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Efeito da irrigação nasal com budesonida em pacientes com rinossinusite crônica com pólipos nasais sem cirurgia prévia

Um estudo randomizado, duplo-cego, controlado por placebo

Dissertação apresentada ao Curso de Pós Graduação da Faculdade de Ciências Médicas da Santa Casa de São Paulo para obtenção do Título de **Mestre(a)** em **Pesquisa em Cirurgia**.

Área de Concentração: **Pesquisa em Cirurgia**

Orientador: **Marcel Menon Miyake**

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Para mim Juliana, nada disso teria sido possível sem meus pais. Obrigada pelo apoio imensurável desde meus primeiros passos.

“Nunca existiu uma grande inteligência sem uma veia de loucura”

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Abreviaturas e Símbolos

CCCRC — *Connecticut Chemosensory Clinical Research Center* (teste olfatório de Connecticut)
EVA — Escala Visual Analógica
IC — Intervalo de Confiança
ITT — *Intention-to-treat* (análise por intenção de tratar)
LMS — *Lund-Mackay Score* (Escore tomográfico de Lund-Mackay)
mg — miligrama
NPS — *Nasal Polyp Score* (Escore de Pólipo Nasal)
p — valor de p (significância estatística)
% — porcentagem
± — mais ou menos (indica variação em torno da média, geralmente desvio padrão)
RSCcPN — Rinossinusite crônica com pólipos nasais
SNOT-22 — *Sinonasal Outcome Test* de 22 itens

Sumário

Resumo

Introdução: A indicação da irrigação nasal com corticoides após a cirurgia sinusal em pacientes com rinossinusite crônica com pólipos nasais (RSCcPN) é bem estabelecida, uma vez que a cirurgia facilita a distribuição por toda a cavidade nasossinusal. No entanto, ainda não se sabe se essa abordagem poderia também oferecer benefício terapêutico antes da cirurgia. Este estudo tem como objetivo comparar o efeito da irrigação nasal com budesonida versus solução salina em pacientes com RSCcPN sem cirurgia prévia.

Métodos: Foi realizado um estudo randomizado, duplo-cego, controlado por placebo, em pacientes com RSCcPN sem cirurgia sinusal prévia. Os pacientes foram randomizados para receber irrigação nasal com 1 mg de budesonida ou solução salina duas vezes ao dia durante quatro semanas. O desfecho primário foi a variação no questionário SNOT-22 (Sinonasal Outcome Test de 22 itens). Os desfechos secundários incluíram a escala visual analógica (EVA), o escore de Pólipo Nasal (NPS), o teste olfatório de Connecticut (CCCRC) e o escore tomográfico de Lund-Mackay (LMS).

Resultados: Um total de 52 pacientes foi randomizado (idade média de 50,1 ± 12,9 anos; 51,9% do sexo feminino). A análise por intenção de tratar (ITT) mostrou que o grupo de irrigação nasal com budesonida apresentou melhora significativa no SNOT-22 [diferença média: 18,1 pontos (IC 95%: 3,4 a 32,8); $p = 0,017$], na EVA [diferença média: 2,24 pontos (IC 95%: 3,6 a 4,13); $p = 0,020$] e no NPS [diferença média: 0,73 pontos (IC 95%: 0,25 a 1,21); $p = 0,003$]. Não foi observada diferença entre os grupos no CCCRC e no LMS.

Conclusão: A irrigação nasal com budesonida pode ser uma ferramenta importante para o controle dos sintomas nasossinusais em pacientes com RSCcPN que não são candidatos à cirurgia sinusal ou que aguardam tratamento cirúrgico.

Palavras-chave: Sinusite; Pólipos Nasais; Irrigação Nasal; Corticoides; Cirurgia dos Seios Paranasais; Qualidade de Vida.

Introdução

A rinossinusite crônica com pólipos nasais (RSCcPN) é uma doença inflamatória crônica das vias aéreas superiores caracterizada por inflamação persistente da mucosa nasossinusal associada à presença de pólipos nasais bilaterais. Estima-se que essa condição acometa aproximadamente 2 a 4% da população geral e esteja associada a impacto significativo na qualidade de vida, incluindo obstrução nasal crônica, hiposmia ou anosmia, distúrbios do sono e comprometimento das atividades diárias. Além disso, a doença apresenta comportamento recorrente e elevada morbidade, sendo considerada um desafio terapêutico relevante na prática clínica otorrinolaringológica (1–3).

Nas últimas décadas, avanços no entendimento da fisiopatologia da RSCcPN demonstraram que a doença está frequentemente associada a um padrão inflamatório do tipo 2, caracterizado por infiltração eosinofílica, aumento da expressão de citocinas como interleucina-4, interleucina-5 e interleucina-13, além de alterações estruturais da mucosa nasossinusal. Esse processo inflamatório crônico favorece o remodelamento tecidual, a formação e recorrência dos pólipos nasais e a persistência dos sintomas, mesmo após intervenções terapêuticas consideradas adequadas. Nesse contexto, a literatura atual enfatiza que o controle sustentado da inflamação local é um dos principais objetivos do tratamento da doença (2,3).

Do ponto de vista terapêutico, os corticosteroides permanecem como a principal estratégia farmacológica no manejo da RSCcPN. O uso de corticosteroides orais demonstra elevada eficácia na redução do volume polipoide e na melhora clínica, especialmente em exacerbações ou em casos de maior gravidade. Entretanto, seu perfil de efeitos adversos sistêmicos limita a utilização prolongada, o que reforça a necessidade de estratégias terapêuticas eficazes e seguras para controle da doença em longo prazo (4).

Nesse cenário, os corticosteroides intranasais em forma de spray representam a terapia de manutenção mais amplamente utilizada, devido ao seu perfil de segurança favorável. Contudo, estudos demonstram que a efetividade dessa via de administração pode ser limitada em pacientes com pólipos nasais volumosos ou doença mais extensa. Isso ocorre, em grande parte, pela baixa penetração do medicamento nas regiões mais profundas das cavidades nasossinusais,

além do reduzido volume administrado, o que compromete a distribuição adequada do fármaco na mucosa inflamada (5,6).

Quando o tratamento clínico otimizado não resulta em controle satisfatório dos sintomas, a cirurgia endoscópica funcional dos seios paranasais (Functional Endoscopic Sinus Surgery – FESS) é indicada. Esse procedimento tem como objetivo remover os pólipos nasais, restaurar a ventilação e drenagem dos seios paranasais e facilitar o acesso das terapias tópicas à mucosa nasossinusal. Embora a cirurgia represente um avanço importante no manejo da doença, estudos demonstram que a recorrência dos pólipos não é incomum, especialmente em pacientes com perfil inflamatório mais intenso, associado a comorbidades como asma, que reforça a necessidade de estratégias adjuvantes eficazes no controle da inflamação local (7).

Nesse contexto, a irrigação nasal com soluções de alto volume tem sido progressivamente incorporada ao manejo da rinossinusite crônica. Evidências sugerem que esse método proporciona melhor distribuição da solução nas cavidades nasais e nos seios paranasais, além de promover remoção mecânica de secreções, mediadores inflamatórios e partículas inaladas, contribuindo para melhora da função mucociliar e redução da carga inflamatória local (8,9).

Mais recentemente, a associação de irrigação nasal com corticosteroides tópicos tem sido amplamente investigada, particularmente no período pós-operatório da FESS. Estudos clínicos demonstram que essa estratégia pode resultar em melhora significativa dos sintomas, melhor controle inflamatório e redução das taxas de recorrência quando comparada ao uso isolado de sprays intranasais. A principal hipótese que sustenta esses achados está relacionada à maior capacidade de distribuição do medicamento nas cavidades nasossinusais proporcionada pelo alto volume da irrigação (8–11).

Adicionalmente, estudos prévios sugerem que a irrigação nasal com corticosteroide apresenta um perfil de segurança favorável, com mínima absorção sistêmica e baixa incidência de efeitos adversos clinicamente significativos. Esses achados reforçam o potencial dessa abordagem como estratégia terapêutica aplicável em diferentes cenários clínicos, incluindo pacientes ainda não submetidos à cirurgia (4).

Apesar desses avanços, uma análise crítica da literatura evidencia que a maior parte dos estudos disponíveis foi conduzida em populações previamente submetidas à cirurgia endoscópica dos

seios paranasais. Nesses casos, a modificação anatômica resultante do procedimento favorece a penetração das soluções irrigadoras e potencializa a ação das terapias tópicas. Consequentemente, a extrapolação desses resultados para pacientes que não foram submetidos à cirurgia endoscópica funcional dos seios paranasais ainda permanece limitada.

Essa lacuna no conhecimento é particularmente relevante, uma vez que muitos pacientes com rinossinusite crônica com pólipos nasais permanecem em tratamento clínico prolongado antes de eventual indicação cirúrgica. Além disso, uma parcela significativa desses pacientes apresenta resposta limitada ou refratária ao tratamento convencional com corticosteroides tópicos em spray nasal, que atualmente constitui a terapia de primeira linha. Nesse contexto, estratégias terapêuticas capazes de melhorar a deposição e a distribuição dos corticosteroides na cavidade nasal e nos seios paranasais, como a irrigação nasal medicada, podem representar uma alternativa promissora para otimizar o controle da doença. No entanto, ainda há uma lacuna na literatura quanto à superioridade dessa abordagem em comparação ao uso tradicional de sprays nasais, especialmente em pacientes que não foram submetidos à cirurgia.

Diante disso, torna-se fundamental investigar a eficácia dessa abordagem em pacientes ainda não submetidos à cirurgia. Assim, o presente estudo foi desenvolvido com o objetivo de avaliar o impacto da irrigação nasal com budesonida, em comparação à irrigação com solução salina, na qualidade de vida de pacientes com rinossinusite crônica com pólipos nasais que não foram submetidos à cirurgia endoscópica funcional dos seios paranasais

Objetivos

Objetivo primário:

Avaliar a eficácia da irrigação de solução isotônica tópica intranasal contendo cloreto de sódio e bicarbonato de sódio associado a budesonida (2 mg/dia) por quatro semanas comparada a solução isotônica tópica intranasal contendo cloreto de sódio e bicarbonato de sódio associado a placebo, em participantes com RSCcPN que nunca foram submetidos a cirurgia sinusal prévia, baseada na melhora subjetiva de sintomas, avaliada pelo Sinonasal Outcome Test (SNOT)-22.

Objetivos secundários:

- Avaliar a eficácia da irrigação de solução tópica intranasal isotônica associada a budesonida (2 mg/dia) por quatro semanas comparada a solução tópica intranasal isotônica associada ao placebo, em participantes com RSCcPN que nunca foram submetidos a cirurgia sinusal prévia, baseada na melhora objetiva dos achados da endoscopia nasal, avaliada pelo Nasal Polyp Score (NPS).

- Avaliar a eficácia da irrigação de solução tópica intranasal isotônica associada a budesonida (2 mg/dia) após quatro semanas comparada a solução tópica intranasal isotônica associada ao placebo, em participantes com RSCcPN que nunca foram submetidos a cirurgia sinusal prévia, baseada nos achados pós-tratamento da tomografia computadorizada de seios da face, avaliada pelo score de Lund-Mackay (LMS).

- Avaliar a eficácia da irrigação de solução tópica intranasal isotônica associada a budesonida (2mg/ dia) após quatro semanas comparada a solução tópica intranasal isotônica associada ao placebo, em participantes com RSCcPN que nunca foram submetidos a cirurgia sinusal prévia, baseada nas alterações olfatorias avaliadas pelo teste olfatório desenvolvido pela Connecticut Chemosensory Clinical Research Center (CCCRC).

- Avaliar a eficácia da irrigação de solução isotônica tópica intranasal contendo cloreto de sódio e bicarbonato de sódio associada ao placebo por quatro semanas comparada aos escores basais, em participantes com RSCcPN que nunca foram submetidos a cirurgia sinusal prévia, baseada na melhora subjetiva de sintomas, avaliada pela Escala Visual e Analógica (EVA).

- Avaliar a segurança da irrigação de solução tópica intranasal isotônica associada a budesonida (2 mg/dia) por quatro semanas comparada a solução tópica intranasal isotônica associada ao placebo, em participantes com RSCcPN que nunca foram submetidos a cirurgia sinusal prévia, baseada nos reportes ocorridos durante as 4 semanas de uso dos medicamentos.

Métodos

Desenho de estudo e participantes

Ensaio clínico randomizado, duplo-cego, controlado por placebo, com objetivo de comparar a eficácia da irrigação nasal com budesonida (2 mg/dia) versus placebo em pacientes com RSCcPN não submetidos à FESS. Os participantes foram recrutados no ambulatório do Departamento de Otorrinolaringologia da Santa Casa de São Paulo entre 2019 e 2024. O protocolo do estudo foi aprovado pelo Comitê de Ética em Pesquisa da Santa Casa de São Paulo (CAE 13229319.9.0000.5479), todos os participantes assinaram termo de consentimento livre e esclarecido.

Critérios de inclusão e exclusão

Foram incluídos pacientes diagnosticados RSCcPN primária difusa de acordo com os critérios do EPOS 2020 (1), refratários ao tratamento clínico com spray nasal de corticoesteróide tópico. Tais critérios englobam os fenótipos de rinossinusite crônica eosinofílica (eCRS) e rinossinusite fúngica alérgica (AFRS). Embora a doença atópica do compartimento central (CCAD) também seja classificada como um tipo de rinossinusite crônica primária difusa do tipo 2, ela não foi

incluída. A doença respiratória exacerbada por aspirina (AERD), apesar de ser considerada um fenótipo de rinossinusite crônica secundária, também foi incluída.

Os critérios de inclusão compreenderam escore endoscópico mínimo de pólipos nasais de 2 em cada narina, escore basal no SNOT-22 ≥ 30, e pelo menos dois dos seguintes sintomas por um período mínimo de 12 semanas: obstrução nasal ou secreção nasal (anterior ou posterior), dor ou pressão facial e redução ou perda do olfato. (1)

Os critérios de exclusão incluíram cirurgia endoscópica prévia dos seios paranasais, tratamento prévio ou atual com biológicos (anti-IgE, anti-IL-4, anti-IL-5), uso atual de terapia imunossupressora, uso de antibióticos nas quatro semanas anteriores à inclusão, ou doença sinonasal associada a condições sistêmicas, como imunodeficiência, vasculite de Churg–Strauss, granulomatose com poliangiite, doenças autoimunes ou doenças do tecido conjuntivo. Também foram excluídos pacientes com anormalidades anatômicas que pudessem impedir a irrigação nasal eficaz (desvio septal obstrutivo, atresia de coana ou obstrução completa da cavidade nasal por pólipos), história de herpes ocular, gestação ou amamentação, hipersensibilidade conhecida à budesonida, glaucoma, ou uso de corticosteroides sistêmicos ou intranasais tópicos nas duas semanas anteriores à inclusão (ou que não aceitassem suspender tais medicações). Além disso, pacientes incapazes ou não dispostos a fornecer consentimento informado ou a cumprir os procedimentos do estudo não foram considerados elegíveis.

Participantes com asma puderam manter sua terapia habitual com corticosteroides inalatórios; no entanto, qualquer paciente que necessitasse de corticosteroides sistêmicos durante o estudo foi retirado do protocolo.

Intervenção

Após confirmação da elegibilidade e conclusão do período de *washout* — definido como duas semanas para corticosteroides intranasais em spray e quatro semanas para corticosteroides sistêmicos (via oral, intravenosa ou intramuscular) — os participantes foram randomizados na proporção 1:1 para o grupo intervenção (budesonida) ou grupo controle (placebo). A randomização foi realizada por uma farmácia de pesquisa independente, utilizando sequência

aleatória gerada por computador e alocação em blocos de tamanho variável (blocos de 10). A lista de randomização permaneceu restrita ao farmacêutico responsável pela preparação e dispensação das soluções, garantindo ocultação da alocação. Participantes, pesquisadores responsáveis pelo acompanhamento clínico e avaliadores dos desfechos permaneceram cegos quanto à alocação dos grupos durante todo o estudo.

O grupo intervenção recebeu solução glicerinada de budesonida a 1% (0,5 mg por gota), enquanto o grupo controle recebeu solução de glicerina a 5%, idêntica em cor, aparência, sabor e embalagem, garantindo o adequado mascaramento entre os grupos. A formulação para irrigação nasal composta por glicerina a 5% e budesonida a 1% é amplamente utilizada na prática clínica no Brasil, principalmente devido ao menor custo e maior disponibilidade em comparação com outras preparações comerciais (11).

Para o preparo da solução de irrigação, os participantes foram orientados a preencher o frasco aplicador com 240 mL de água filtrada, adicionar um sachê de solução salina e duas gotas da solução designada (budesonida ou placebo). Considerando que cada gota da solução de budesonida contém 0,5 mg do fármaco, cada preparo de irrigação resultava em uma dose de 1 mg de budesonida. Aproximadamente metade do volume preparado (120 mL) foi utilizada para irrigação de cada cavidade nasal. O procedimento foi realizado duas vezes ao dia, durante quatro semanas, em ambiente domiciliar, resultando em uma dose total diária de 2 mg de budesonida no grupo intervenção. A primeira administração foi realizada no hospital, sob supervisão da equipe de pesquisa, com o objetivo de padronizar a técnica de irrigação, assegurar a correta utilização do dispositivo e verificar a ausência de obstrução nasal significativa que pudesse comprometer a administração da solução.

As soluções foram armazenadas em temperatura ambiente controlada (15 °C–30 °C), em seus frascos originais e protegidas da luz. Cada participante recebeu gratuitamente um kit padronizado de irrigação nasal, composto por um frasco aplicador reutilizável e 60 sachês de solução salina. O kit incluía ainda um manual ilustrado com orientações passo a passo sobre a técnica de irrigação nasal medicamentosa, além de um calendário de 30 dias para registro diário das irrigações realizadas, utilizado para monitoramento da frequência de uso e da adesão ao tratamento.

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Todos os medicamentos, dispositivos e materiais utilizados no estudo foram fornecidos sem custo aos participantes. Além disso, foi disponibilizado auxílio financeiro no valor de 27 reais por visita presencial, destinado a cobrir despesas relacionadas a transporte e alimentação, com o objetivo de reduzir barreiras logísticas e favorecer a participação no estudo.

Com o intuito de reforçar a adesão ao protocolo e esclarecer eventuais dúvidas, foi realizado contato telefônico padronizado uma semana após a inclusão no estudo. Durante essa ligação, os participantes foram questionados sobre a realização adequada da irrigação nasal, possíveis dificuldades relacionadas ao tratamento e preenchimento do calendário de registro das doses.

Os participantes foram avaliados presencialmente em visitas de acompanhamento após duas e quatro semanas de tratamento. Em cada visita, foram coletados desfechos subjetivos e objetivos previamente definidos no protocolo do estudo, incluindo SNOT-22, o CCCRC, a EVA para sintomas nasais e o NPS. Foi estabelecido critério mínimo de adesão ao tratamento para permanência no estudo, definido como a não omissão de mais de uma dose por semana.

A segurança da intervenção foi monitorada de forma sistemática ao longo do estudo. Em todas as visitas presenciais, os participantes foram ativamente questionados quanto à ocorrência de eventos adversos. Adicionalmente, foi realizado exame físico padronizado, incluindo avaliação clínica geral e aferição de sinais vitais, com o objetivo de monitorar possíveis efeitos adversos associados à intervenção.

Desfechos

O **desfecho primário** foi a mudança no escore do SNOT-22 do momento basal até quatro semanas. O SNOT-22 é um questionário validado composto por 22 itens que avaliam sintomas sinonasais, com escores variando de 0 a 110 (escores mais altos indicam maior gravidade) e uma diferença clinicamente importante mínima (MDIC) de 14 pontos (12).

Os **desfechos secundários** incluíram a gravidade dos sintomas relatados pelos pacientes por meio de uma escala visual analógica (0–10 cm) para sintomas sinonasais globais (13). Como atualmente não existe uma MDIC validada para uma EVA global sinonasal, adotamos um limiar provisório de 1 ponto na escala de 0 a 10. Esse limiar representa aproximadamente 10% da escala total, consistente com MDICs estabelecidas para instrumentos EVA em outras condições respiratórias e baseadas em sintomas, além de proporcionalmente alinhado com a MDIC validada do SNOT-22 (aproximadamente 11% da sua escala total) (14–16).

O escore endoscópico de pólipos nasais foi avaliado em uma escala de 0 a 4 por narina (0–8 no total). A pontuação foi realizada por dois rinologistas independentes e cegos quanto à alocação dos grupos, utilizando gravações endoscópicas revisadas centralmente. Além do valor numérico do NPS, os avaliadores também forneceram um julgamento subjetivo de melhora entre os diferentes momentos de avaliação. Uma mudança de 1 ponto foi considerada a MDIC, em consonância com estudos prévios (17–19).

Por fim, o escore de Lund–Mackay foi avaliado por meio de tomografia computadorizada dos seios paranasais realizada ao final da intervenção, sendo pontuado por um avaliador independente e cego quanto à alocação, em uma escala de 0 a 24, na qual escores mais elevados indicam maior grau de opacificação dos seios paranasais (20).

Avaliação de segurança

A segurança e a tolerabilidade foram avaliadas por meio do monitoramento de eventos adversos, sinais vitais e exame físico em todas as visitas do estudo.

Análise estatística

Todas as análises seguiram o princípio de intenção de tratar (*intention-to-treat*). Dados ausentes foram imputados utilizando o método da última observação carregada adiante (*last observation carried forward*). As características basais foram resumidas de forma descritiva.

A normalidade dos desfechos contínuos foi avaliada pelo teste de Shapiro–Wilk; como os desfechos (SNOT-22, VAS, NPS e CCCRC) não apresentaram distribuição normal, as comparações entre os grupos quanto à mudança do basal até a Semana 4 foram realizadas por meio do teste de Mann–Whitney U. O teste do qui-quadrado foi utilizado para comparar a proporção de pacientes que atingiram a diferença clinicamente importante mínima (MDIC).

Para avaliar se características demográficas e clínicas (idade, sexo, raça, asma, alergia ambiental, sensibilidade à aspirina, profissão e tabagismo) modificaram o efeito da intervenção sobre os escores do SNOT-22, foram ajustados modelos de regressão linear multivariada para desfechos contínuos e modelos de regressão logística para desfechos binários. Cada modelo incluiu um termo de interação entre o grupo de tratamento e a covariável de interesse. Efeitos de interação com $p < 0,10$ foram considerados indicativos de possível modificação de efeito.

O cálculo do tamanho da amostra foi baseado no SNOT-22, utilizando uma MDIC de 14 pontos derivada da validação em português do Brasil (12), desvio-padrão de 21,95, $\alpha = 0,05$ e poder estatístico de 80%. Considerando uma taxa de perda de seguimento de 20%, foi estimada a necessidade mínima de 26 pacientes por grupo (7,21).

As análises foram realizadas no SPSS versão 26 (IBM, Armonk, NY), sendo considerado significativo $p < 0,05$, exceto para os termos de interação conforme descrito acima.

Resultados

Effect of Budesonide Nasal Irrigation in Patients With Chronic Rhinosinusitis With Nasal Polyps Without Prior Sinus Surgery: A Randomized, Double-Blind, Placebo-Controlled Study

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Abstract

Background: The indication for nasal irrigation with corticosteroids after sinus surgery in patients with Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) is well established, as surgery facilitates distribution throughout the sinonasal cavity. However, it remains unknown whether this approach could also provide therapeutic benefit prior to surgery. This study aims to compare the effect of budesonide versus saline nasal irrigation in surgically naive CRSwNP patients.

Methods: A randomized, double-blind, placebo-controlled parallel-group study was conducted in 52 patients with diffuse type 2 CRSwNP with no previous sinus surgery. Patients were randomized to receive either 1 mg budesonide or saline nasal irrigation twice daily for four weeks. The primary outcome was the change in the 22-item Sinonasal Outcome Test (SNOT-22). Secondary outcomes included the Visual Analogue Scale (VAS), Nasal Polyp Score (NPS), and the Connecticut (CCCRC) olfactory test.

Results: A total of 52 patients were randomized (mean age 50.1 ± 12.9 years; 51.9% female). The intention-to-treat (ITT) analysis showed that the budesonide nasal irrigation group

demonstrated a significantly greater improvement in SNOT-22 (mean difference: 18.1 points [95% CI: 3.4 to 32.8; p = 0.017]), VAS (mean difference 2.24 points [95% CI: 0.35 to 4.13; p = 0.018]) and NPS (mean difference: 0.73 points [95% CI: 0.25 to 1.21]; p = 0.003). No significant differences were observed between groups in CCCRC.

Conclusion: Budesonide nasal irrigation may be an important tool for controlling sinonasal symptoms in patients with CRSwNP who are not candidates for sinus surgery or while awaiting surgical treatment.

1. Background

Chronic rhinosinusitis with nasal polyps (CRSwNP) is an inflammatory disease of the upper airways affecting approximately 2%–4% of the general population, associated with substantial morbidity and a marked negative impact on quality of life. Management is challenging due to high rates of refractoriness and recurrence [1–3].

Oral corticosteroids are considered the gold standard for medical treatment but are limited by systemic side effects, restricting their use to short courses [4]. Intranasal corticosteroid sprays, while safer, have limited efficacy in patients with extensive polyps because the small spray volume and low penetration fail to adequately reach polyp surfaces and the inflamed sinonasal mucosa [5]. Persistent symptoms despite medical therapy often lead to functional endoscopic sinus surgery (FESS) to remove polyps, restore sinonasal ventilation and facilitate topical steroid distribution [6].

High-volume, low-pressure nasal irrigation with corticosteroid diluted in isotonic saline is a well-established adjunctive therapy after FESS. Surgery improves mucosal exposure, and the larger drug volume enhances sinonasal deposition and local bioavailability compared with sprays, allowing delivery to deeper recesses and polyp surfaces inaccessible to conventional devices. These advantages translate into improved symptom control and reduced recurrence without increasing systemic side effects, despite the higher administered dose. Theoretically, patients who did not respond to clinical treatment with intranasal corticosteroid spray and who would otherwise be referred for FESS could benefit from corticosteroid nasal irrigation, since

the greater volume, dose, and distribution achieved through irrigation have been demonstrated in patients who have already undergone surgery; but this intervention is still poorly studied [7–10]. Therefore, this study aims to compare the effect of budesonide versus saline nasal irrigation in surgically naïve CRSwNP patients, assessing short- term symptom improvement through validated patient-reported outcome measures and objective assessments.

2. Methods

2.1 Study Design and Participants

This was a randomized, double-blind, placebo-controlled clinical trial designed to compare the efficacy of isotonic saline nasal irrigation combined with budesonide (1 mg) versus placebo in patients with CRSwNP who had never undergone endoscopic sinus surgery. Participants were recruited from the outpatient clinic of the Department of Otolaryngology, Santa Casa de São Paulo, between 2019 and 2024. The study protocol was approved by the Institutional Review Board of Santa Casa de São Paulo (CAE 13229319.9.0000.5479), and written informed consent was obtained from all participants.

2.2 Inclusion and Exclusion Criteria

Patients included in the study had a diagnosis of primary diffuse CRSwNP, according to EPOS 2020 criteria [3], which encompasses the phenotypes of eosinophilic CRS (eCRS) and allergic which encompasses the phenotypes of eCRS and allergic fungal rhinosinusitis (AFRS). Although central compartment atopic disease (CCAD) is also classified as a type-2 primary diffuse CRS, it was not included. Aspirin-exacerbated respiratory disease (AERD), despite being considered a secondary CRS phenotype, was also included. Inclusion criteria included a minimum endoscopic nasal polyp score (NPS) of 2 in each nostril, a baseline Sino-Nasal Outcome Test-22 (SNOT-22) score ≥30, and at least two of the following symptoms for a minimum of 12 weeks: Nasal obstruction or discharge (anterior or posterior), facial pain or pressure, and a reduced or lost sense of smell.

Exclusion criteria included prior endoscopic sinus surgery, pre- vious treatment with biologics (anti-IgE, anti-IL-4, anti-IL-5), current use of immunosuppressive therapy, antibiotic use within 4 weeks prior to enrollment, or sinonasal disease associated with systemic conditions such as

immunodeficiency, Churg– Strauss vasculitis, granulomatosis with polyangiitis, autoimmune disease, or connective tissue disorders. Patients with anatomical abnormalities that could prevent effective nasal irrigation (obstructive septal deviation, choanal atresia, or complete nasal cavity obstruction by polyps), history of ocular herpes, pregnancy or breastfeeding, known hypersensitivity to budesonide, glaucoma, or use of systemic or topical nasal corticosteroids within 2 weeks prior to inclusion (or unwillingness to discontinue such medications) were also excluded. In addition, patients unable or unwilling to provide informed consent or comply with study procedures were not eligible.

Participants with asthma were allowed to continue their regular inhaled corticosteroid therapy; however, any patient requiring systemic corticosteroids during the study was withdrawn.

2.3 Intervention

Following eligibility confirmation and completion of a washout period—2 weeks for any intranasal corticosteroid sprays or 4 weeks for any systemic corticosteroids (oral, intravenous, or intramuscular)—participants were randomized (1:1) to the intervention group (budesonide) or the control group (placebo). Randomization was performed by a research pharmacy in blocks of 10, with variable block sizes, using a computer-generated sequence. Only the pharmacist was aware of group allocation; participants and study staff remained blinded throughout.

The intervention group received glycerinated budesonide solution 1% (0.5 mg/per drop), while the control group received 5% glycerin solution identical in color, appearance, taste, and packaging. The nasal irrigation formulation composed of 5% glycerin and 1% budesonide is widely employed in clinical practice in Brazil, primarily due to its lower cost and greater availability compared to other commercial preparations [11]. Solutions were stored at controlled room temperature (15° C–30° C) in their original light- protected containers. Each patient received a nasal irrigation kit containing one applicator bottle and 60 saline sachets. For preparation, participants were instructed to fill the applicator with 240 mL of filtered water, add one sachet and two drops of the assigned solution. Approximately half of the prepared volume (120 mL) was irrigated into each nostril twice daily for four weeks at home. The first dose of treatment was administered at the hospital under supervision to ensure correct technique and to verify that no nasal obstruction would interfere with the administration. All study medications and devices were provided free of charge.

Participants attended follow-up visits at two and four weeks. At each visit, subjective and objective outcomes were collected and adverse events were assessed. The following outcome measures were obtained: SNOT-22, “Connecticut Chemosensory Clinical Research Center” (CCCRC) smell test, visual analog scale (VAS), and NPS. Patients were permitted to miss no more than one dose per week to remain in the study.

2.4 Outcomes

The primary endpoint was the change in SNOT-22 score from baseline to four weeks. The SNOT-22 is a validated 22-item questionnaire assessing sinonasal symptoms, with scores ranging from 0 to 110 (higher scores indicate greater severity) and a minimal clinically important difference (MCID) of 14 points [12].

Secondary endpoints included patient-reported symptom severity using a Visual Analogue Scale (VAS; 0–10 cm) for global sinonasal symptoms [13]. Since there is currently no validated MCID for a global sinonasal VAS, we adopted a provisional threshold of 1 point on the 0–10 scale. This threshold represents approximately 10% of the total scale, consistent with established MCIDs for VAS instruments in other respiratory and symptom-based conditions, and proportionally aligned with the validated SNOT-22 MCID (∼11% of its total scale) [14–16]. Endoscopic NPS was assessed on a scale from 0 to 4 per nostril (0–8 total). Scoring was performed by two independent, blinded rhinologists using centrally reviewed endoscopy recordings. In addition to the numerical NPS, review- ers provided a subjective judgment of improvement between time points. A 1-point change was considered the MCID, consistent with prior studies [17–19]. Finally, Lund–Mackay Score (LMS) was evaluated on sinus CT performed at the end of the intervention, scored by an independent blinded reviewer on a scale from 0 to 24, with higher scores indicating greater opacification [20].

2.5 Safety Assessment

Safety and tolerability were assessed by monitoring adverse events, vital signs, and physical examination at all study visits.

2.6 Statistical Analysis

All analyses followed the intention-to-treat principle. Missing data were imputed using last observation carried forward. Base- line characteristics were summarized descriptively. Normality of continuous outcomes was assessed with the Shapiro–Wilk test; as outcomes (SNOT-22, VAS, NPS, CCCRC) were not normally distributed, between-group comparisons of change from baseline to Week 4 were performed with the Mann–Whitney U test. The chi-square test was used to compare the proportion of patients achieving the MCID. To assess whether demographic and clinical characteristics (age, sex, race, asthma, environmental allergy, aspirin sensitivity, profession, and smoking status) modified the effect of the intervention on SNOT-22 scores, multivariable linear regression models were fitted for continuous outcomes and logistic regression models for binary outcomes. Each model included an interaction term between the treatment group and the covariate of interest. Interaction effects with $p < 0.10$ were considered indicative of potential effect modification. Sample size estimation was based on the SNOT-22, using an MCID of 14 points derived from the Brazilian-Portuguese validation [12], a standard deviation of 21.95, $\alpha = 0.05$ and 80% power. Considering a 20% dropout rate, a minimum of 26 patients per group was required [7, 21]. Analyses were performed in SPSS v26 (IBM, Armonk, NY), with $p < 0.05$ considered significant, except for interaction terms as noted above.

3. Results

3.1 Participants

Overall, 58 patients were recruited, of whom 52 underwent randomization (Figure 1). A total of 43 patients completed the study — 26 in the budesonide group and 17 in the placebo group. All patients were actively questioned about the use of rescue corticosteroids throughout the entire follow-up period, and no patient reported having used them. Demographic and base- line clinical characteristics were generally comparable between groups (Table 1).

Figure 1 | Patients Enrolled and Included in the Analysis

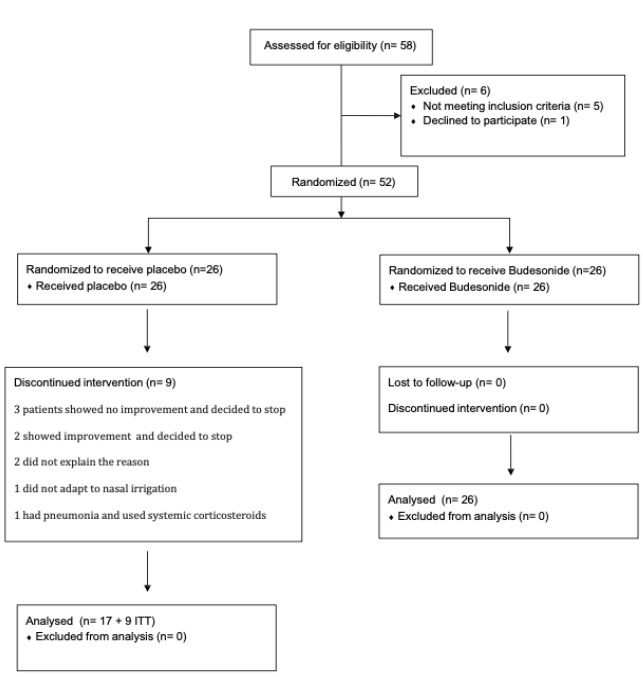

TABLE 1 | Baseline demographic and clinical characteristics of patients in the placebo and budesonide groups.

	Placebo ($n = 26$)	**Budesonide ($n = 26$)**
Age, mean (SD)	46,5 (12.1)	53,8 (13.7)
Male sex, No. (%)	11 (42.3)	14 (53.8)
White race, No. (%)	12 (46.2)	11 (42.3)
African American race, No. (%)	5 (19.2)	4 (15.4)
Asian race, No. (%)	0 (0)	1 (3.8)
Asthma, No. (%)	13 (50.0)	10 (38.5)
Environmental allergy, No. (%)	16 (61.5)	18 (69.2)
Aspirin sensitivity, No. (%)	2 (7,6)	3 (11.5)
Profession with exposure to toxic aerosols, No. (%)	8 (30.8)	7 (26.9)
Smoking, No. (%)	3 (11.5)	3 (11.5)

Note: Data are presented as mean (standard deviation) for continuous variables and number (percentage) for categorical variables.

3.2 Primary End Point (Table 2) Sinonasal Outcome Test (SNOT-22)

3.2.1 Sinonasal Outcome Test (SNOT-22)

After 4 weeks, the intention-to-treat analysis showed a mean improvement of −33.2 points [95% CI: −38.7 to −27.6] in the budesonide group and −15.1 points [95% CI: −20.0 to −10.2] in the placebo group (Figure 2). The between-group difference was 18.1 points [95% CI: 3.4 to 32.8; $p = 0.017$], significantly favor- ing budesonide. Clinically meaningful improvement, defined as

exceeding the MCID, was observed in 19 of 26 patients (73.1%) in the budesonide group and 8 of 26 (30.8%) in the placebo group ($p = 0.049$).

3.3 Secondary End Points (Table 2)

3.3.1 Visual Analog Scale

Patients treated with budesonide also showed greater benefit on VAS scores. After 4 weeks, mean improvement was −3.53 points [95% CI: −5.1 to −1.94] in the budesonide group compared with −1.29 points [95% CI: −2.48 to −0.97] in the placebo group, yielding a between-group difference of 2.24 points [95% CI: 0.352 to 4.13; $p = 0.018$] (Figure 2). Clinically significant improvement beyond the MCID was achieved by 20 of 26 patients (76.9%) in the budesonide group and 13 of 26 (50.0%) in the placebo group ($p = 0.044$).

3.3.2 Nasal Polyp Score

Inter-rater reliability was strong ($\kappa = 0.805$; $p < 0.001$). After 4 weeks, mean reduction in NPS was −0.67 points [95% CI: −0.92 to −0.42] in the budesonide group versus −0.06 points [95% CI: −0.33 to 0.21] in the placebo group. The mean between-group dif- ference was 0.73 points [95% CI: 0.25 to 1.21; $p = 0.003$], confirming a statistically and clinically significant superiority of budesonide over placebo (Figure 2). Clinically relevant improvement was observed in 20 of 26 patients (76.9%) in the budesonide group compared with 13 of 26 (50.0%) in the placebo group ($p = 0.04$).

3.3.3 CCCRC Test

Changes in olfactory function, as measured by the CCCRC test, did not differ significantly between groups. At 4 weeks, the mean improvement was +0.58 points [95% CI: −0.12 to 1.28] in the budesonide group compared with +0.34 points [95% CI: −0.41 to 1.09] in the placebo group, resulting in a between- group difference of 0.24 points [95% CI: −0.72 to 1.20; $p = 0.63$] (Figure 2). While the difference was not statistically significant, a higher proportion of patients in the budesonide group achieved improvement exceeding the MCID, 11 of 26 (42.3%) versus 6 of 26 (23.1%) in the placebo group ($p = 0.139$).

3.3.4 Lund–Mackay Score

At the end of the 4-week treatment period, 23 patients in the budesonide group underwent computed tomography, with a mean Lund–Mackay score of 15.7 [SD 2.4]. In the placebo group, 14 patients were evaluated, showing a mean score of 12.8 [SD 2.4]. The mean between- group difference was 2.9 points [95% CI, −2.04 to 7.84; $p = 0.25$], suggesting greater disease severity in the budesonide group.

3.3.5 Interaction Analysis

No significant interactions were observed between SNOT-22 outcomes and any of the demographic or clinical characteristics evaluated (age, sex, race, asthma, environmental allergy, aspirin sensitivity, profession, or smoking status).

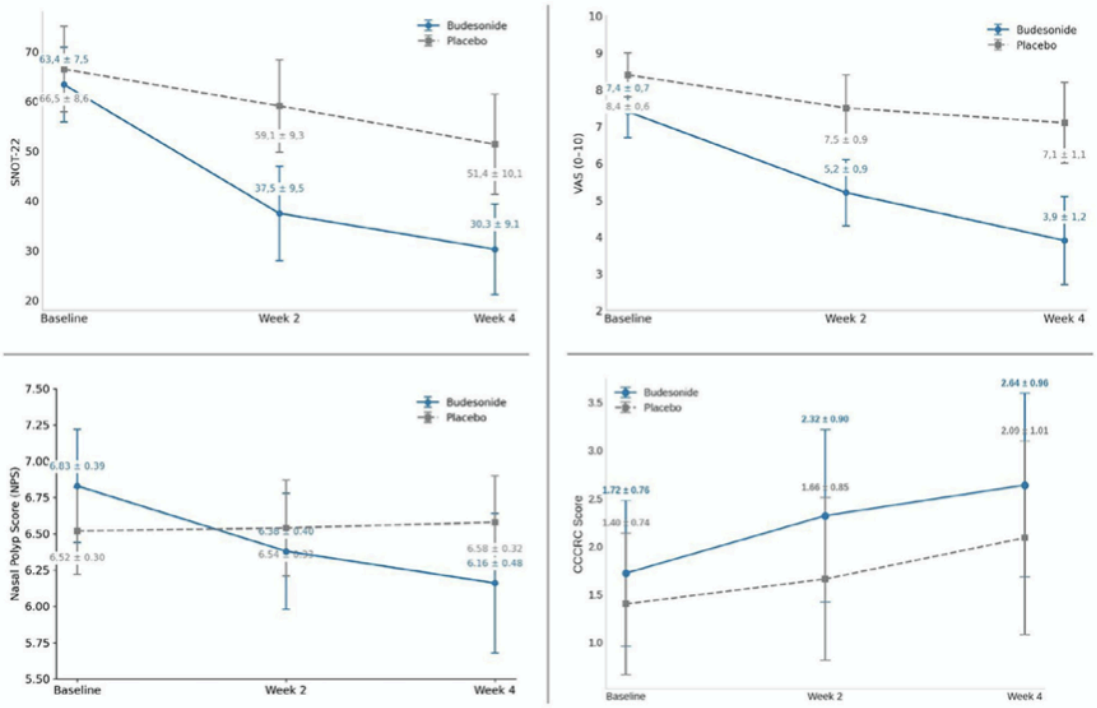

FIGURE 2 | Primary and secondary end points for all patients. The *p*-value reflects the comparison of mean changes between groups from baseline to week 4. Error Bars indicates the 95% CI.

TABLE 2 | Outcomes of primary and secondary endpoints in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) treated with budesonide nasal irrigation versus placebo.

	Budesonide ($n = 26$)			Placebo ($n = 26$)			
	Baseline, Mean (SD)	Week 4, Mean (SD)	Absolute Change From Baseline, LS Mean (95% CI)	Baseline, Mean (SD)	Week 4, Mean (SD)	Absolute Change From Baseline, LS Mean (95% CI)	Absolute Difference for Budesonide vs. Control, LS Mean (95% CI)	*p*-value
Primary End Point								
SNOT 22	63.4 (19.5)	30.3 (23.7)	**−33.15 (−44.84 to −21.47)**	66.5 (22.3)	51.4 (26.3)	−15.08 (−25.20 to −4.95)	**18.07 (3.37 to 32.77)**	**0.020**
Secundary End Points								
VAS	7.43 (1.81)	3.9 (3.02)	**−3.52 (−5.11 to −1.41)**	8.36 (1.66)	7.07 (2.88)	−1.28 (−2.48 to −0.97)	**−2.23 (−4.12 to −0.35)**	**0.018**
NPS	6.83 (1.01)	6.16 (1.24)	**−0.67 (−1.09 to −0.25)**	6.52 (0.78)	6.58 (0.83)	0.06 (−0.23 to 0.35)	**−0.73 (−1.21 to −0.25)**	**0.003**
CCCRC	1.72 (1.99)	2.64 (2.49)	**0.92 (0.23 to 1.62)**	1.40 (1.93)	2.09 (2.63)	0.68 (−0.06 to 1.42)	**0.24 (−1.20 to 0.72)**	**0.565**
LMS[a]	—	15.7 (2.4)	—	—	12.8 (2.4)	—	**2.90 (−2.04 to 7.84)**	**0.250**

Note: Values are expressed as mean difference (95% CI). Bolded values indicates statistically significant differences between the budesonide and placebo groups.
Abbreviations: CCCRC, Connecticut Chemosensory Clinical Research Center test; LMS, Lund–Mackay Score; SNOT-22, Sino-Nasal Outcome Test-22; VAS, Visual Analog Scale.
[a]Computed tomography of the paranasal sinuses performed after 4 weeks of intervention; 23 patients in the budesonide group and 14 in the placebo group).

3.4 Safety

The frequency of adverse events did not differ between groups (Table 3). Headache was the most frequently reported adverse event in the budesonide group (5 vs. 1 in the placebo group). In addition, one patient experienced a self-limited episode of epis- taxis. However, these differences were not statistically significant, and no treatment discontinuations were required.

TABLE 3 | Adverse events reported in the placebo and budesonide groups.

	Placebo ($n = 26$)	Budesonide ($n = 26$)
Adverse event, No. (%)	14 (53.8)	15 (57.7)
Epistaxis, No. (%)	0 (0)	1 (3.8)
Cough, No. (%)	2 (7.7)	2 (7.7)
Otalgia, No. (%)	3 (11.5)	3 (11.5)
Skin reactions, No. (%)	0 (0)	2 (7.7)
Nausea, No. (%)	1 (3.8)	1 (3.8)
Tachycardia, No. (%)	1 (3.8)	0 (0)
Nasal irritation, No. (%)	2 (7.7)	2 (7.7)
Headache, No. (%)	1 (3.8)	5 (19.2)
Others, No. (%)	7 (26.9)	6 (23.1)

Note: Data are presented as number (percentage).

3.5 Discussion

This is the first double-blinded placebo controlled clinical trial to evaluate the efficacy nasal irrigation with budesonide in patients with diffuse CRSwNP who had not undergone FESS. Budesonide irrigation demonstrated superiority over placebo in improving sinonasal symptoms, as evidenced by significant reductions in SNOT- 22 and VAS scores after 4 weeks of treatment,

as well as a reduction in polyp size. This improvement was observed both in the mean differences between groups and in the proportion of patients achieving an MCID. These findings support the concept that corticosteroid irrigations are effective not only in postoperative patients with wide paranasal sinus exposure, as previously established in the literature, but also as a therapeutic option for surgically naïve patients with CRSwNP [7, 8, 10]

Adherence to treatment was excellent in the budesonide group, with no dropouts, whereas nine patients in the placebo arm dis- continued due to lack of response. These findings underscore not only the clinical efficacy but also the tolerability and acceptance of budesonide irrigation. Safety outcomes were consistent with previous reports, with adverse events generally mild, transient, and comparable between groups [8, 20, 21].

The interaction analyses indicated that demographic and clin- ical characteristics, including polyp size, asthma, and aspirin intolerance, did not significantly modify the treatment effect. This suggests that the benefits of budesonide nasal irrigation are consistent across patient subgroups, supporting its broad applicability in clinical settings.

Importantly, the study population was homogeneous, including only patients with moderate-to-severe CRSwNP without prior FESS, thereby overcoming limitations of previous trials that enrolled heterogeneous populations, such as those combining patients with CRS with and without polyps, or with and without previous sinus surgery [8, 10, 17, 20]. Moreover, it is noteworthy that, although AFRS was included among the eligibility criteria, no patients with this condition were screened or enrolled in the study, reinforcing the homogeneity of the analyzed population.

The nasal irrigation formulation composed of 5% glycerin and 1% budesonide is widely employed in clinical practice in Brazil, primarily due to its lower cost and greater availability compared to other commercial preparations. This characteristic supports its adoption as a viable therapeutic alternative in different healthcare settings, particularly in contexts where accessibility is a determining factor for treatment adherence [11].

Several limitations should be acknowledged. The relatively short follow-up period (4 weeks) prevents conclusions regarding the durability of symptom improvement or long-term reduction in surgical requirements. The post-treatment CT scores (Lund– Mackay) in the budesonide

group were slightly higher than those in the control group. Since pre-intervention imaging was not performed for ethical reasons, it is not possible to determine whether this difference was already present at baseline. Never- theless, the higher LMS score in the budesonide group should not be interpreted as treatment-related worsening, as there were no dropouts in this group and the clinical outcomes — SNOT-22, VAS, and NPS — showed greater improvement with budesonide than with placebo. Therefore, the radiological difference may reflect unmeasured baseline disparities or selective attrition in the placebo group, rather than a negative effect of the intervention. Finally, we used the value of 1 point as the MCID for the VAS because it represents a provisional threshold, supported by previous methodological studies and extrapolations from related instruments, given that no formally established MCID exists for global VAS in CRSwNP. Importantly, the improvements observed in our study exceeded this threshold by a wide margin, reinforcing the clinical relevance of the effects found. Despite these limitations, the study has important clinical implications. Many patients with CRSwNP face barriers to surgery—whether due to medical contraindications, socioeconomic factors, or long waiting times. Budesonide nasal irrigation represents a safe, effective, and accessible alternative for symptom control in these scenarios. By demonstrating rapid and meaningful symptom improvement, this intervention may reduce patient burden while awaiting surgical treatment and potentially delay or reduce the need for more invasive procedures [3, 22].

4. Conclusion

Budesonide nasal irrigation is an effective, well-tolerated therapy for non-operated CRSwNP patients, improving quality of life and reducing polyp size. These findings support its use as a practical and evidence-based option in both primary management and in patients for whom surgery is not immediately feasible.

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Myralis Farmacêutica provided the squeeze bottles, and Farmácia Saint Germain supplied the budesonide and glycerinated solutions, as well as the infrastructure for treatment blinding.

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The authors have nothing to report.

Conflicts of Interest

Miyake MM reports consulting fees from Myralis Farmacêutica and honoraria for lectures from Myralis Farmacêutica, GlaxoSmithKline, Sanofi, Pfizer, and AstraZeneca.

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Considerações finais

Este é o primeiro ensaio clínico duplo-cego, controlado por placebo, a avaliar a eficácia da irrigação nasal com budesonida em pacientes com rinossinusite crônica difusa com pólipos nasais que não haviam sido submetidos à cirurgia endoscópica funcional dos seios paranasais. A irrigação com budesonida demonstrou superioridade em relação ao placebo na melhora dos sintomas sinonasais, evidenciada por reduções significativas nos escores do SNOT-22 e da EVA após 4 semanas de tratamento, além de redução do tamanho dos pólipos. Essa melhora foi observada tanto nas diferenças médias entre os grupos quanto na proporção de pacientes que atingiram a mínima diferença de importância clínica (MDIC). Esses achados reforçam que as irrigações com corticosteroides podem desempenhar um papel terapêutico relevante não apenas no cenário pós-operatório, amplamente descrito na literatura, mas também em pacientes com RSCcPN ainda não submetidos à cirurgia.

A adesão ao tratamento foi excelente no grupo da budesonida, sem perdas de seguimento, enquanto nove participantes no grupo placebo não completaram o estudo ao longo do período de acompanhamento. Embora não seja possível atribuir de forma definitiva os motivos dessas interrupções, esse achado pode refletir, ao menos em parte, diferenças na percepção de benefício clínico entre os grupos. Em conjunto, esses resultados sugerem boa tolerabilidade e aceitação da irrigação nasal com budesonida.

Os desfechos de segurança foram consistentes com relatos prévios da literatura, com eventos adversos geralmente leves, transitórios e comparáveis entre os grupos. Optamos por não realizar dosagem de cortisol sérico ou aferição de pressão intra-ocular uma vez que, na literatura, são sólidos os trabalhos que realizaram tais medidas para averiguar presença de efeitos adversos, em doses e via de administração similares, porém, por tempo prolongado (12 a 24 meses).

As análises de interação indicaram que características demográficas e clínicas, incluindo tamanho dos pólipos, presença de asma e intolerância à aspirina, não modificaram significativamente o efeito do tratamento. Esses resultados sugerem que o benefício observado com a irrigação nasal com budesonida tende a ser consistente entre diferentes subgrupos clínicos, o que reforça sua aplicabilidade na prática clínica.

É importante destacar que a população do estudo foi homogênea, incluindo exclusivamente pacientes com RSCcPN moderada a grave sem cirurgia prévia, superando limitações de estudos anteriores que incluíram populações heterogêneas, como pacientes com rinossinusite crônica com e sem pólipos, ou com e sem cirurgia prévia dos seios paranasais. Além disso, embora a rinossinusite fúngica alérgica estivesse incluída entre os critérios de elegibilidade, nenhum paciente com essa condição foi identificado ou incluído no estudo, reforçando ainda mais a homogeneidade da população analisada.

A formulação de irrigação nasal composta por glicerina a 5% e budesonida a 1% é amplamente utilizada na prática clínica no Brasil, principalmente devido ao menor custo e maior disponibilidade em comparação com outras preparações comerciais. Essa característica favorece sua adoção como uma alternativa terapêutica viável em diferentes contextos de saúde, especialmente em cenários em que a acessibilidade é um fator determinante para a adesão ao tratamento.

Algumas limitações devem ser reconhecidas. O período relativamente curto de seguimento (4 semanas) impede conclusões sobre a durabilidade da melhora dos sintomas ou sobre um possível impacto de longo prazo na necessidade de intervenção cirúrgica. Estudos com maior tempo de acompanhamento são necessários para avaliar a manutenção dos benefícios clínicos observados e o papel dessa estratégia no manejo longitudinal da doença.

Além disso, estudos recentes têm investigado diferentes formas de administração de corticosteroides tópicos em pacientes com rinossinusite crônica. Luz-Matsumoto et al. compararam a aplicação de 1000 μg/dia de budesonida por spray nasal e por irrigação, observando melhora dos escores endoscópicos no grupo que utilizou spray, sem diferença significativa entre os grupos no SNOT-22.
Esses achados, entretanto, não excluem a irrigação nasal com budesonida como alternativa terapêutica plausível. Em primeiro lugar, a dose de 1000 μg/dia é substancialmente superior à dose máxima tradicionalmente recomendada para rinite alérgica (até 256–400 μg/dia, dependendo da formulação), e o estudo não teve como objetivo primário avaliar absorção sistêmica ou eventos adversos relacionados a essa exposição mais elevada. Assim, embora a dose total administrada tenha sido idêntica nas duas modalidades, o comportamento farmacocinético pode não ser equivalente.

Na irrigação nasal, a medicação é diluída em grande volume de solução salina, sendo que mais de 90% do volume instilado — e, consequentemente, parte expressiva da budesonida — é eliminada após o procedimento. Dessa forma, a fração efetivamente retida na mucosa nasal tende a ser menor do que aquela depositada por meio do spray pressurizado, no qual a medicação é administrada em pequeno volume e com maior potencial de permanência local. Essa diferença na deposição e retenção pode ter contribuído para o melhor desempenho endoscópico observado no grupo do spray, mesmo com dose nominal idêntica. Adicionalmente, a ausência de um grupo controle sem corticosteroide impede determinar a magnitude do efeito absoluto de cada estratégia, diferentemente do desenho adotado em nosso estudo. Assim, os resultados devem ser interpretados como complementares, contribuindo para a compreensão das diferentes abordagens terapêuticas.
Esses dados também abrem perspectivas para investigações futuras, como a comparação da irrigação nasal com budesonida em dose convencional (por exemplo, 400 μg/dia), cujo perfil de segurança é mais bem estabelecido; ou a avaliação sistemática do perfil de segurança do spray nasal em doses elevadas, como 1000 μg/dia, particularmente no que se refere à absorção sistêmica e possíveis efeitos no eixo hipotálamo-hipófise-adrenal.

Interessante notar que os escores tomográficos pós-tratamento no grupo da budesonida foram ligeiramente maiores do que no grupo controle. Como exames de imagem pré-intervenção não foram realizados por razões éticas, não é possível determinar se essa diferença já estava presente no momento basal. No entanto, o escore LMS mais elevado no grupo da budesonida não deve ser interpretado como piora relacionada ao tratamento, uma vez que não houve perdas de seguimento nesse grupo e os desfechos clínicos — SNOT-22, EVA e NPS — demonstraram melhora significativa ao longo do acompanhamento no grupo tratado com budesonida. Assim, a diferença radiológica observada pode refletir variações basais não mensuradas ou possíveis efeitos das perdas ocorridas no grupo placebo, e não necessariamente um impacto negativo da intervenção.

Por fim, utilizamos o valor de 1 ponto como MDIC para a EVA por representar um limiar provisório, sustentado por estudos metodológicos prévios e extrapolações de instrumentos relacionados, considerando que não existe uma MDIC formalmente estabelecida para EVA global em RSCcPN. É importante destacar que as melhoras observadas em nosso estudo ultrapassaram amplamente esse limiar, reforçando a relevância clínica dos efeitos encontrados.

O presente estudo traz implicações clínicas importantes, muitos pacientes com RSCcPN enfrentam barreiras para a realização de cirurgia, seja por contraindicações médicas, fatores socioeconômicos ou longos tempos de espera nos sistemas de saúde. Nesse cenário, estratégias terapêuticas eficazes e acessíveis antes da intervenção cirúrgica assumem grande relevância. A irrigação nasal com budesonida mostrou-se uma alternativa segura, bem tolerada e associada à melhora clínica significativa em curto prazo. Ao focar especificamente em pacientes ainda não submetidos à cirurgia, este estudo contribui para preencher uma lacuna relevante na literatura e reforça o potencial papel da irrigação com corticosteroides como parte do manejo clínico otimizado da rinossinusite crônica com pólipos nasais.

Conclusão

A irrigação nasal com budesonida melhorou significativamente a qualidade de vida e reduziu o tamanho dos pólipos em pacientes com rinossinusite crônica com pólipos nasais sem cirurgia prévia. Trata-se de uma alternativa terapêutica segura, eficaz e acessível, particularmente valiosa para pacientes que não são candidatos cirúrgicos ou que enfrentam longos períodos de espera para FESS.

Anexos

Informações do artigo

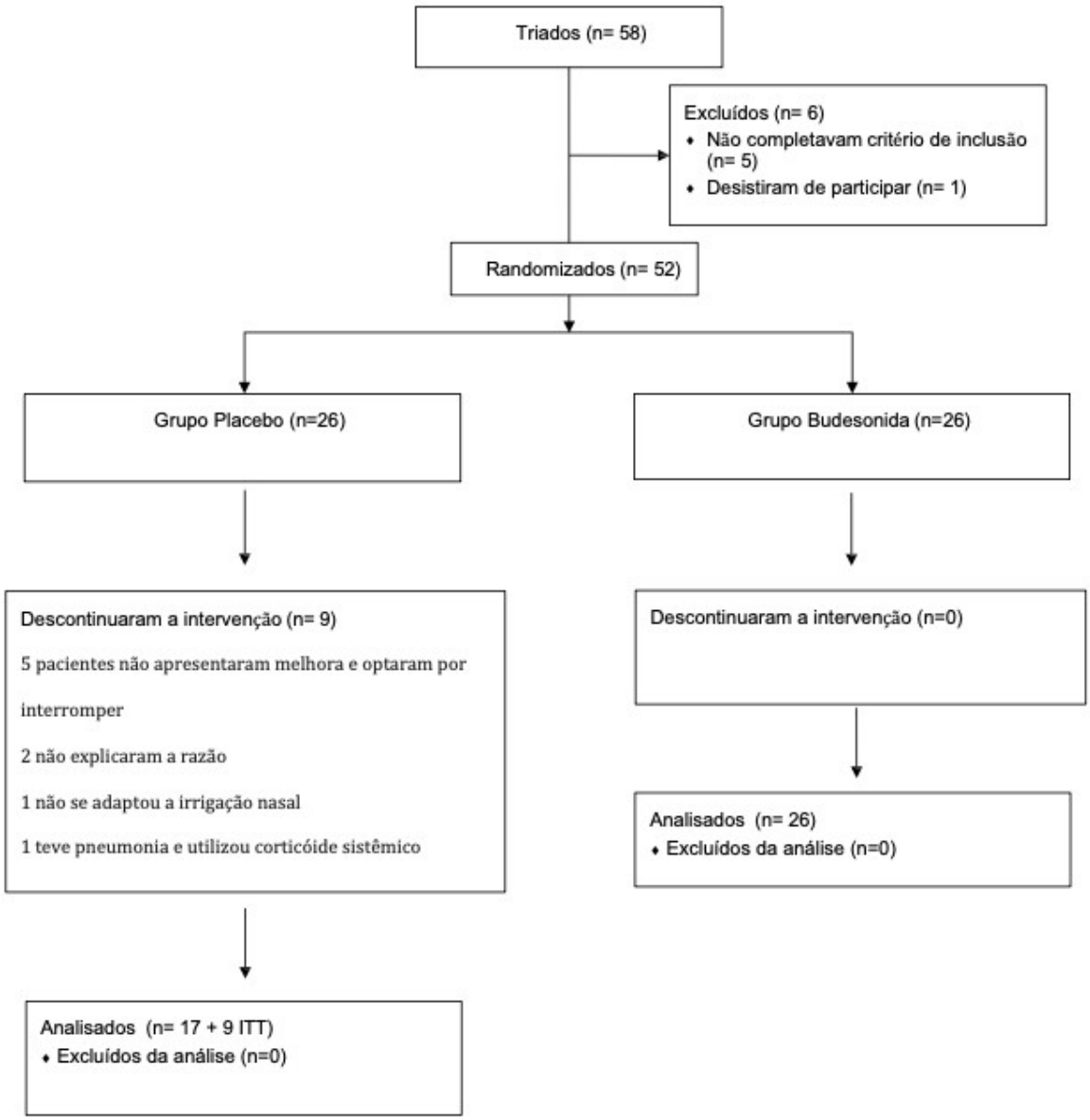
Afiliação dos autores: Departamento de Otorrinolaringologia da Santa Casa de São Paulo, Faculdade de Ciências Médicas.

Potenciais conflitos de interesse: Miyake MM relata honorários de consultoria da Myralis Farmacêutica e honorários por palestras da Myralis Farmacêutica, GlaxoSmithKline, Sanofi, Pfizer e AstraZeneca.

Financiamento/Apoio: Este foi um estudo iniciado pelo investigador. A Myralis Farmacêutica forneceu os frascos para irrigação, e a Farmácia Saint Germain forneceu a budesonida e as soluções glicerinadas, além da infraestrutura para o mascaramento do tratamento. Nenhum autor recebeu compensação financeira relacionada a esta pesquisa.

O artigo foi publicado na IFAR (International Forum of Allergy & Rhinology) em Fevereiro 2026 - Manuscript ID ALR-25-0684. As regras de submissão seguem em anexo.

Figura 1. Pacientes recrutados e incluídos na análise.



ITT: princípio da intenção de tratar. Dados ausentes foram imputados pelo método de última observação carregada.

Tabela 1. Características clínicas e demográficas basais dos pacientes

	Placebo (n=26)	Budesonida (n=26)
Idade, média (DP)	46,5 (12,1)	53,8 (13,7)
Sexo masculino, n (%)	11 (42,3)	14 (53,8)
Raça branca, n (%)	12 (46,2)	11 (42,3)
Raça negra, n (%)	5 (19,2)	4 (15,4)
Raça asiática, n (%)	0 (0)	1 (3,8)
Asma, n (%)	13 (50,0)	10 (38,5)
Alergia ambiental, n (%)	16 (61,5)	18 (69,2)
Sensibilidade à aspirina, n (%)	2 (7,7)	3 (11,5)
Profissão com exposição a aerossóis tóxicos, n (%)	8 (30,8)	7 (26,9)
Tabagismo, n (%)	3 (11,5)	3 (11,5)

Tabela 2. Efeitos Adversos

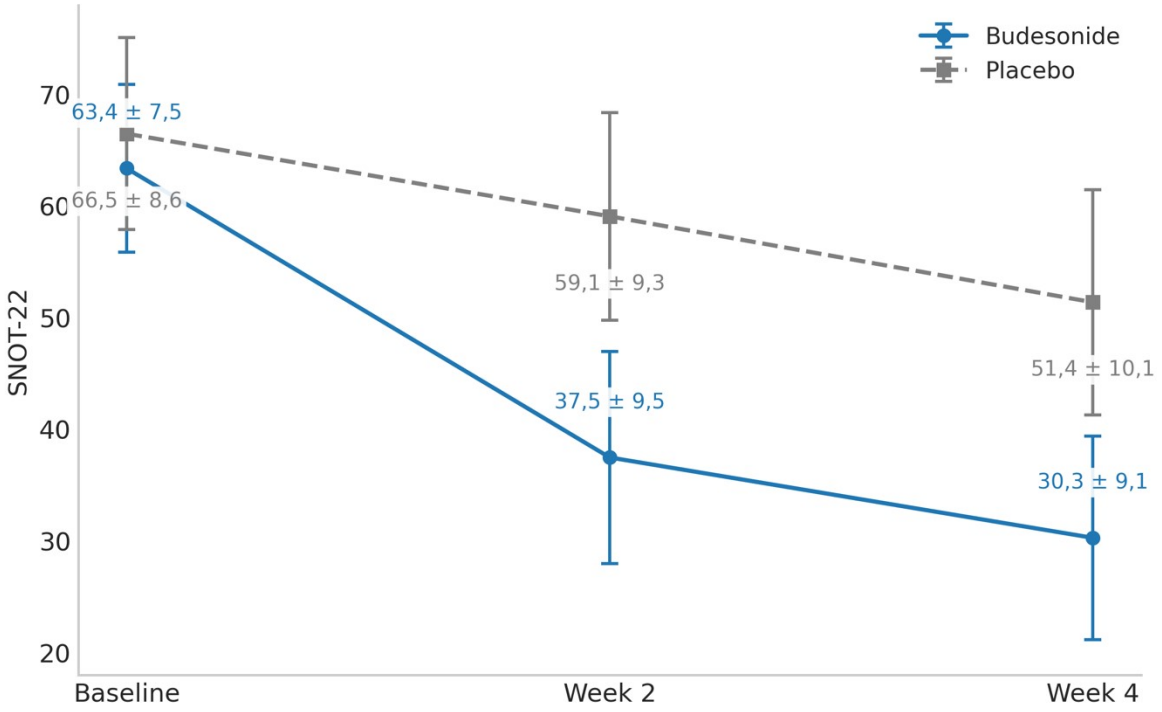
Efeitos Adversos, n (%)	Placebo (n=26)	Budesonida (n=26)
Evento adverso (total)	14 (53,8%)	15 (57,7%)
Epistaxe	0 (0%)	1 (3,8%)
Tosse	2 (7,7%)	2 (7,7%)
Otalgia	3 (11,5%)	3 (11,5%)
Reações cutâneas	0 (0%)	2 (7,7%)
Náusea	1 (3,8%)	1 (3,8%)
Taquicardia	1 (3,8%)	0 (0%)
Irritação nasal	2 (7,7%)	2 (7,7%)
Cefaleia	1 (3,8%)	5 (19,2%)
Outros	7 (26,9%)	6 (23,1%)

Tabela 3. Desfechos primário e secundários em pacientes com rinossinusite crônica com pólipos nasais (CRSwNP) tratados com irrigação nasal com budesonida versus placebo.

	Basal, Média (SD)	**Budesonida (n=26)** Semana 4, Média (SD)	Diferença após 4 semanas, (95% CI)	Basal, Média (SD)	**Placebo (n=26)** Semana 4, Média (SD)	Diferença após 4 semanas, (95% CI)	**Diferença absoluta Budesonida vs Controle, LS Média (95% CI)**	***Valor de p***
Desfecho primário								
SNOT 22	63,4 (19,5)	30,3 (23,7)	-33,15 (-44,84 a -21,47)	66,5 (22,3)	51,4 (26,3)	-15,08 (-25,20 a -4,95)	**18,07 (3,37 a 32,77)**	**0,020**
Desfechos secundários								
EVA	74,3 (18,1)	39,0 (30,2)	-35,27 (-51,13 a -19,41)	83,6 (16,6)	70,7 (28,8)	-12,88 (-24,80 a -0,97)	**-22,39 (-41,26 a -3,52)**	**0,018**
NPS	6,83 (1,01)	6,16 (1,24)	-0,67 (-1,09 a 0,25)	6,52 (0,78)	6,58 (0,83)	0,06 (-0,23 a 0,35)	**-0,73 (-1,21 a -0,25)**	**0,003**
CCCRC	1,72 (1,99)	2,64 (2,49)	0,92 (0,23 a 1,62)	1,40 (1,93)	2,09 (2,63)	0,68 (-0,06 a 1,42)	**0,24 (-1,20 a 0,72)**	**0,565**
LMS *	-	15,7 (2,4)	-	-	12,8 (2,4)	-	**2,90 (-2,04 a 7,84)**	**0,250**

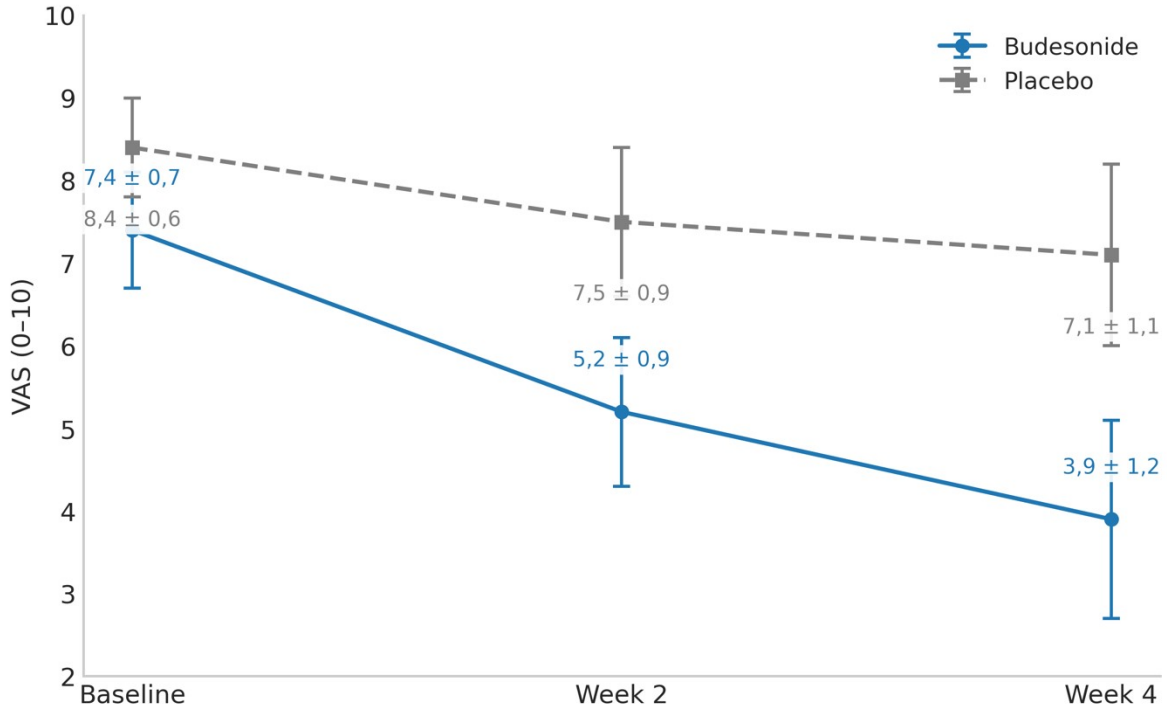
Os valores são expressos como diferença média (IC 95%). SNOT-22: Sino-Nasal Outcome Test-22; EVA: Escala Visual Analógica; CCCRC: Teste Olfatório de Connecticut;LMS: Escore de Lund–Mackay (*Tomografia computadorizada dos seios paranasais realizada após 4 semanas de intervenção; 23 pacientes no grupo budesonida e 14, no grupo placebo).

Figura 2. Evolução dos escores SNOT-22 ao longo de 4 semanas de tratamento em pacientes com RSCcPN tratados com irrigação nasal com budesonida versus placebo.



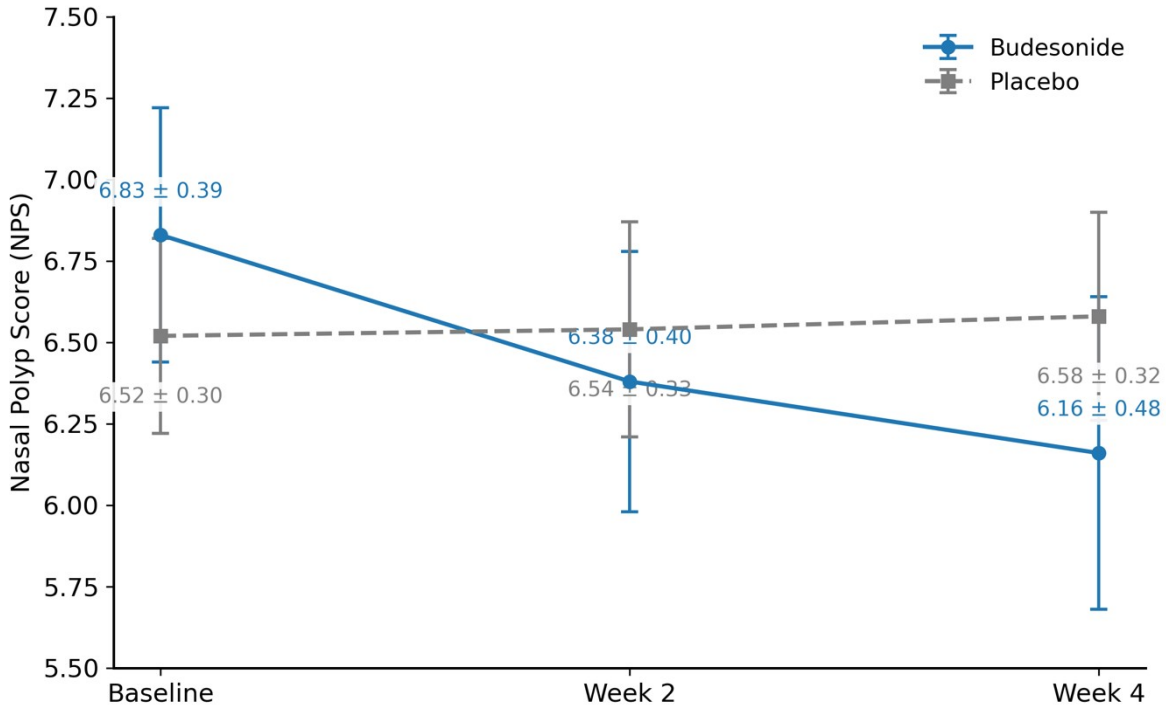
As barras de erro representam o intervalo de confiança de 95% (IC 95%). A diferença entre os grupos na semana 4 foi estatisticamente significativa *(p = 0,020)*.

Figura 3. Evolução dos escores EVA ao longo de 4 semanas de tratamento em pacientes com RSCcPN tratados com irrigação nasal com budesonida versus placebo.



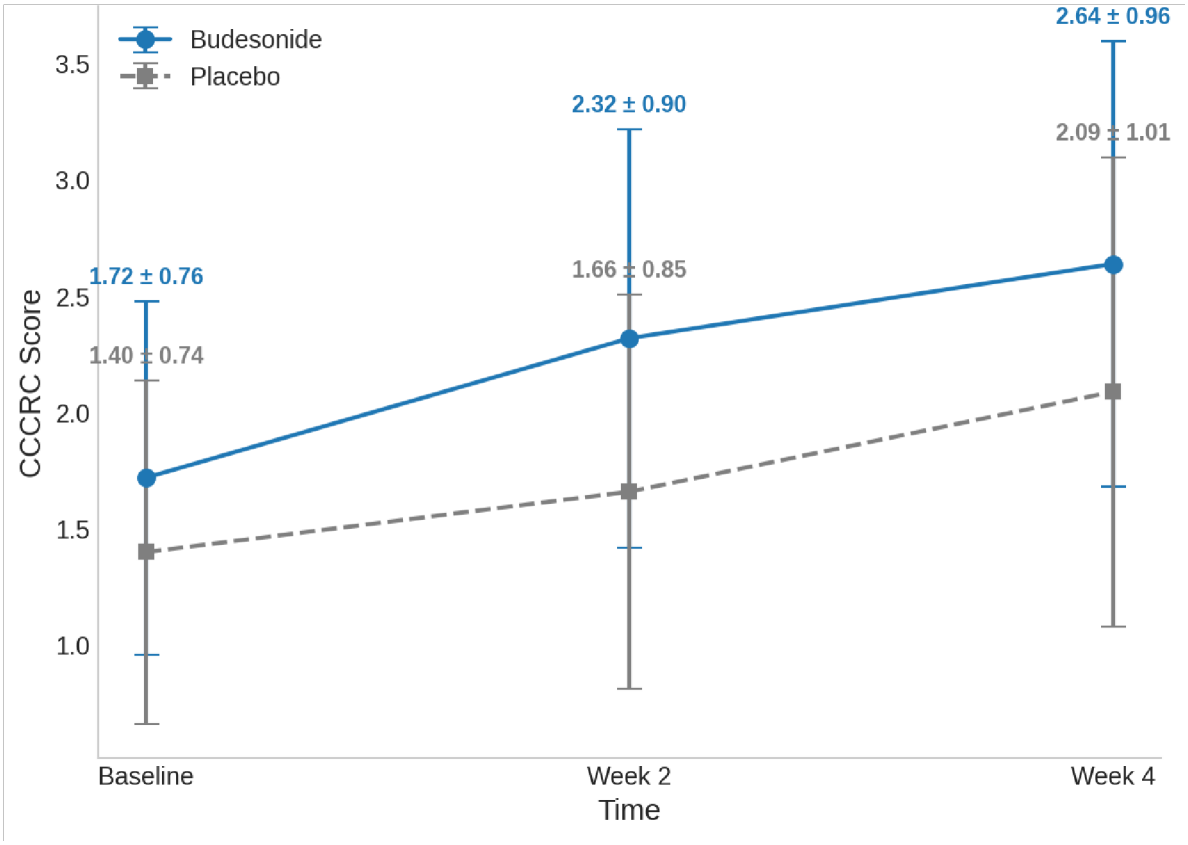
As barras de erro representam o intervalo de confiança de 95% (IC 95%). A diferença entre os grupos na semana 4 foi estatisticamente significativa *(p = 0,018)*.

Figura 4. Evolução dos escores NPS ao longo de 4 semanas de tratamento em pacientes com RSCcPN tratados com irrigação nasal com budesonida versus placebo.



As barras de erro representam o intervalo de confiança de 95% (IC 95%). A diferença entre os grupos na semana 4 foi estatisticamente significativa *(p = 0,003)*.

Figura 5. Evolução dos escores CCCRC ao longo de 4 semanas de tratamento em pacientes com RSCcPN tratados com irrigação nasal com budesonida versus placebo.



As barras de erro representam o intervalo de confiança de 95% (IC 95%). A diferença entre os grupos na semana 4 não foi estatisticamente significativa *(p = 0,565)*.

AUTHOR INSTRUCTIONS

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Journal

1. Kobler JB, Chang EW, Zeitels SM, et al. Dynamic imaging of vocal fold oscillation with four-dimensional optical coherence tomography. Laryngoscope 2010; 120:1354-1362.

Book

2. Kay AB, Kaplan AP, Bousquet J, et al. Allergy and Allergic Diseases. 2nd ed. Hoboken, NJ: Wiley-Blackwell; 2009.

Chapter in a book

3. Corrigan C. T Cells and Cytokines in Asthma and Allergic Inflammation. In: Kay AB, Kaplan AP, Bousquet J, et al., eds. Allergy and Allergic Diseases. 2nd ed. Hoboken, NJ: Wiley-Blackwell; 2009:48-82.

Web site

4. Health on the Net Foundation. Health on the Net Foundation code of conduct (HONcode) for medical and health Web sites. Available at: http://www.hon.ch/HONcode/Conduct.html. Accessed August 26, 2008.

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Tables must be created using the table tool in Word (DOC or RTF). Each table must be in a separate file, and the files should be named by table # (i.e., table 1, table 2, etc.). Number the tables consecutively in the order in which they are cited in the text. Include a brief descriptive title for each table. Do not use bulleted lists in tables. **Do not embed tables in the manuscript text.**

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PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: Irrigação Nasal Pré-Operatória com Budesonida em Pacientes com Rinossinusite Crônica com Polipose Nasal: Ensaio Clínico Randomizado, Duplo-Cego e Controlado por Placebo.

Pesquisador: Marcel Menon Miyake

Área Temática:

Versão: 6

CAAE: 13229319.9.0000.5479

Instituição Proponente: IRMANDADE DA SANTA CASA DE MISERICORDIA DE SAO PAULO

Patrocinador Principal: MYRALIS INDUSTRIA FARMACEUTICA LTDA

DADOS DO PARECER

Número do Parecer: 5.359.691

Apresentação do Projeto:

O tratamento da rinossinusite crônica com polipose nasal (RSCcPN) é desafiador devido à falta de alternativas terapêuticas eficientes. A cirurgia endoscópica funcional nasossinusal é indicada na maioria dos casos devido à refratariedade ao tratamento clínico, e mesmo após o procedimento cirúrgico, os pólipos apresentam alto índice de recorrência e cirurgias repetidas são frequentemente necessárias. A irrigação nasal com budesonida é eficaz no tratamento pós-operatório, entretanto nunca foi estudada em pacientes não operados.

O objetivo deste estudo é avaliar a eficácia da irrigação de solução tópica intranasal isotônica de cloreto de sódio e bicarbonato de sódio (240 mL Nasoar® – Myralis Indústria Farmacêutica Ltda.) associado a budesonida (2 mg), duas vezes ao dia, por quatro semanas comparada a soluçãontópica intranasal isotônica (240 mL Nasoar® – Myralis Indústria Farmacêutica Ltda.), em participantes com RSCcPN que nunca foram submetidos a

cirurgia sinusal prévia, através de um ensaio clínico fase II randomizado (1:1), duplo-cego e placebo controlado. Será necessário que 26 participantes por grupo completem o estudo. O desfecho primário deste estudo será a avaliação subjetiva da melhora de sintomas, através dos questionários Escala de Likert, Sinonasal Outcome Test-22 e Escala Visual Analógica.

Caso a irrigação nasal com budesonida prove-se eficaz também em participantes pré-operatórios, este tratamento pode prevenir ou postergar indicações cirúrgicas, reduzindo os elevados custos

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associados ao tratamento da rinossinusite crônica com polipose nasal.
Esta emenda prevê uma nova dose a ser administrada, de 2 mg de budesonida/dia, ao invés
de 1 mg/dia, que havia sido proposta no projeto original. Esta atualização foi necessária para alinhar a dose utilizada neste projeto de pesquisa com as doses utilizadas nas publicações científicas mais recentes

Objetivo da Pesquisa:
Objetivo Primário:
Avaliar a eficácia da irrigação de solução isotônica tópica intranasal contendo cloreto de sódio e bicarbonato de sódio (480 mL Nasoar® – Myralis Indústria Farmacêutica Ltda.) associado a budesonida (2 mg) por quatro semanas comparada a solução isotônica tópica intranasal contendo cloreto de sódio e bicarbonato de sódio (480 mL Nasoar® – Myralis Indústria Farmacêutica Ltda.) associado ao Placebo, em participantes com RSCcPN
que nunca foram submetidos a cirurgia sinusal prévia, baseada na melhora subjetiva de sintomas, avaliadas pela Escala de Likert (EL), pelo Sinonasal Outcome Test (SNOT)-22 e pela Escala Visual e Analógica (EVA).

Avaliação dos Riscos e Benefícios:
Riscos:
Apesar da segurança da irrigação nasal com corticosteroides já ter sido amplamente estudada, existe um teórico risco de efeitos colaterais associados a sua absorção sistêmica. Como a budesonida será administrada intranasal, há a possibilidade de irritação da mucosa nasal e estes efeitos serão monitorados em todas as visitas.
Atualmente, existem poucas alternativas disponíveis para o tratamento da RSCcPN. O desenvolvimento de novas medicações são fundamentais para o manejo desta doença. Portanto, os potenciais riscos em que a população do estudo estarão submetidas poderão proporcionar a diminuicão de riscos e desconfortos de toda a população com RSCcPN.
Benefícios:
Se bem sucedida, a irrigação com budesonida ajudará a tratar pacientes com RSCcPN, proporcionando uma apresentação mais eficiente de uma droga bem estabelecida no controle dos sintomas desta doença, segura e com grande disponibilidade no mercado brasileiro. Este tratamento tem o potencial de se tornar o a principal alternativa terapêutica no manejo da RSCcPN. Além disso, permitirá também a redução significativa no número de indicações cirúrgicas e na necessidade de múltiplas reabordagens para ressecção de pólipos.
Não há aumento do risco com a emenda proposta

Comentários e Considerações sobre a Pesquisa:

sem alteração em relação ao projeto original

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Necessita Apreciação da CONEP:
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ORIGINAL ARTICLE OPEN ACCESS

Effect of Budesonide Nasal Irrigation in Patients With Chronic Rhinosinusitis With Nasal Polyps Without Prior Sinus Surgery: A Randomized, Double-Blind, Placebo-Controlled Study

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ABSTRACT

Background: The indication for nasal irrigation with corticosteroids after sinus surgery in patients with Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) is well established, as surgery facilitates distribution throughout the sinonasal cavity. However, it remains unknown whether this approach could also provide therapeutic benefit prior to surgery. This study aims to compare the effect of budesonide versus saline nasal irrigation in surgically naive CRSwNP patients.

Methods: A randomized, double-blind, placebo-controlled parallel-group study was conducted in 52 patients with diffuse type 2 CRSwNP with no previous sinus surgery. Patients were randomized to receive either 1 mg budesonide or saline nasal irrigation twice daily for four weeks. The primary outcome was the change in the 22-item Sinonasal Outcome Test (SNOT-22). Secondary outcomes included the Visual Analogue Scale (VAS), Nasal Polyp Score (NPS), and the Connecticut (CCCRC) olfactory test.

Results: A total of 52 patients were randomized (mean age 50.1 ± 12.9 years; 51.9% female). The intention-to-treat (ITT) analysis showed that the budesonide nasal irrigation group demonstrated a significantly greater improvement in SNOT-22 (mean difference: 18.1 points [95% CI: 3.4 to 32.8; $p = 0.017$]), VAS (mean difference 2.24 points [95% CI: 0.35 to 4.13; $p = 0.018$]) and NPS (mean difference: 0.73 points [95% CI: 0.25 to 1.21]; $p = 0.003$). No significant differences were observed between groups in CCCRC.

Conclusion: Budesonide nasal irrigation may be an important tool for controlling sinonasal symptoms in patients with CRSwNP who are not candidates for sinus surgery or while awaiting surgical treatment.

1 | Background

Chronic rhinosinusitis with nasal polyps (CRSwNP) is an inflammatory disease of the upper airways affecting approximately 2%–4% of the general population, associated with substantial morbidity and a marked negative impact on quality of life. Management is challenging due to high rates of refractoriness and recurrence [1–3].

Oral corticosteroids are considered the gold standard for medical treatment but are limited by systemic side effects, restricting their use to short courses [4]. Intranasal corticosteroid sprays, while safer, have limited efficacy in patients with extensive polyps because the small spray volume and low penetration fail to adequately reach polyp surfaces and the inflamed sinonasal mucosa [5]. Persistent symptoms despite medical therapy often lead to functional endoscopic sinus surgery (FESS) to remove

polyps, restore sinonasal ventilation and facilitate topical steroid distribution [6].

High-volume, low-pressure nasal irrigation with corticosteroid diluted in isotonic saline is a well-established adjunctive therapy after FESS. Surgery improves mucosal exposure, and the larger drug volume enhances sinonasal deposition and local bioavailability compared with sprays, allowing delivery to deeper recesses and polyp surfaces inaccessible to conventional devices. These advantages translate into improved symptom control and reduced recurrence without increasing systemic side effects, despite the higher administered dose. Theoretically, patients who did not respond to clinical treatment with intranasal corticosteroid spray and who would otherwise be referred for FESS could benefit from corticosteroid nasal irrigation, since the greater volume, dose, and distribution achieved through irrigation have been demonstrated in patients who have already undergone surgery; but this intervention is still poorly studied [7–10]. Therefore, this study aims to compare the effect of budesonide versus saline nasal irrigation in surgically naïve CRSwNP patients, assessing short-term symptom improvement through validated patient-reported outcome measures and objective assessments.

2 | Methods

2.1 | Study Design and Participants

This was a randomized, double-blind, placebo-controlled clinical trial designed to compare the efficacy of isotonic saline nasal irrigation combined with budesonide (1 mg) versus placebo in patients with CRSwNP who had never undergone endoscopic sinus surgery. Participants were recruited from the outpatient clinic of the Department of Otolaryngology, Santa Casa de São Paulo, between 2019 and 2024. The study protocol was approved by the Institutional Review Board of Santa Casa de São Paulo (CAE 13229319.9.0000.5479), and written informed consent was obtained from all participants.

2.2 | Inclusion and Exclusion Criteria

Patients included in the study had a diagnosis of primary diffuse CRSwNP, according to EPOS 2020 criteria [3], which encompasses the phenotypes of eosinophilic CRS (eCRS) and allergic which encompasses the phenotypes of eCRS and allergic fungal rhinosinusitis (AFRS). Although central compartment atopic disease (CCAD) is also classified as a type-2 primary diffuse CRS, it was not included. Aspirin-exacerbated respiratory disease (AERD), despite being considered a secondary CRS phenotype, was also included. Inclusion criteria included a minimum endoscopic nasal polyp score (NPS) of 2 in each nostril, a baseline Sino-Nasal Outcome Test-22 (SNOT-22) score ≥30, and at least two of the following symptoms for a minimum of 12 weeks: Nasal obstruction or discharge (anterior or posterior), facial pain or pressure, and a reduced or lost sense of smell.

Exclusion criteria included prior endoscopic sinus surgery, previous treatment with biologics (anti-IgE, anti-IL-4, anti-IL-5), current use of immunosuppressive therapy, antibiotic use within 4 weeks prior to enrollment, or sinonasal disease associated with systemic conditions such as immunodeficiency, Churg–Strauss vasculitis, granulomatosis with polyangiitis, autoimmune disease, or connective tissue disorders. Patients with anatomical abnormalities that could prevent effective nasal irrigation (obstructive septal deviation, choanal atresia, or complete nasal cavity obstruction by polyps), history of ocular herpes, pregnancy or breastfeeding, known hypersensitivity to budesonide, glaucoma, or use of systemic or topical nasal corticosteroids within 2 weeks prior to inclusion (or unwillingness to discontinue such medications) were also excluded. In addition, patients unable or unwilling to provide informed consent or comply with study procedures were not eligible.

Participants with asthma were allowed to continue their regular inhaled corticosteroid therapy; however, any patient requiring systemic corticosteroids during the study was withdrawn.

2.3 | Intervention

Following eligibility confirmation and completion of a washout period—2 weeks for any intranasal corticosteroid sprays or 4 weeks for any systemic corticosteroids (oral, intravenous, or intramuscular)—participants were randomized (1:1) to the intervention group (budesonide) or the control group (placebo). Randomization was performed by a research pharmacy in blocks of 10, with variable block sizes, using a computer-generated sequence. Only the pharmacist was aware of group allocation; participants and study staff remained blinded throughout.

The intervention group received glycerinated budesonide solution 1% (0.5 mg/per drop), while the control group received 5% glycerin solution identical in color, appearance, taste, and packaging. The nasal irrigation formulation composed of 5% glycerin and 1% budesonide is widely employed in clinical practice in Brazil, primarily due to its lower cost and greater availability compared to other commercial preparations [11]. Solutions were stored at controlled room temperature (15°C–30°C) in their original light-protected containers. Each patient received a nasal irrigation kit containing one applicator bottle and 60 saline sachets. For preparation, participants were instructed to fill the applicator with 240 mL of filtered water, add one sachet and two drops of the assigned solution. Approximately half of the prepared volume (120 mL) was irrigated into each nostril twice daily for four weeks at home. The first dose of treatment was administered at the hospital under supervision to ensure correct technique and to verify that no nasal obstruction would interfere with the administration. All study medications and devices were provided free of charge.

Participants attended follow-up visits at two and four weeks. At each visit, subjective and objective outcomes were collected and adverse events were assessed. The following outcome measures were obtained: SNOT-22, "Connecticut Chemosensory Clinical Research Center" (CCCRC) smell test, visual analog scale (VAS), and NPS. Patients were permitted to miss no more than one dose per week to remain in the study.

2.4 | Outcomes

The primary endpoint was the change in SNOT-22 score from baseline to four weeks. The SNOT-22 is a validated 22-item

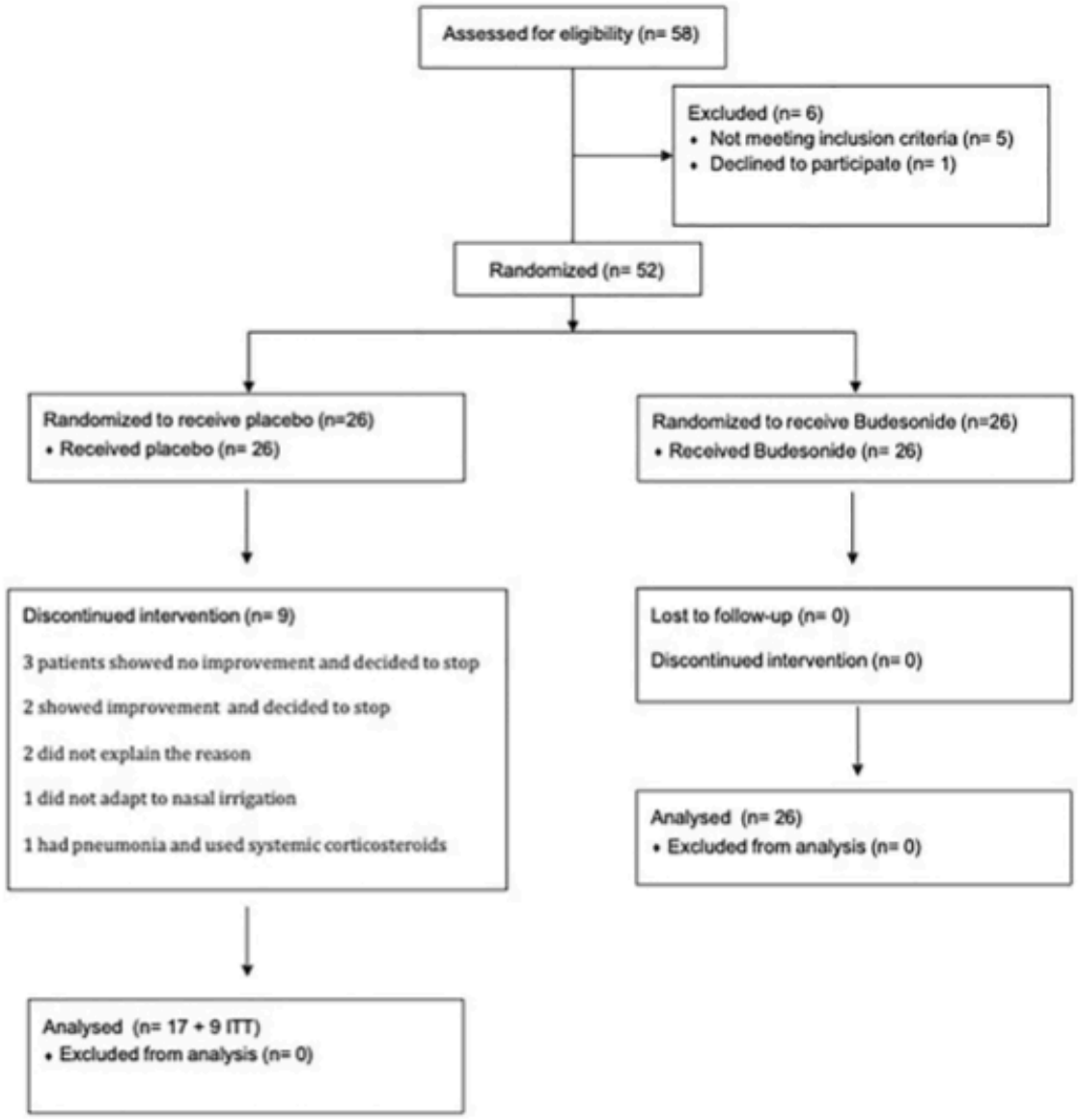

FIGURE 1 | Patients enrolled and included in the analysis.

questionnaire assessing sinonasal symptoms, with scores ranging from 0 to 110 (higher scores indicate greater severity) and a minimal clinically important difference (MCID) of 14 points [12].

Secondary endpoints included patient-reported symptom severity using a Visual Analogue Scale (VAS; 0–10 cm) for global sinonasal symptoms [13]. Since there is currently no validated MCID for a global sinonasal VAS, we adopted a provisional threshold of 1 point on the 0–10 scale. This threshold represents approximately 10% of the total scale, consistent with established MCIDs for VAS instruments in other respiratory and symptom-based conditions, and proportionally aligned with the validated SNOT-22 MCID (~11% of its total scale) [14–16]. Endoscopic NPS was assessed on a scale from 0 to 4 per nostril (0–8 total). Scoring was performed by two independent, blinded rhinologists using centrally reviewed endoscopy recordings. In addition to the numerical NPS, reviewers provided a subjective judgment of improvement between time points. A 1-point change was considered the MCID, consistent with prior studies [17–19].

Finally, Lund–Mackay Score (LMS) was evaluated on sinus CT performed at the end of the intervention, scored by an independent blinded reviewer on a scale from 0 to 24, with higher scores indicating greater opacification [20].

2.5 | Safety Assessment

Safety and tolerability were assessed by monitoring adverse events, vital signs, and physical examination at all study visits.

2.6 | Statistical Analysis

All analyses followed the intention-to-treat principle. Missing data were imputed using last observation carried forward. Baseline characteristics were summarized descriptively. Normality of continuous outcomes was assessed with the Shapiro–Wilk test; as outcomes (SNOT-22, VAS, NPS, CCCRC) were not normally distributed, between-group comparisons of change from baseline to Week 4 were performed with the Mann–Whitney U test. The chi-square test was used to compare the proportion of patients achieving the MCID. To assess whether demographic and clinical characteristics (age, sex, race, asthma, environmental allergy, aspirin sensitivity, profession, and smoking status) modified the effect of the intervention on SNOT-22 scores, multivariable linear regression models were fitted for continuous outcomes and logistic regression models for binary outcomes. Each model included an interaction term between the treatment group and the covariate of interest. Interaction effects with $p < 0.10$ were considered indicative of potential effect modification. Sample size estimation was based on the SNOT-22, using an MCID of 14 points derived from the Brazilian-Portuguese validation [12], a standard deviation of 21.95, $\alpha = 0.05$ and 80% power. Considering a 20% dropout rate, a minimum of 26 patients per group was required [7, 21]. Analyses were performed in SPSS v26 (IBM, Armonk, NY), with $p < 0.05$ considered significant, except for interaction terms as noted above.

3 | Results

3.1 | Participants

Overall, 58 patients were recruited, of whom 52 underwent randomization (Figure 1). A total of 43 patients completed the study — 26 in the budesonide group and 17 in the placebo group. All patients were actively questioned about the use of rescue corticosteroids throughout the entire follow-up period, and no patient reported having used them. Demographic and baseline clinical characteristics were generally comparable between groups (Table 1).

TABLE 1 | Baseline demographic and clinical characteristics of patients in the placebo and budesonide groups.

	Placebo ($n = 26$)	Budesonide ($n = 26$)
Age, mean (SD)	46,5 (12.1)	53,8 (13.7)
Male sex, No. (%)	11 (42.3)	14 (53.8)
White race, No. (%)	12 (46.2)	11 (42.3)
African American race, No. (%)	5 (19.2)	4 (15.4)
Asian race, No. (%)	0 (0)	1 (3.8)
Asthma, No. (%)	13 (50.0)	10 (38.5)
Environmental allergy, No. (%)	16 (61.5)	18 (69.2)
Aspirin sensitivity, No. (%)	2 (7,6)	3 (11.5)
Profession with exposure to toxic aerosols, No. (%)	8 (30.8)	7 (26.9)
Smoking, No. (%)	3 (11.5)	3 (11.5)

Note: Data are presented as mean (standard deviation) for continuous variables and number (percentage) for categorical variables.

3.2 | Primary End Point (Table 2)

3.2.1 | Sinonasal Outcome Test (SNOT-22)

After 4 weeks, the intention-to-treat analysis showed a mean improvement of −33.2 points [95% CI: −38.7 to −27.6] in the budesonide group and −15.1 points [95% CI: −20.0 to −10.2] in the placebo group (Figure 2). The between-group difference was 18.1 points [95% CI: 3.4 to 32.8; $p = 0.017$], significantly favoring budesonide. Clinically meaningful improvement, defined as exceeding the MCID, was observed in 19 of 26 patients (73.1%) in the budesonide group and 8 of 26 (30.8%) in the placebo group ($p = 0.049$).

3.3 | Secondary End Points (Table 2)

3.3.1 | Visual Analog Scale

Patients treated with budesonide also showed greater benefit on VAS scores. After 4 weeks, mean improvement was −3.53 points [95% CI: −5.1 to −1.94] in the budesonide group compared with −1.29 points [95% CI: −2.48 to −0.97] in the placebo group, yielding a between-group difference of 2.24 points [95% CI: 0.352 to 4.13; $p = 0.018$] (Figure 2). Clinically significant improvement beyond the MCID was achieved by 20 of 26 patients (76.9%) in the budesonide group and 13 of 26 (50.0%) in the placebo group ($p = 0.044$).

3.3.2 | Nasal Polyp Score

Inter-rater reliability was strong ($\kappa = 0.805$; $p < 0.001$). After 4 weeks, mean reduction in NPS was −0.67 points [95% CI: −0.92 to −0.42] in the budesonide group versus −0.06 points [95% CI: −0.33 to 0.21] in the placebo group. The mean between-group difference was 0.73 points [95% CI: 0.25 to 1.21; $p = 0.003$], confirming a statistically and clinically significant superiority of budesonide over placebo (Figure 2). Clinically relevant improvement was observed in 20 of 26 patients (76.9%) in the budesonide group compared with 13 of 26 (50.0%) in the placebo group ($p = 0.04$).

3.3.3 | CCCRC Test

Changes in olfactory function, as measured by the CCCRC test, did not differ significantly between groups. At 4 weeks, the mean improvement was +0.58 points [95% CI: −0.12 to 1.28] in the budesonide group compared with +0.34 points [95% CI: −0.41 to 1.09] in the placebo group, resulting in a between-group difference of 0.24 points [95% CI: −0.72 to 1.20; $p = 0.63$] (Figure 2). While the difference was not statistically significant, a

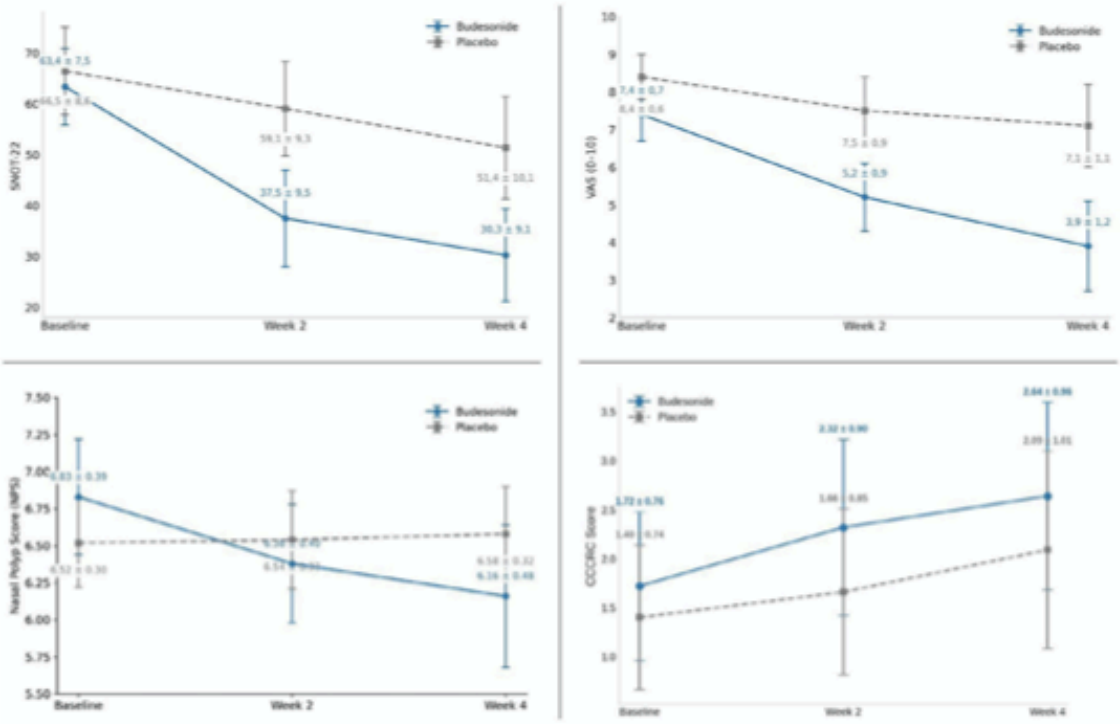

FIGURE 2 | Primary and secondary end points for all patients. The *p*-value reflects the comparison of mean changes between groups from baseline to week 4. Error Bars indicates the 95% CI.

higher proportion of patients in the budesonide group achieved improvement exceeding the MCID, 11 of 26 (42.3%) versus 6 of 26 (23.1%) in the placebo group ($p = 0.139$).

3.3.4 | Lund–Mackay Score

At the end of the 4-week treatment period, 23 patients in the budesonide group underwent computed tomography, with a mean Lund–Mackay score of 15.7 [SD 2.4]. In the placebo group, 14 patients were evaluated, showing a mean score of 12.8 [SD 2.4]. The mean between- group difference was 2.9 points [95% CI, −2.04 to 7.84; $p = 0.25$], suggesting greater disease severity in the budesonide group.

3.3.5 | Interaction Analysis

No significant interactions were observed between SNOT-22 outcomes and any of the demographic or clinical characteristics evaluated (age, sex, race, asthma, environmental allergy, aspirin sensitivity, profession, or smoking status).

3.4 | Safety

The frequency of adverse events did not differ between groups (Table 3). Headache was the most frequently reported adverse event in the budesonide group (5 vs. 1 in the placebo group). In addition, one patient experienced a self-limited episode of epistaxis. However, these differences were not statistically significant, and no treatment discontinuations were required.

3.5 | Discussion

This is the first double-blinded placebo controlled clinical trial to evaluate the efficacy nasal irrigation with budesonide in patients with diffuse CRSwNP who had not undergone FESS. Budesonide irrigation demonstrated superiority over placebo in improving sinonasal symptoms, as evidenced by significant reductions in SNOT- 22 and VAS scores after 4 weeks of treatment, as well as a reduction in polyp size. This improvement was observed both in the mean differences between groups and in the proportion of patients achieving an MCID. These findings support the concept that corticosteroid irrigations are effective not only in postoperative patients with wide paranasal sinus exposure, as previously established in the literature, but also as a therapeutic option for surgically naïve patients with CRSwNP [7, 8, 10]

Adherence to treatment was excellent in the budesonide group, with no dropouts, whereas nine patients in the placebo arm discontinued due to lack of response. These findings underscore not only the clinical efficacy but also the tolerability and acceptance of budesonide irrigation. Safety outcomes were consistent with

TABLE 2 | Outcomes of primary and secondary endpoints in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) treated with budesonide nasal irrigation versus placebo.

	Budesonide ($n = 26$)			Placebo ($n = 26$)				
	Baseline, Mean (SD)	Week 4, Mean (SD)	Absolute Change From Baseline, LS Mean (95% CI)	Baseline, Mean (SD)	Week 4, Mean (SD)	Absolute Change From Baseline, LS Mean (95% CI)	Absolute Difference for Budesonide vs. Control, LS Mean (95% CI)	*p*-value
Primary End Point								
SNOT 22	63.4 (19.5)	30.3 (23.7)	**−33.15 (−44.84 to −21.47)**	66.5 (22.3)	51.4 (26.3)	−15.08 (−25.20 to −4.95)	**18.07 (3.37 to 32.77)**	**0.020**
Secundary End Points								
VAS	7.43 (1.81)	3.9 (3.02)	**−3.52 (−5.11 to −1.41)**	8.36 (1.66)	7.07 (2.88)	−1.28 (−2.48 to −0.97)	**−2.23 (−4.12 to −0.35)**	**0.018**
NPS	6.83 (1.01)	6.16 (1.24)	**−0.67 (−1.09 to −0.25)**	6.52 (0.78)	6.58 (0.83)	0.06 (−0.23 to 0.35)	**−0.73 (−1.21 to −0.25)**	**0.003**
CCCRC	1.72 (1.99)	2.64 (2.49)	**0.92 (0.23 to 1.62)**	1.40 (1.93)	2.09 (2.63)	0.68 (−0.06 to 1.42)	**0.24 (−1.20 to 0.72)**	**0.565**
LMS[a]	—	15.7 (2.4)	—	—	12.8 (2.4)	—	**2.90 (−2.04 to 7.84)**	**0.250**

Note: Values are expressed as mean difference (95% CI). Bolded values indicates statistically significant differences between the budesonide and placebo groups.

Abbreviations: CCCRC, Connecticut Chemosensory Clinical Research Center test; LMS, Lund–Mackay Score; SNOT-22, Sino-Nasal Outcome Test-22; VAS, Visual Analog Scale.

[a]Computed tomography of the paranasal sinuses performed after 4 weeks of intervention; 23 patients in the budesonide group and 14 in the placebo group).

TABLE 3 | Adverse events reported in the placebo and budesonide groups.

	Placebo ($n = 26$)	Budesonide ($n = 26$)
Adverse event, No. (%)	14 (53.8)	15 (57.7)
Epistaxis, No. (%)	0 (0)	1 (3.8)
Cough, No. (%)	2 (7.7)	2 (7.7)
Otalgia, No. (%)	3 (11.5)	3 (11.5)
Skin reactions, No. (%)	0 (0)	2 (7.7)
Nausea, No. (%)	1 (3.8)	1 (3.8)
Tachycardia, No. (%)	1 (3.8)	0 (0)
Nasal irritation, No. (%)	2 (7.7)	2 (7.7)
Headache, No. (%)	1 (3.8)	5 (19.2)
Others, No. (%)	7 (26.9)	6 (23.1)

Note: Data are presented as number (percentage).

previous reports, with adverse events generally mild, transient, and comparable between groups [8, 20, 21].

The interaction analyses indicated that demographic and clinical characteristics, including polyp size, asthma, and aspirin intolerance, did not significantly modify the treatment effect. This suggests that the benefits of budesonide nasal irrigation are consistent across patient subgroups, supporting its broad applicability in clinical settings.

Importantly, the study population was homogeneous, including only patients with moderate- to-severe CRSwNP without prior FESS, thereby overcoming limitations of previous trials that enrolled heterogeneous populations, such as those combining patients with CRS with and without polyps, or with and without previous sinus surgery [8, 10, 17, 20]. Moreover, it is noteworthy that, although AFRS was included among the eligibility criteria, no patients with this condition were screened or enrolled in the study, reinforcing the homogeneity of the analyzed population.

The nasal irrigation formulation composed of 5% glycerin and 1% budesonide is widely employed in clinical practice in Brazil, primarily due to its lower cost and greater availability compared to other commercial preparations. This characteristic supports its adoption as a viable therapeutic alternative in different healthcare settings, particularly in contexts where accessibility is a determining factor for treatment adherence [11].

Several limitations should be acknowledged. The relatively short follow-up period (4 weeks) prevents conclusions regarding the durability of symptom improvement or long-term reduction in surgical requirements. The post-treatment CT scores (Lund–Mackay) in the budesonide group were slightly higher than those in the control group. Since pre-intervention imaging was not performed for ethical reasons, it is not possible to determine whether this difference was already present at baseline. Nevertheless, the higher LMS score in the budesonide group should not be interpreted as treatment-related worsening, as there were no dropouts in this group and the clinical outcomes — SNOT-22, VAS, and NPS — showed greater improvement with budesonide

than with placebo. Therefore, the radiological difference may reflect unmeasured baseline disparities or selective attrition in the placebo group, rather than a negative effect of the intervention. Finally, we used the value of 1 point as the MCID for the VAS because it represents a provisional threshold, supported by previous methodological studies and extrapolations from related instruments, given that no formally established MCID exists for global VAS in CRSwNP. Importantly, the improvements observed in our study exceeded this threshold by a wide margin, reinforcing the clinical relevance of the effects found. Despite these limitations, the study has important clinical implications. Many patients with CRSwNP face barriers to surgery—whether due to medical contraindications, socioeconomic factors, or long waiting times. Budesonide nasal irrigation represents a safe, effective, and accessible alternative for symptom control in these scenarios. By demonstrating rapid and meaningful symptom improvement, this intervention may reduce patient burden while awaiting surgical treatment and potentially delay or reduce the need for more invasive procedures [3, 22].

4 | Conclusion

Budesonide nasal irrigation is an effective, well-tolerated therapy for non-operated CRSwNP patients, improving quality of life and reducing polyp size. These findings support its use as a practical and evidence-based option in both primary management and in patients for whom surgery is not immediately feasible.

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The authors have nothing to report.

Conflicts of Interest

Miyake MM reports consulting fees from Myralis Farmacêutica and honoraria for lectures from Myralis Farmacêutica, GlaxoSmithKline, Sanofi, Pfizer, and AstraZeneca.

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