viruses, however, are known to bind specific receptors of the cell.¹⁰⁻¹² Thus, it remains questionable whether simple irrigation could sufficiently eliminate viruses.

Inactivation of viruses by chlorine added to the tap water is another plausible explanation. The required chlorine concentration for tap water is >0.1 mg/L in Japan, and the levels are actually 0.5, 0.5, and 0.8 mg/L in Osaka, Nagoya, and Tokyo, respectively, to ensure viral inactivation.^{13,14}

By contrast, gargling with povidone-iodine did not significantly reduce URTI incidence or bronchial extension. First, povidone-iodine has strong bacteri-/virucidal effects,^{3,4} and demolishes normal flora in the pharynx and oral cavity, which interferes with pathogenic viral invasion.¹⁵⁻¹⁷ Second, povidone-iodine injures pharyngeal tissue. The cytotoxicity of povidone-iodine varies with the study,¹⁸⁻²¹ and use in wound care is now under debate.²²⁻²⁴ Although there may be some adverse effects on fibroblast and other fragile cells, whether it hurts robust tissues is questionable. Third, the irritant nature of povidone-iodine might interfere with one's thorough gargling. However, no povidone-iodine user except two withdrawers complained of discomfort or difficulties in gargling.

Annual healthcare costs attributable to acute URTIs, including clinical and hospital fees and prescription medicines, totaled 500 billion yen (US\$5 billion), with an additional 80 to 120 billion yen (around US\$1 billion) spent on over-the-counter drugs. In the United States, the direct costs were estimated at \$17 billion.¹ If mere gargling with tap water could reduce URTI incidence by up to 36%, as much as 200 billion yen would be saved. Economic issues will be addressed in another paper.

The strong point of our study is its external validity. Many people expressed interest in this research project, and all subjects whose participation was requested were willing to do so. Only a few subjects dropped out during the follow-up period. The response rate was quite high, and thus, the results yield high generalizability.

Our study has some limitations, however. First, the assignments were not masked to the study participants, and URTI symptoms may have been biased by participants' preconceived ideas. Nevertheless, the general population believes that gargling with povidone-iodine is more effective than simple water gargling. Hence, one would expect results of the study to be biased in the direction opposite of the actual outcome. Second, URTI diagnosis was made by only subjectively graded

symptoms. Influenza and some bacterial infections were, therefore, not ruled out completely. Because precise diagnosis is costly, and even influenza and beta-hemolytic streptococcus infection are likely to be self-limited in healthy people, symptom-centered diagnosis is acceptable in community healthcare settings.

This study suggests that simple water gargling is effective to prevent URTIs among healthy people. This virtually cost-free modality would appreciably benefit people both physically and economically around the world.

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This study was carried out by the Great Cold Investigators-I group. The group is composed as follows: chairperson: Takashi Kawamura (Kyoto University); trial coordinator: Kazunari Satomura (Kyoto University); statistical analyst: Tetsuhisa Kitamura (Okayama University); efficacy and safety observer: Takuro Shimbo (Kyoto University); consultants: Masahiko Ando, Tsuguya Fukui (Kyoto University), Kaoru Shimokata (Nagoya University); and local administrators: Motoi Watanabe (Hokkaido University of Education), Mitsuhiro Kamei (private practice), Yoshihisa Takano (private practice), Akiko Tamakoshi (Nagoya University), Sachiko Yamada (Aichi Prefectural College of Nursing and Health), Kyoko Takashima (Tsukuba University), Narufumi Suganuma (University of Fukui), Hideo Namai (Japan International Cooperation Agency), Tetsuhisa Kitamura (Okayama University), Yoko Komura (Japan International Cooperation Agency), Hisamitsu Baba (Kobe University), Hiroshi Itoh (Ritsumeikan University), Masaharu Yoshihara (Hiroshima University), Kazunari Satomura (Kyoto University), Yukihiro Yamaguchi (Kenwakai Ohtemachi Hospital), Hidetsuna Watanabe (Fukushima University), Norihiko Iida (Kansai University), and Shuichi Saeki (Ehime University).

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