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Improved Outcomes After Low-Concentration Hypochlorous Acid Nasal Irrigation in Pediatric Chronic Sinusitis

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Objectives/Hypothesis: We aimed to evaluate the effectiveness of low-concentration hypochlorous acid (HOCl) nasal irrigation compared to isotonic normal saline for pediatric chronic rhinosinusitis.

Study Design: This was a randomized, prospective, active-controlled study.

Methods: This study investigated the effectiveness of 4 weeks of low-concentration hypochlorous irrigation by analyzing five categorized subjective symptoms and x-ray findings in pediatric patients with rhinosinusitis. Thirty-seven patients were enrolled, and 26 patients successfully completed the study.

Results: Total symptom scores significantly improved with both HOCl and normal saline nasal irrigation, but there was no difference between the two groups. X-ray scores also improved in both groups; improvement was much greater in the HOCl group than the placebo group.

Conclusions: Nasal irrigation with HOCl is an effective adjuvant treatment compared to isotonic normal saline for pediatric sinusitis.

Key Words: Nasal irrigation, pediatric, sinusitis, hypochlorous chloride.

Level of Evidence: 1b

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INTRODUCTION

Sinusitis is very common in the pediatric population. Its main symptoms are rhinorrhea, posterior nasal dripping, cough, nasal congestion, mouth breathing, and sleep disturbances. In addition to antibiotic therapy, adjunctive managements can be tried, including saline irrigation, steam inhalation, systemic or local steroids, mucolytic drugs, and decongestants.[1] The American Academy of Pediatrics clinical practice guideline[2,3] has suggested nasal irrigation as a useful management method for pediatric sinusitis. This method removes debris from the nasal cavity while promoting sinus drainage.[3–5] Nasal irrigation reduces mucosal inflammation by decreasing the amount of bacteria, fungi, and allergens.[6] Isotonic normal saline is commonly used for rhinosinusitis nasal irrigation. In particular, hypertonic saline has been utilized to improve mucociliary transport.[7] However, nasal irrigation by itself lacks antibacterial activity. It may be less effective for uncontrolled rhinosinusitis because mucin is hydrophobic and negatively charged.[8] An effective adjuvant treatment for rhinosinusitis would be useful in protecting against the emerging bacterial resistance that is prevalent in pediatric sinusitis.[9]

In our previous report, low-concentration (3.5 ppm) free chlorine and hypochlorous acid (HOCl) was produced by a short electrical impulse. The resulting solution demonstrated bactericidal and fungicidal activity without toxicity to the nasal mucosa.[10] Therefore, nasal irrigation with low-concentration HOCl was suggested as an effective adjuvant treatment for rhinosinusitis.[10] The purpose of this study was to evaluate the effectiveness of low-concentration HOCl nasal irrigation in pediatric chronic rhinosinusitis.

MATERIALS AND METHODS

Participants

This was a prospective, randomized study of the effectiveness of 4 weeks of hypochlorous irrigation on subjective symptoms and x-ray findings in pediatric patients with chronic sinusitis. Informed consent was obtained from all subjects, and the institutional review board for research of Yonsei University College of Medicine approved this study (1-2011-0083). A total of 37 patients volunteered for this study, and 26 patients were analyzed (Fig. 1). These subjects were recruited from the otorhinolaryngology clinic patient population at Severance Hospital from November 2013 to February 2015.

The inclusion criteria were 1) age between 5 and 18 years, 2) symptom (mucopurulent rhinorrhea, nasal obstruction, or posterior nasal dripping) duration of at least 12 weeks,

Additional supporting information can be found in the online version of this article

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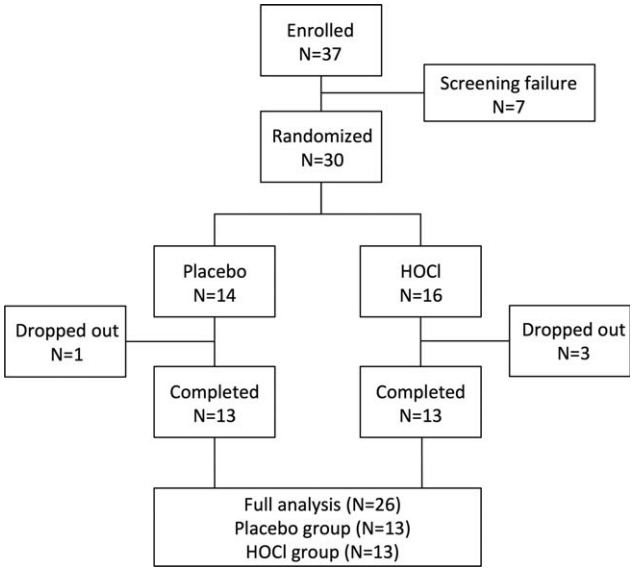

Fig. 1. Study flow and subject disposition. A total of 37 subjects between 5 and 18 years old were enrolled, and 26 subjects successfully completed the study. Subjects were randomly allocated to placebo and hypochlorous acid (HOCl) groups.

3) endoscopic finding of mucopurulent discharge in the nasal cavity, and 4) confirmation of sinusitis with paranasal (PNS) sinus
x-ray showing significant mucosal thickening ($\geq$4 mm) or total sinus opacification (radiology score $\geq$ 2).

The exclusion criteria were 1) positive Multiple Allegro-Sorbent Test result, 2) nasal polyposis, 3) history of asthma, 4) immunodeficiency disease, 5) treatment with steroids or antibiotics during the study, and 6) history of nasal surgery.

A total of 37 patients were enrolled, but seven patients failed screening. Among the 30 patients who were randomized, four patients dropped out. A total of 26 patients who completed 4 weeks of treatment were analyzed in this study (Fig. 1).

Study Design

Physical examination of the nasal cavity was performed with endoscopy, and the presence of mucopurulent discharge or nasal polyps was examined. PNS x-ray (Waters, Caldwell, and skull lateral view) was performed to radiologically diagnose sinusitis. Blood sampling (complete blood count, routine chemistry) and chest posterior to anterior x-ray were also performed to exclude patients with abnormal results. All participants were asked to complete a case record form, including a questionnaire with total symptoms score (TSS). An independent study nurse randomly divided patients into two groups (HOCl and placebo groups) according to a computer-generated randomization list. Patients were blinded to the assignment, whereas investigators were informed of group assignments to allow early detection of adverse reactions during the study. Three independent investigators blinded to group information performed PNS x-ray scoring. Patients were evaluated by irrigation technique, daily use, and adverse events. Patients were excluded from the study if they performed nasal irrigation inconsistently.

Nasal Irrigation Method

All patients were educated by a study nurse about how to perform nasal irrigation using the same method. Thirteen patients in the HOCl group received nasal irrigation two times daily with 30 mL of low-concentration HOCl that was produced by electrolysis of isotonic 0.9% $NaCl/H_2O$ (normal saline) using a Salicid device (Dolki Korea, Wonju, South Korea). Thirteen patients in the placebo group also received normal saline with sham Salicid equipment as an irrigant. These patients were not informed of the sham allocation. Nasal irrigation was performed in a sitting or standing position with the head pulled back to allow irrigant to flow in the nasal cavity. This position was maintained for 10 seconds, and then the nasal irrigation apparatus was removed from the nose. All patients were educated about the method by the same study nurse.

TSS

All patients and their parents were asked to complete the TSS questionnaire before and at the 2nd and 4th week after enrollment. TSS included five categorized symptoms: 1) rhinosinusitis symptoms (i.e., rhinorrhea, cough, posterior nasal dripping, headache, facial pain or pressure), 2) nasal obstruction (i.e., mouth breathing, hyposmia, nasal congestion), 3) allergic symptoms (i.e., sneezing, runny nose, itching nose or eyes), 4) emotional symptoms (i.e., sadness, irritation, frustration, restlessness, sleep disturbance), and 5) impairment of daily activities (i.e., school absences, inattention). The intensity of these five categorized symptoms was rated according to a seven-grade visual scale with 1 indicating never and 7 indicating always. Total scores, representing the sum of scores, ranged from 5 to 35.

Radiographic Score

All patients were examined by PNS view x-ray, including Water, Caldwell, and skull lateral views. The radiologic scores for bilateral maxillary, ethmoid, frontal, and sphenoid sinuses were rated on the following scale: 0 = normal, 1 = mucosal thickening ($\geq$4 mm) without opacity or fluid level, 2 = partial opacification or fluid level, 3 = total opacification. All sinuses were evaluated and scored separately by three independent physicians who were not informed of group information. The sum of scores from each group was averaged and analyzed. Changes in the PNS x-ray score between pretreatment and 4 weeks after treatment were compared for the HOCl and placebo groups.

Safety Assessment

The development and frequency of adverse events or feelings were monitored. An investigator conducted vital signs, blood tests, and endoscopic examination assessment at baseline, at 2 weeks, and at the end of the study (4 weeks). In particular, patients who had worsened subjective symptoms or x-ray scores were carefully reviewed.

Statistical Analysis

Analyses were performed using SPSS Statistics version 20 software (IBM, Armonk, NY). All collected data were presented as mean $\pm$ standard deviation. The independent samples t test was used to compare changes in PNS x-ray score and TSS between the two groups. P-values less than .05 were considered significant.

RESULTS

Twenty-six children with chronic sinusitis were registered in this study. The mean age of all participants was 8.1 $\pm$ 2.9 years (HOCl group: 8.2 years; placebo

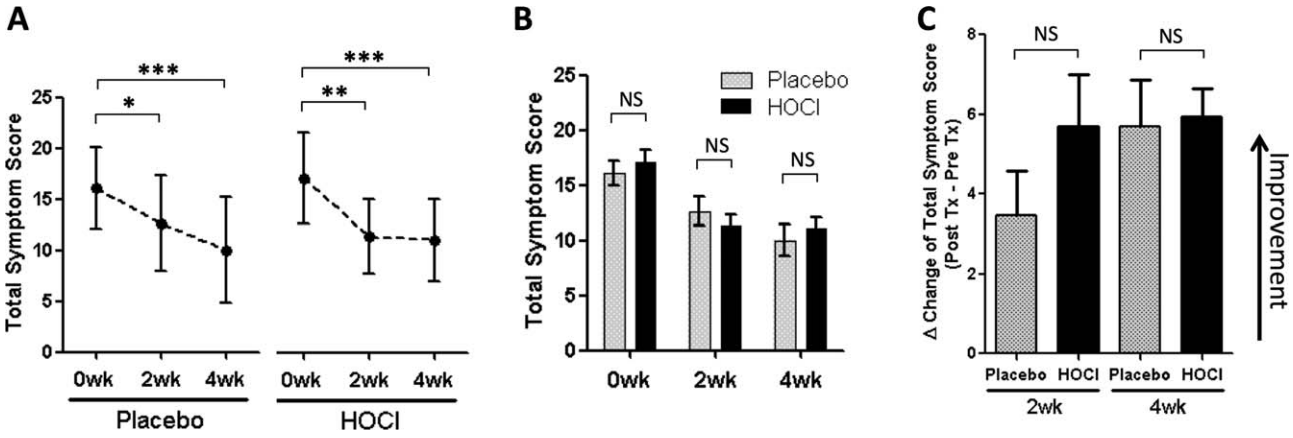

Fig. 2. Comparison of total symptom score (TSS) in hypochlorous acid (HOCl) and placebo groups. (A) TSS was reduced significantly after 4 weeks for both the HOCl and placebo groups. (B) Comparison of TSS at 0, 2, and 4 weeks of treatment. (C) TSS change (Δ) showed improvement after 2 and 4 weeks of treatment in both groups, but the degree of change between the HOCl and placebo groups was not statistically different. NS = not significant; Tx = treatment. *; $p < 0.05$, **; $p < 0.01$, ***; $p < 0.001$.

group: 8.0 years). There were no significant differences in age, total symptom score, or x-ray score at baseline before treatment (see Supporting Table 1 in the online version of this article). Four weeks of HOCl treatment significantly improved the symptoms of rhinosinusitis ($P = .005$), allergic rhinitis ($P = .003$), and emotional stress ($P = .025$; see Supporting Fig. 1 and Supporting Table 2 in the online version of this article). However, HOCl irrigation did not significantly reduce nasal obstruction or impairment in daily activity. Placebo was also noted to significantly improve symptoms of rhinosinusitis ($P = .004$) and emotional stress ($P = .013$). However, placebo did not significantly reduce nasal obstruction, allergic rhinitis, and impairment of daily activity. TSS was significantly reduced from 17.0 ± 3.9 to 11.1 ± 3.9 ($P = .0001$) by HOCl and from 16.1 ± 3.8 to 10.4 ± 4.5 ($P = .0004$) by placebo (see Supporting Table 2 in the online version of this article and Fig. 2A). In the HOCl group, all patients indicated improvement in TSS after 4 weeks, whereas one patient in the placebo group showed worsening TSS (from 19 to 21).

To assess adverse events, all subjective symptoms were evaluated at 2 weeks after treatment when patients visited the clinic. TSS at 2 weeks was significantly reduced in both HOCl ($P = .001$) and placebo ($P = .01$) groups compared to pretreatment TSS (Fig. 2A). However, the degree of TSS improvement in both groups was not different (Fig. 2B, C).

PNS x-rays were scored in all participants at baseline and 4 weeks after treatment (Fig. 3A). X-ray scores significantly improved from 5.2 ± 2.8 to 2.7 ± 2.7 with HOCl ($P = .0004$, Fig. 3B). Eleven patients in the HOCl group showed improvement in x-ray score, but two of 13 patients showed no change in x-ray score. In the placebo group, x-ray scores also improved from 3.9 ± 2.3 to 3.1 ± 1.7, but the change was not statistically significant ($P = .068$, Fig. 3B). One of 13 patients in the placebo group had a worsening x-ray score (from 2 to 3) at the end of the study, and four of 13 patients showed no change. Changes in x-ray score were significantly greater in the HOCl group (2.5 ± 1.9, n = 13, $P = .023$) compared to the placebo group (0.9 ± 1.5, n = 13, Fig. 3C).

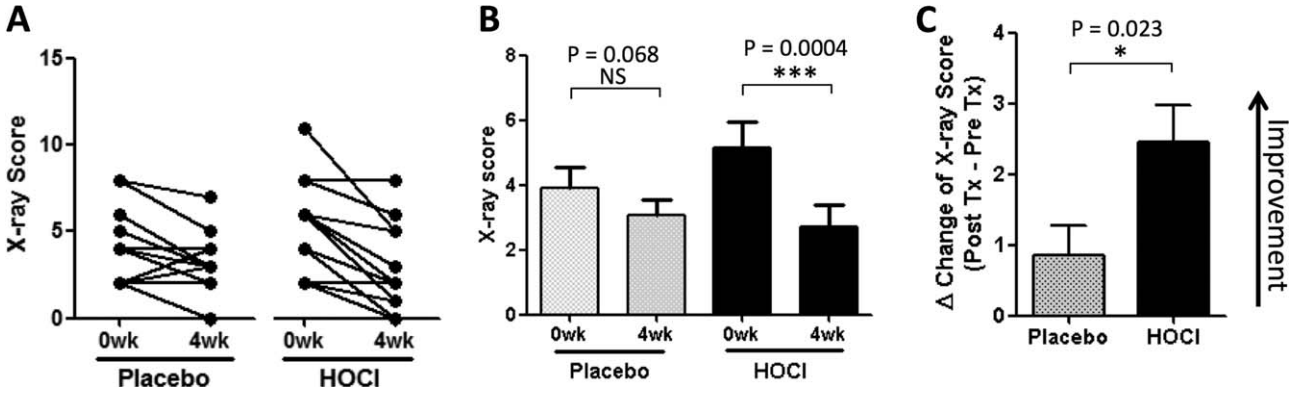

Fig. 3. Comparison of x-ray scores for hypochlorous acid (HOCl) and placebo groups. (A) Plot of x-ray score changes in individual subjects before and after 4 weeks of treatment. (B) X-ray score at 0 and 4 weeks of treatment showed significant improvement in the HOCl group, but not in the placebo group. (C) Comparison of x-ray score change (Δ) indicates that x-ray score significantly improved in the HOCl group compared to the placebo group. NS = not significant; Tx = treatment. *; $p < 0.05$, ***; $p < 0.001$.

To evaluate adverse events and tolerability, all participants were asked about any uncomfortable symptoms or feelings with daily use of nasal irrigation. An investigator evaluated nasal cavities by endoscopy. No patients in either the HOCl or the placebo group reported any significant uncomfortable feelings during treatment or had worsening of mucosal conditions during the study. Four patients dropped out during the study because they caught a cold and their parents wanted to stop the study. An investigator evaluated their nasal cavities before they dropped out, and no adverse events were observed.

DISCUSSION

Chronic sinusitis is very common, with an estimated prevalence of up to 74% in children.[11] The majority of pediatric otolaryngologists prescribe oral antibiotics, nasal steroids, and saline irrigation as the initial medical treatment.[12] Some authors have recommended that surgical treatment may be needed if medical treatments fail to resolve chronic sinusitis within 3 months.[13,14] However, the outcome of endoscopic sinus surgery in pediatric sinusitis is difficult to predict. Postoperative management is also challenging for both clinicians and children. There are diverse criteria for surgery in the pediatric population, and management of sinusitis with nonsurgical treatment is very important. Unfortunately, the increasing use of broad-spectrum antibiotics has resulted in a pattern of emerging bacterial resistance in pediatric chronic sinusitis.[9] Patients may develop allergies to topical antibiotics, or these agents may contribute to bacterial resistance.[15] Antiseptic agents such as povidone-iodine or silver sulfadiazine were proven to have cytotoxic effects on cell components related to wound healing.[16] Therefore, these agents may have limited use as nasal irrigants.

Chlorine is an essential disinfecting element of bleaching agents that are commonly used to sterilize tap or swimming pool water.[17,18] In water, chlorine reacts to form HOCl and hypochlorite anion (OCl^-), and their relative amount varies with the pH.[19] In a pH that is <7.5, a greater amount of HOCl exists than OCl^-. The HOCl solution used in this study is different from bleach and is safer than diluted bleach. Bleach is mainly composed of OCl^-, which is more stable during storage. However, OCl^- has a lower bactericidal effect than HOCl, as bacterial cell walls also have a negative charge and push out OCl^-. The HOCl molecules are similar in size and structure to water and easily penetrate into bacterial cell walls, resulting in excellent bactericidal ability. HOCl is roughly 100 times more potent as a germicide than OCl^-.[20] However, its low storage stability has limited its use as a pharmaceutical formulation.

HOCl can be produced through electrolysis of a salt solution.[21] We reported the production of 3.5 ppm HOCl with sterile tap water and NaCl using a Salicid device.[10] This low-concentration HOCl had excellent bactericidal activity against *Aspergillus fumigatus, Haemophilus influenza, Klebsiella pneumoniae, Rhizopus oryzae, Candida albicans, Staphylococcus aureus*, and *Streptococcus pneumonia*.[10] Landa-Solis et al. reported that a super-oxidized water solution containing 20 ppm HOCl has 99.9% bactericidal and fungicidal activity over *Escherichia coli, S. aureus, Pseudomonas aeruginosa, Salmonella typhi*, and *C. albicans* after 30 seconds of contact.[18] The HOCl solution was also produced by electrolysis of NaCl solution using purified neutral pH water. Bacteria commonly loses its viability when it encounters phagocytosing leukocytes,[22] which may occur before the onset of cellular digestion.[23] HOCl is produced by human immune cells to defeat pathogens. HOCl, produced in activated neutrophils by myeloperoxidase-mediated peroxidation of chloride ions, contributes to bacterial destruction.[24] Because of this effect, HOCl was suggested as a potential application for antimicrobial wound irrigation and treatment.[15] In animal models with chronic granulating wounds infected with *E. coli*, HOCl showed obvious bacterial killing without inhibiting the wound healing process.[15] In this study, improvement in sinusitis with HOCl nasal irrigation was observed. Although bacteriological analysis was not carried out in this study, HOCl irrigation likely sterilizes pathogens in the nasal cavity to improve sinus infections. It would be interesting to culture bacteria before and after HOCl nasal irrigation in patients.

Safety is a crucial issue to consider regarding the use of HOCl nasal irrigant for pediatric patients. In this study, no adverse events were observed in the HOCl group and patients had no complaints of uncomfortable feelings. The safety standard for HOCl in drinking water suggested by the World Health Organization (WHO) is ≤ 5 mg/L.[25] Cytotoxic assays in cultured human nasal epithelial cells showed that 3.5 ppm HOCl did not cause any toxic effect. In addition, cell morphology was not altered, as demonstrated by scanning electron and light microscopy.[10] Morphologic study is essential because electron microscopy has shown that epithelial morphology is damaged or altered by hypotonic, hypertonic, and pure water solutions.[26] The safety of HOCl was demonstrated in animal and cell experiments.[21]

Specific adverse effects in humans and animals exposed to chlorine in drinking water have not been observed, and the International Agency for Research on Cancer has concluded that they are not classified as carcinogenic to humans.[27] In mammal cells, HOCl is nonirritating and nonsensitizing, and cytotoxicity has been found to be relatively low.[19,28,29] WHO and the Food and Agriculture Organization of the United Nations also declared that HOCl is similar in size and structure to water and possesses no charge, unlike OCl^-. Therefore, an HOCl solution is not a toxic chemical and different from diluted bleach, meaning that it can be used for drinking water or food.[30]

This study has some limitations. First, control participants who did not perform any nasal irrigation were not compared to the HOCl or placebo groups because of ethical issues regarding withholding treatment. Second, simple x-rays were used instead of computed tomography (CT) scans because of issues regarding radiation exposure in children. The x-ray score may not be as perfect as that of the CT scan. Lastly, this study has a relatively small sample size. However, it was a randomized controlled study that achieved significant improvement in nasal symptoms and radiologic findings.

CONCLUSION

The use of low-concentration HOCl nasal irrigation for 4 weeks in pediatric chronic sinusitis was found to be more effective than isotonic normal saline for improving x-ray findings. Therefore, we suggest that low-concentration HOCl nasal irrigation is a useful adjuvant management method for pediatric sinusitis.

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