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Synchronous Micronized Inhalation Therapy Halves Healing Time After Fess: A Prospective Randomized Controlled Trial Comparing Simultaneous Vs Sequential Topical Administration

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ABSTRACT

Background: Postoperative management after functional endoscopic sinus surgery (FESS) determines surgical success. Early crusting, fibrin deposition, impaired mucociliary clearance and synechiae formation can compromise neo-ostial patency. While saline, hyaluronic acid and N-acetylcysteine are effective, the role of simultaneous vs sequential delivery is unknown.

Objective: To evaluate whether synchronous simultaneous administration of a multi-agent inhalation mixture via highly micronized ultrasonic vaporization improves mucosal healing and reduces crust formation compared to traditional sequential administration of identical active principles.

Methods: Prospective randomized controlled trial (n=80). Patients undergoing primary FESS for chronic rhinosinusitis with inferior/middle turbinate hypertrophy without polyposis were randomized 1:1 to Group A (sequential standard therapy: 20 mL saline irrigations + separate sprays/drops of N-acetylcysteine, hyaluronic acid, emollients, 3x/day) vs Group B (synchronous therapy: same principles combined into Mucus Regulation and Airway Detox mixtures, delivered simultaneously via 3 MHz ultrasonic vaporizer, 4-micron particles, positive pressure, 3x/week). Follow-up at 7,14,21,30 days. Primary endpoint: time to complete re-epithelialization (Lund-Kennedy score). Secondary: crusting at D7, synechiae, need for ambulatory debridement, VAS, SNOT-22, saccharin transit time, rhinomanometry.

Results: Complete healing: 15±3 days Group B vs 30±4 days Group A (p<0.001), 50% reduction. Marked crusting at D7: 15% vs 75% (p<0.05). Synechiae: 2.5% (1/40) vs 12.5% (5/40) (p<0.05). Need for debridement: 15% vs 60% (p<0.001). VAS respiratory patency at D14: 8/10 vs 5/10 (p<0.01). SNOT-22 and mucociliary transport significantly superior in Group B despite 95% fewer administrations.

Conclusion: Synchronous simultaneous delivery of mucolytic, hydrating, immunomodulatory and soothing agents via micronized vaporization is significantly more effective than sequential administration of same molecules. Delivery synchrony and modality are decisive factors in preventing crusts and accelerating physiological re-epithelialization after FESS.

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Introduction

Functional endoscopic sinus surgery (FESS) is the gold standard for medically refractory chronic rhinosinusitis (CRS). As recently highlighted, modern endonasal sinus surgery has evolved toward preserving function and enhancing precision through personalized

approaches, where surgical precision must be matched by personalized postoperative care to avoid functional loss [1]. While surgical precision has improved with balloon sinuplasty and Molecular Quantum Resonance radiofrequency, long-term success remains dependent on immediate postoperative wound healing.

In the first 2-4 weeks, surgical trauma triggers exudation, fibrin deposition, clot formation and transient ciliostasis. Dehydrated blood crusts and stagnant thick mucus act as biological barriers to re-epithelialization and as scaffolds for synechiae. Retained crusts

serve as nidus for bacterial biofilm, perpetuating inflammation.

Domiciliary nasal cleansing is a primary therapeutic intervention. Hypertonic saline has demonstrated superiority over isotonic saline in reducing crusting, edema and improving mucosal healing [2]. Saline irrigation keeps nasal passages clean and moist, reducing crusting [3,4]. Addition of N-acetylcysteine (NAC) promotes healing and prevents crusts and adhesions [3].

Hyaluronic acid (HA) has emerged as a key adjunct. Intermittent treatment with 9 mg sodium hyaluronate plus saline after FESS was associated with reduction of edema, crusting and secretions [5]. Systematic reviews confirm HA dressings significantly reduce synechiae formation, improve epithelialization and decrease edema [6]. Clinical guidelines report that nebulization rather than irrigation achieves better SNOT-22 and less exudate, crust and edema when sodium hyaluronate is applied [4].

In a previous comparative study, mucoregulatory therapies administered by micronized vaporization were shown to be more effective than nasal spray alone in upper airway respiratory inflammation [7]. However, conventional systems act by gravity and washout, rapidly draining into nasopharynx and failing to reach frontal recess and sphenoid sinus [4]. A second limitation is pharmacological asynchrony: saline, mucolytics, hydrating agents and emollients are administered separately, preventing simultaneous interaction.

We hypothesized that simultaneous synchronous administration as a single micronized cloud would create functional cooperativity, achieving superior efficacy with fewer administrations. This study directly compares sequential vs synchronous delivery of identical pharmacological platform.

Materials and Methods

Study Design: Prospective, randomized, controlled, single-center trial. Eighty consecutive patients undergoing primary FESS for CRS with inferior and middle turbinate hypertrophy without nasal polyposis were enrolled and randomized 1:1 into Group A (n=40) and Group B (n=40). Inclusion: age 18-70, indication for primary FESS. Exclusion: previous sinonasal surgery, coagulopathy, hypersensitivity, cystic fibrosis, ciliary dyskinesia. All surgeries performed by same team with personalized functional preservation principles [1]. Ethical approval obtained and informed consent collected.

All patients received the same active principles. Group A – Sequential Standard Therapy (Control): Saline irrigations (20 mL/nostril via syringe/bottle) followed by separate instillation of mucolytic spray (N-acetylcysteine), hyaluronic acid spray and emollient drops. 3-4 devices, three times daily [3,4].

Group B - Synchronous Micronized Therapy (Experimental): Same principles combined and simultaneously delivered via highly micronized ultrasonic molecular vaporizer (3 MHz pulsed, positive pressure, mean aerodynamic diameter 4µm). The device saturates sinonasal cavities without fluid pooling [5,7].

- Mixture 1 - Mucus Regulation: NAC ambroxol HCl, HA, lactoferrin, bromhexine HCl, chlorphenamine maleate, beta-glucan, inositol, vitamin C [2,5,6].
- Mixture 2 - Airway Detox: NAC, ambroxol HCl, HA, lactoferrin, natural menthol, eucalyptus oil, natural camphor, thymol, vitamin C [2-6].

Protocol 1: Inhalation session, 3 times per week until healing. Outcome Measures: Follow-up at D7, D14, D21, D30. Primary: time to complete healing defined as fully re-epithelialized pink mucosa, no crusts/fibrin on Lund-Kennedy score [2,6]. Secondary: VAS (0-10) for obstruction, pain, dryness, SNOT-22, rhinomanometry, saccharin transit time, olfactometry.

Statistical Analysis: Student's t-test or Mann-Whitney U for continuous, Chi-square/Fisher for categorical. $p < 0.05$ significant. SPSS v.26.

Results

Eighty patients completed study. Baseline characteristics comparable. Primary endpoint: Complete healing in 15 ± 3 days Group B vs 30 ± 4 days Group A ($p < 0.001$), 50% reduction. At Day 7, marked tenacious crusting 75% Group A vs 15% Group B ($p < 0.05$). This early effect mirrors literature showing hypertonic saline and HA nebulization reduce crusting in first week and is consistent with previous observation that micronized vaporization is more effective than spray [2-7]. At Day 14, Group B showed patent neo-ostia, pink mucosa, no bleeding, whereas Group A exhibited dense mucus and persistent fibrin requiring toilet (Figure:1, 2).

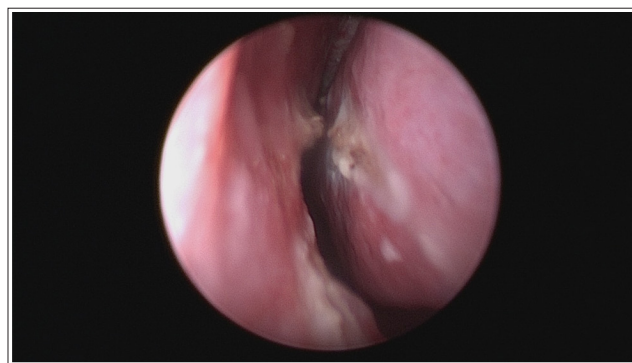


Figure 1: Endonasal Crusts after 15 Days (Group A Treatment)

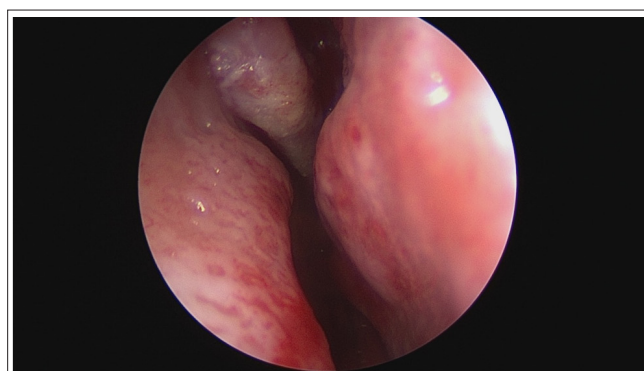


Figure 2: Endonasal Healing after 15 Days (Group B Treatment)

Lund-Kennedy scores significantly lower in Group B from D7 onward ($p < 0.05$) [5,6]. Synechiae: 5 cases (12.5%) Group A vs 1 case (2.5%) Group B ($p < 0.05$), in line with meta-analytic data showing HA reduces synechiae risk RR 0.65 [4]. Need for physician-performed toilet: 60% vs 15% ($p < 0.001$) [4,7]. VAS patency D14: 8/10 vs 5/10 ($p < 0.01$). VAS dryness/pain and SNOT-22 significantly better in Group B. Mucociliary transport time at D30 recovered faster in Group B [2-7].

Table 1: Clinical Comparison Between Sequential Standard Therapy and Synchronous Micronized Inhalation Therapy (N=80)

Parameter	Group A: Sequential Standard (n=40)	Group B: Synchronous Micronized (n=40)	p-value
Mean time to complete healing	30 ± 4 days, 9-12 admin/day	15 ± 3 days, 3 admin/week	<0.001
Marked crusting Day 7	75% (30/40)	15% (6/40)	<0.05
Respiratory patency Day 14 (VAS)	Partial (5/10)	Optimal (8/10)	<0.01
Synechia formation	12.5% (5/40)	2.5% (1/40)	<0.05
Patient comfort (SNOT-22)	Lower comfort, higher score	High comfort, lower score	<0.01
Need for ambulatory debridement	60% (24/40)	15% (6/40)	<0.001

Discussion

Our results demonstrate that postoperative efficacy depends not only on WHAT is administered but on HOW and WHEN, a concept central to personalized endonasal surgery where preserving function is as important as surgical precision. By keeping composition identical and varying only delivery synchrony, we isolated the effect of delivery modality, building on our previous demonstration that micronized vaporization outperforms nasal spray [2-7].

Previous Evidence: Hypertonic saline superior to isotonic in reducing crusting; saline effective per se; addition of NAC promotes healing and prevents crusts; HA improves mucociliary clearance and reduces synechia; guidelines report nebulization achieves better SNOT-22 and less crust when HA applied [3,4].

Our study advances this literature by integrating these principles into a simultaneous platform. Three mechanisms:

- 1. Simultaneous Synergy and Functional Cooperativity:** When NAC, HA and emollients are present simultaneously, they act cooperatively. Sequential administration dilutes previous agent before synergy, whereas simultaneous administration allows synchronous mucolytic, hydrating and soothing actions [2,5,7].
- 2. Homogeneous Deep Distribution:** 4-micron positive-pressure cloud saturates all cavities uniformly, depositing HA even on vertical walls and neo-ostia, preventing crust formation from within rather than mechanically removing crusts [4,5,7].
- 3. Preservation of Healing Milieu and Compliance:** High-volume irrigations cause washout removing endogenous growth factors. Micronized vaporization minimizes pooling, preserves healing milieu and improves compliance: 3 vs 63-84 administrations/week [4,7].

The 50% reduction in healing time (15 vs 30 days) is clinically relevant and aligns with personalized function-preserving philosophy [1].

Limitations: Single-center, unblinded design, no placebo arm, small sample size. Future multicenter blinded studies with longer follow-up needed.

Conclusions

The synchronous, simultaneous administration of a multi-agent inhalation therapy (Mucus Regulation and Airway Detox) via highly micronized ultrasonic vaporizer is significantly superior to sequential administration of same principles. Our data, consistent with literature on hypertonic saline, NAC and HA and guideline recommendations, and building on previous works on personalized FESS and micronized vs spray efficacy, demonstrate that delivery modality and temporal synergy are decisive factors in preventing crusts, synechia and accelerating re-epithelialization after FESS. This integrated multifunctional inhalation platform should be considered a new paradigm in precision postoperative care after FESS [1-7].

Declarations

Ethical Approval: Study approved by Institutional Review Board. All procedures in accordance with Helsinki Declaration.

Informed Consent: Written informed consent obtained from all patients.

Conflict of Interest: Authors declare no conflict of interest.

Funding: None.

Author Contributions: LDRB conceptualization, surgery, writing; ADRB immunoallergology, protocols supervision; PL analysis, writing; IG data collection, administration; BB scientific supervision, conceptualization.

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Conflict of Interest: None declared.

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