Comparison of Sinus Distribution between Nasal irrigation and Nasal spray Using Fluorescein-labeled in patients with Chronic Rhinosinusitis: A Randomized Clinical Trial

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Abstract

Objective : This study aims to compare the potential sinus distribution between high-volume nasal irrigation and nasal spray in chronic rhinosinusitis patients who have not undergone sinus surgery. Design and Setting : A randomized clinical study was conducted at the Otolaryngology-Head & Neck Surgery Department, Ramathibodi Hospital, Faculty of Medicine, Mahidol University. Participants : 40 patients undergoing endoscopic sinus surgery for chronic rhinosinusitis. Thirty-eight patients met the inclusion criteria and were randomly assigned to receive nasal irrigation or nasal spray mixed with fluorescein sodium preoperatively. Main outcome measures : The primary outcome was the mean difference in the staining score of fluorescein in all sinuses between the two groups. Results : The total staining score of fluorescein in all sinuses via nasal irrigation was statistically more significant than the score via nasal spray, with a mean difference score of 2.90, 95%CI: 1.22-4.58, p-value 0.001. The most significantly affected sinuses were specific to the maxillary and anterior ethmoid sinuses, whereas the frontal and sphenoid sinuses had the slightest solution distribution from both techniques. Conclusion : Nasal irrigation is a potential route to deliver drugs into the sinus in unoperated CRS patients. However, it is not considered a superior method to nasal spray at the most challenging anatomical areas, i.e., the frontal and sphenoid sinuses. Keywords : Corticosteroid use, Endoscopic sinus surgery, Irrigations, Topical therapy for chronic rhinosinusitis, Medical therapy for chronic rhinosinusitis, Nasal polyp, Nasal spray, Chronic rhinosinusitis

Abstract

Objective: This study aims to compare the potential sinus distribution between high-volume nasal irrigation and nasal spray in chronic rhinosinusitis (CRS) patients who have not undergone sinus surgery.

Design and Setting: A randomized clinical study was conducted at "Blinded for review".

Participants: Forty patients undergoing endoscopic sinus surgery for CRS. Thirty-eight patients met the inclusion criteria and were randomly assigned to receive nasal irrigation or nasal spray mixed with fluorescein sodium preoperatively.

Main outcome measures : The primary outcome was the mean difference in the staining score of fluorescein in all sinuses between the two groups.

Results: The total staining score of fluorescein in all sinuses via nasal irrigation was statistically more significant than the score via nasal spray, with a mean difference score of 2.90, 95%CI: 1.22-4.58, p -value 0.001. The most significantly affected sinuses were specific to the maxillary and anterior ethmoid sinuses, whereas the frontal and sphenoid sinuses had the slightest solution distribution from both techniques.

Conclusion: Nasal irrigation is a potential route to deliver drugs into the sinus in unoperated CRS patients. However, it is not considered a superior method to nasal spray at the most challenging anatomical areas, i.e., the frontal and sphenoid sinuses.

Keywords: Corticosteroid use, Endoscopic sinus surgery, Irrigations, Topical therapy for chronic rhinosinusitis, Medical therapy for chronic rhinosinusitis, Nasal polyp, Nasal spray,Chronic rhinosinusitis

Key points

- Most effective topical therapy gives the CRS patients a lower chance of invasive intervention in terms of sinus surgery.
- The modification of the delivery system has been developed focusing on the distribution method of the drug into the sinus.
- Nasal irrigation is a potential route to administer drugs into the sinus in unoperated CRS patients.
- The overall sinus distribution of nasal irrigation had significantly more superiority than the nasal spray.
- This intervention brings the advantage of opportunely providing anti-inflammatory medications into the sinus using a one-step approach for initial CRS treatment.

Introduction

While there is a growing trend to use corticosteroid nasal irrigation instead of spray in

postoperative care after endoscopic sinus surgery (ESS)**(1-8)** , there is some, albeit very limited evidence that supports this application as an initial treatment before sinus surgery as being the superior method. A few previous studies investigated the concept of sinus distribution on pre-surgical sinus cavities with the aim of determining the most effective methods to deliver the medicine into the sinus.**(9-11)** Unfortunately, the results from the studies could not show any significant benefit of nasal irrigation in sinus penetration. However, most studies were conducted in either healthy subjects or cadavers, which could not represent the actual status of pathological sinus cavities and dynamic physiology while rinsing the sinus.**(9, 10)** Furthermore, one study examining sinus penetration in unoperated chronic rhinosinusitis (CRS) patients used low-volume nasal irrigation, which could not represent the ideal volume to enhance sinus penetration even in the post-surgical sinus status.**(11)**

Therefore, according to such knowledge gap, this study aims to compare the sinus distribution of high-volume nasal irrigation and nasal spray to determine the effective route for drug administration before sinus surgery in CRS patients.

Methods

Study design and setting

This study was a randomized clinical trial conducted at "Blinded for review". The study was approved by the local ethical committee and was conducted in accordance with the ethical standards of the Declaration of Helsinki. The reporting trials have been followed the CONSORT guideline.

Participants

CRS patients over 18 years old who indicated and were scheduled for ESS between

January 2020-August 2021 were enrolled in this study. The diagnosis of CRS was based on the criteria according to a European position paper on rhinosinusitis and nasal polyps.**(12)** The exclusion criteria included patients with underlying diseases that affect mucociliary function, i.e., cystic fibrosis, ciliary dyskinesia, previous radiotherapy at head and neck regions, patients who had previous sinonasal surgery or sinonasal tumors, patients who had evidence of sinus aplasia or severe deviated nasal septum on computerized tomography (CT) scan, pregnant women, patients who had allergic to fluorescein and who refused to participate in the study.

All patients underwent preoperative CT scan of the nose and paranasal sinuses, and Lund-Mackay (LM) staging system **(13)** , was assessed for each nasal cavity separately. Nasal endoscopic exam was carried out to distinguish phenotype features, CRS with nasal polyp (CRSwNP) and CRS without nasal polyp (CRSsNP). In addition, the participants completed the Thai Sinonasal Outcome Test 22 items (SNOT-22)**(14)** on the admission date for a baseline assessment.

Study interventions

Patients who met the eligible criteria were then randomized into two groups by a

computer-generated randomized sequence with a block size of four. Sequentially numbered sealed opaque envelopes were provided to the independent investigators

Patients in the nasal irrigation group received a mixture of 250 mL of normal saline solution and 10% fluorescein sodium 10 mL, irrigated 125 mL each nostril, using a syringe of 20 mL (contain a volume of 25 mL) (Terumo, Tokyo, Japan) with a nozzle, 30 minutes before entering the operating room. Patients in the nasal spray group received a mixture of corticosteroid suspension and 10% fluorescein sodium 10 mL, utilizing a single-use mometasone nasal spray bottle (Sandoz, Ljubljana, Slovenia), with 2 puffs sprayed into each nostril 30 minutes before entering the operating room. The trained in-charge nurses supervised and instructed all the patients to bend their heads forward, 30-45 degrees, to the vertical plane during irrigation and spray. After receiving the interventions, the patients were asked to sit upright until they could lay down in the operating room, preparing for anesthesia.

Surgical techniques

All patients underwent ESS under general anesthesia and video recorded by either a blinded

rhinologist staff or a fellowship-trained rhinologist supervised by rhinologist staff. The sinuses were sequentially opened into the common cavity fashion: uncinectomy and middle meatal antrostomy, anterior and posterior ethmoidectomy, sphenoidotomy and frontal sinusotomy (Draf IIa). The blue-light filter system with 0, 45, and 70-degree nasal endoscopes (Karl Storz, Tuttlingen, Germany) were applied during video record at each interesting anatomical area, including the OMU, maxillary sinus, anterior and posterior ethmoid air cells, sphenoid sinus and frontal sinus, respectively aiming to examine the degree of fluorescein stain. The normal saline irrigation and the application of cotton pledget were not allowed to be used during the procedure. Patients with significant intraoperative bleeding must be excluded from the data analysis due to fluorescein obscuring.

Outcome measurements

The primary outcome was the mean difference in the fluorescein staining score under a

blue-light filter system in all interesting areas between the two groups. The distribution of fluorescein at each interesting area was graded from the video record independently by two blinded assessors. The degree of fluorescein stain was graded according to a study by Harvey RJ. et al.**(9)** which grade 0 was defined as no staining of fluorescein on the sinus cavity, grade 1 was partial staining of fluorescein (present on one wall of the sinus cavity), grade 2 was staining of fluorescein on two or more walls of the sinus cavity, and grade 3 was pooling of fluorescein in the sinus cavity.**(Figure 1)**

The secondary outcomes included the mean differences in the staining score of

fluorescein under a blue-light filter system in each area and subgroup analysis according to the phenotype features, CRSwNP and CRSsNP, and the severity of the disease by the LM staging system.

Statistical analysis

The sample size of this study was estimated according to a study by Harvey RJ. et al.**(9)** , determining the sample size based on two independent mean formulas using type I error (alpha) of 0.05 and a power of 0.8. The authors consider the sample size of 70 in total numbers as the most appropriate to detect a significant

difference between groups. Further, data loss was estimated at 15%; the final estimation for the total sample size was 80. Each side of the paranasal sinus system representing its distinct fluorescein stain; thus, the sample size in the study was defined as the number by the side of the nostril with reference to 40 subjects in total.

Baseline characteristics were described using mean and standard deviation for continuous variables and percentage for categorical variables. Interrater reliability testing for fluorescein grading scores by two assessors was determined by the concordance correlation coefficient. The comparison of outcomes was performed using a linear mixed-effects model for analysis. All analyses were performed using Stata version 13.0 (StataCorp, College Station, TX). All test statistics were reported in terms of magnitude of effect with mean difference and 95% confident interval (CI), where a p -value of less than 0.05 was considered statistically significant.

Results

Participant flow and baseline characteristics

Forty patients were enrolled in the study. However, two patients were excluded due to a

history of previous sinus surgery. Thirty-eight patients were randomized to receive nasal irrigation (n=19, 38 sides) or nasal spray (n=19, 38 sides). Five sides of the nasal cavity were excluded for data analysis due to significant perioperative bleeding. Finally, there were 19 subjects with 36 sides in the nasal irrigation group and 19 subjects with 35 sides in the nasal spray group for the intention-to-treat analysis.**(Figure 2)** Of these 38 participants, the baseline characteristics were balanced between two groups, as shown in **Table 1** .

Total staining score of fluorescein in all anatomical areas

The concordance correlation coefficient to determine the interrater reliability for the

grading score was 0.98. The total staining score of fluorescein in all anatomical areas in the nasal irrigation group was statistically more significant than that of the nasal spray group, with a mean difference score of 2.90, 95%CI:1.22-4.58, p -value 0.001.**(Table 2)**

Staining score of fluorescein in each anatomical area

In the nasal irrigation group, the staining score of fluorescein was statistically significantly higher at the maxillary sinus (mean difference=1.38, 95%CI:0.83-1.93, p -value <0.001) and anterior ethmoid sinus (mean difference=0.53, 95%CI:0.13-0.93, p -value 0.009). The rest of the sinuses had no significant difference in fluorescein staining.**(Table 2)**

Subgroup analysis according to the phenotype features, CRSwNP and CRSsNP

For both phenotype features, CRSwNP and CRSsNP, the nasal irrigation had a better

distribution of fluorescein with statistical significance, however the effect size was greater in CRSsNP patients (CRSwNP; mean difference=2.28, 95%CI:0.33-4.23, p -value 0.02 and CRSsNP; mean difference=4.36, 95%CI:1.44-7.27, p -value 0.003).**(Table 3)**

Subgroup analysis according to the severity of the disease by the LM staging system

According to the LM staging system, where participants were placed into three sub-

categories, mild disease was defined as the LM score of 0-3; moderate disease was defined with a score of between 4-8, and severe disease was more than 8. The nasal irrigation had a significantly better sinus distribution in moderate sinus disease (mean difference=2.61, 95%CI:0.22-5.00, p -value 0.03) and severe sinus disease (mean difference=2.96, 95%CI:0.48-5.44, p -value 0.02).**(Table 4)**

Discussion

Saline irrigation has been paramount for CRS treatment, with its role recently being

considered as a vehicle to deliver anti-inflammatory drugs into the sinus. The sinus ostium is not the sole targeted area for medical exposure, but the distribution of the drug to the sinus mucosa is also key to restoring the disease. Thus, the modification of the delivery system has been developed with a much greater focus on the distribution method of the drug into the sinus cavity. There has been a growing amount of robust evidence on the administration of corticosteroids via nasal irrigation with respect to technically distributing medication into the sinus and clinically improving symptoms; however, most studies to date have been conducted on post-surgical sinus status.**(2-5)** Therefore, corticosteroid nasal irrigation as an initial treatment before the sinus surgery has not been adopted as a general practice. Clinically, Jiramongkolchai P. et al.**(15)** recently conducted a randomized controlled trial that showed the comparable efficacy of corticosteroid irrigation and spray in CRSsNP patients who have not undergone sinus surgery regarding the improvement of SNOT-22 scores. In addition, Tait et al.**(16)** carried out another randomized controlled trial to investigate the efficacy of large-volume, low-pressure corticosteroid irrigation compared with a placebo in CRS patients, of which 70% of patients in the study never had any sinus surgery. The authors reported that the mean change of SNOT-22 scores from baseline was greater for the treatment group in the subgroup of patients who had no prior sinus surgery; however, the results were not significantly different.

Regarding the technical concept, some publications investigated the extent of sinus

distribution among the delivery system in the unoperated sinus.**(9-11, 17)** However, most studies have been done on the cadavers, and in healthy subjects, which might not sufficiently represent the actual physiology of diseased sinuses and the natural mechanisms of oropharyngeal functions during sinus irrigation. Moreover, the role of the mucociliary function that might impact the sinus penetration of the solution was one of the biases from previous studies. Wormald PJ. et al.**(10)** reported the restriction of radioactivity via nuclear medicine imaging in unopened sinus cavities on healthy control subjects. Most radioactivity appeared in the maxillary sinuses from nasal douching, while there no radioactivity was detected in any sinus cavity from the spray and nebulizer techniques. Harvey RJ. et al.**(9)** conducted a study on cadavers and reported a significant limitation of contrast distribution in unoperated sinuses, particularly in sphenoid and frontal sinuses, regardless of the delivery technique. Another study conducted in the pathological sinuses by Grobler A. et al.**(17)** found that both unoperated sinuses and sinuses with a small sinus ostium even after sinus surgery had unreliable penetration. However, the results of this study were not compared with the other delivery methods. The following research by Snidvongs K. et al.**(11)** utilized a comparative study between nasal irrigation and nasal spray. Nevertheless, they used low-volume nasal irrigation and found neither the nasal irrigation nor the nasal spray could enhance sinus penetration in the unopened sinus.

The present study's advantage was the fact that it was designed to dynamically evaluate

the potential sinus distribution of different delivery methods in actual pathological sinuses. In addition, the alternative intervention that was intended to be investigated has been proven as a gold standard in terms of high-volume irrigation to deliver drugs into the opened sinus cavity.**(6)** This study confirmed that the overall sinus distribution of nasal irrigation had significantly more superiority than the nasal spray with the conclusive effect size. In addition, the effect of nasal irrigation could create a greater sinus distribution in each anatomical site. However, consistent with previous studies, the maxillary and anterior ethmoid sinuses were the most significantly affected areas.**(9,10)** The OMU was the area that could reach the solution regardless of the delivery method. The rest of the sinuses, particularly the frontal and sphenoid sinuses, had the least significant solution distribution from both techniques. These limitations were explained by their anatomical locations, which sit at the most posterior and superior parts of the paranasal sinus system. Also, the bony septation and the sinus pathology under the unoperated sinus were critical barriers blocking the flow pathway. In the subgroup analysis, the difference in sinus distribution between the two methods was significantly greater, and remarkable in the moderate to severe sinus diseases, in which nasal irrigation had a better result. In the CRSwNP patients, nasal irrigation, regardless, provided significantly greater overall sinus distribution than nasal spray but had less significant effect than the CRSsNP subgroup.

Theoretically, saline irrigation has mechanisms as removing crust and mucous, reducing

antigen load, enhancing ciliary beat, and response for a vehicle to deliver the drugs into the sinus. This intervention brings the advantage of opportunely providing anti-inflammatory medications into the sinus using a one-step approach, resulting in more satisfactory compliance of the patients. Furthermore, sufficient therapy duration might help relieve inflammation at the OMU, maxillary and ethmoid sinuses, ultimately promoting the distribution of the drug into the most challenging parts, i.e., the frontal and sphenoid sinuses. Fortunately, as per the updated evidence, the adverse events of corticosteroid irrigation showed no serious effects, even in long-term use.**(18-20)**

The limitation of this study was that sinus penetration of a solution can be influenced by

multiple factors, not only the delivery technique, and such factors, i.e., the head position and the surgical status of the sinus cavity, were beyond the context of this study. In addition, finding of this study could not represent the symptomatic outcomes in clinical applications and could not entirely be used as a substitute for the standard therapy. Therefore, using corticosteroid irrigation as the initial treatment for CRS in selected phenotypes, i.e., moderate to high severity sinus diseases on CT scan or CRSsNP, might potentially benefit clinical outcomes. Further study on specific phenotypes or even endotypes might increase the extension of clinical application.

Conclusion

Nasal irrigation is a potential route to administer drugs into the sinus in unoperated CRS

patients. Patients with phenotyping of moderate to high severity disease of sinuses and the CRSsNP might benefit from having drugs delivered into the sinus via nasal irrigation. However, the alternative technique is not superior to using nasal spray at the most challenging anatomical areas, i.e., the frontal and sphenoid sinuses.

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Table 1. Baseline characteristics

	Nasal irrigation (n=19, 36 sides)	**Nasal spray** (n=19, 35 sides)	*p*-**value**
Age (mean+SD)	53.74+17.09	47.58+16.89	0.27
Male (n, %)	5 (26.32%)	11 (57.89%)	0.05
Allergic rhinitis (n, %)	4 (21.05%)	5 (26.32%)	1.00
Asthma (n, %)	8 (42.11%)	4 (21.05%)	0.16
Current smoking (n, %)	0	1 (5.26%)	1.00
Nasal polyp (n, %)	14 (73.68%)	14 (73.68%)	1.00
SNOT-22 (mean+SD)	26.95+13.63	31.74+15.64	0.32
Lund-Mackey CT score (mean+SD)	15.32+5.76	13.21+5.33	0.25

Table 2.Fluorescein staining score at all anatomical areas and each area between groups

	Nasal irrigation (mean+SE)	**Nasal spray** (mean+SE)	**Mean difference (95%CI)**	*p*-**value**
All anatomical areas	6.59+0.60	3.69+0.61	2.90 (1.22, 4.58)	**0.001**
OMU	1.80+0.17	1.41+0.17	0.39 (-0.09, 0.87)	0.12
Maxillary sinus	1.90+0.20	0.52+0.20	1.38 (0.83, 1.93)	**<0.001**
Anterior ethmoid sinus	1.24+0.14	0.71+0.15	0.53 (0.13, 0.93)	**0.009**
Posterior ethmoid sinus	0.84+0.13	0.51+0.13	0.34 (-0.03, 0.70)	0.07
Sphenoid sinus	0.52+0.14	0.35+0.14	0.16 (-0.23, 0.55)	0.41
Frontal sinus	0.30+0.11	0.19+0.11	0.11 (-0.21, 0.42)	0.51

Table 3. Subgroup analysis of fluorescein staining according to the phenotype features, CRSwNP and CRSsNP

	Nasal irrigation (mean+SE)	**Nasal spray** (mean+SE)	**Mean difference (95%CI)**	***p*-value**
CRSsNP				
All anatomical areas	7.33+1.05	2.97+1.05	4.36 (1.44, 7.27)	**0.003**
OMU	2.14+0.30	1.45+0.30	0.69 (-0.13, 1.51)	0.98
Maxillary sinus	2.16+0.34	0.21+0.34	1.95 (1.00, 2.89)	**<0.001**
Anterior ethmoid sinus	1.34+0.25	0.55+0.25	0.79 (0.08, 1.49)	**0.03**
Posterior ethmoid sinus	0.95+0.23	0.37+0.23	0.58 (-0.06, 1.21)	0.08
Sphenoid sinus	0.46+0.25	0.19+0.25	0.27 (-0.42, 0.95)	0.45
Frontal sinus	0.40+0.20	0.18+0.20	0.21 (-0.33, 0.76)	0.44
CRSwNP				
All anatomical areas	6.28+0.70	4.00+0.71	2.28 (0.33, 4.23)	**0.02**
OMU	1.65+0.20	1.39+0.20	0.26 (-0.29, 0.81)	0.36
Maxillary sinus	1.79+0.23	0.65+0.23	1.14 (0.50, 1.77)	**<0.001**
Anterior ethmoid sinus	1.20+0.17	0.78+0.17	0.42 (-0.05, 0.89)	0.08
Posterior ethmoid sinus	0.80+0.15	0.57+0.15	0.23 (-0.19, 0.66)	0.29
Sphenoid sinus	0.54+0.16	0.42+0.17	0.12 (-0.34, 0.58)	0.61
Frontal sinus	0.25+0.13	0.19+0.13	0.06 (-0.31, 0.43)	0.75

Table 4. Subgroup analysis of fluorescein staining according to the severity of the disease by the Lund-Mackay (LM) staging system

	Nasal irrigation (mean+SE)	**Nasal spray** (mean+SE)	**Mean difference (95%CI)**	***p*-value**
Mild disease (LM 0-3)				
All anatomical areas	6.90+1.98	2.75+1.82	4.15 (-1.14, 9.43)	0.12
OMU	2.39+0.53	1.50+0.51	0.89 (-0.54, 2.32)	0.22
Maxillary sinus	2.56+0.64	0.00+0.56	2.56 (0.90, 4.22)	**0.003**
Anterior ethmoid sinus	1.90+0.54	0.50+0.40	1.40 (0.08, 2.71)	**0.04**
Posterior ethmoid sinus	- 0.04+0.44	0.25+0.39	0.29 (-0.85, 1.44)	0.62
Sphenoid sinus	0.19+0.47	0.00 +0.41	0.19 (-1.04, 1.42)	0.76
Frontal sinus	1.17+0.31	0.50+0.33	0.33 (-0.56, 1.23)	0.47
Moderate disease (LM 4-8)				
All anatomical areas	6.49+0.94	3.88+0.77	2.61 (0.22, 5.00)	**0.03**

	Nasal irrigation (mean+SE)	**Nasal spray** (mean+SE)	**Mean difference (95%CI)**	***p*-value**
OMU	1.78+0.26	1.50+0.21	0.27 (-0.39, 0.93)	0.42
Maxillary sinus	1.97+0.30	0.55+0.25	1.42 (0.67, 2.18)	**<0.001**
Anterior ethmoid sinus	1.02+0.21	0.80+0.18	0.22 (-0.33, 0.77)	0.43
Posterior ethmoid sinus	0.84+0.20	0.50+0.17	0.34 (-0.17, 0.85)	0.19
Sphenoid sinus	0.61+0.21	0.37+0.18	0.24 (-0.31, 0.78)	0.39
Frontal sinus	0.20+0.17	0.15+0.14	0.05 (-0.37, 0.48)	0.80
Severe disease (LM 9-12)				
All anatomical areas	6.63+0.80	3.67+0.98	2.96 (0.48, 5.44)	**0.02**
OMU	1.76+0.22	1.22+0.27	0.53 (-0.15, 1.21)	0.12
Maxillary sinus	1.79+0.25	0.64+0.31	1.14 (0.36, 1.93)	**0.004**
Anterior ethmoid sinus	1.34+0.18	0.63+0.24	0.71 (0.13, 1.29)	**0.02**
Posterior ethmoid sinus	0.93+0.17	0.61+0.21	0.32 (-0.21, 0.85)	0.23
Sphenoid sinus	0.48+0.18	0.43+0.23	0.05 (-0.52, 0.62)	0.86
Frontal sinus	0.37+0.14	0.16+0.17	0.21 (-0.22, 0.65)	0.33