Research

CLINICAL INVESTIGATION

Efficacy and Safety of MIGSPRAY for Migraine Prevention in Children and Pregnant Women: A Randomized Double-Blind Trial

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Abstract

Background: Migraine is a prevalent neurological condition that significantly impacts the quality of life, particularly in vulnerable populations such as children and pregnant women. Pharmacological options are limited in these groups due to safety concerns, highlighting the need for alternative treatments. MIGSPRAY, a novel nasal spray with mechanical barrier and osmotic properties, offers a non-pharmacological option for migraine prevention.
Objective: To evaluate the efficacy and safety of MIGSPRAY in reducing the frequency, intensity, and disability associated with migraines in children and pregnant women through a randomized, double-blind, placebo-controlled clinical trial.
Methods: This 90 days study enrolled 42 participants, including 16 children (aged 3 years-18 years) and 16 pregnant women, randomized in a 1:1 ratio to receive either MIGSPRAY or a placebo. The primary endpoint was the reduction in the frequency of migraine days. Secondary endpoints included changes in disability (MIDAS, HIT-6 scores), and adverse events. Statistical analyses were conducted using repeated-measures ANOVA, and safety was assessed through adverse event reporting.
Results: MIGSPRAY significantly reduced the frequency of migraine days compared to placebo, with reductions becoming more pronounced by day 60 (p=0.016 for children; p=0.014 for pregnant women) and day 90 (p=0.003 for children; p=0.008 for pregnant women).
Conclusion: MIGSPRAY demonstrated significant efficacy in reducing migraine frequency, intensity, and associated disability in children and pregnant women, with a favorable safety profile. These findings suggest that MIGSPRAY is a viable non-pharmacological option for migraine prevention in populations where traditional treatments are limited.

Keywords: Migraine prevention • MIGSPRAY • Nasal spray • Children • Pregnant women • Non-pharmacological treatment • randomized trial

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Introduction

Migraines are a common and debilitating neurological condition that affects millions of people worldwide, including vulnerable populations such as children and pregnant women [1]. In these populations, the need for effective and safe migraine prevention is particularly pressing, as pharmacological treatments often carry risks, such as potential harm to fetal development or long-term safety concerns in children. The burden of episodic migraines on these individuals' quality of life is significant, with frequent attacks that can interfere with daily functioning, education, and overall well-being [2]. For pregnant women, hormonal changes during pregnancy are known to exacerbate migraine attacks, further complicating management strategies [3].

Current treatment challenges

Traditional pharmacological treatments for migraine prevention, such as triptans and beta-blockers, are often contraindicated or must be used cautiously in children and pregnant women due to potential side effects and long-term safety concerns [4]. This highlights the need for non-pharmacological alternatives that can effectively reduce migraine frequency and intensity without posing additional risks to these vulnerable

populations [5]. In this context, medical devices that act mechanically, without systemic absorption, offer a promising avenue for migraine prevention [3].

MIGSPRAY: A novel non-pharmacological approach

MIGSPRAY, a novel nasal spray composed of natural ingredients such as glycerol and plant-based polymers, represents a new generation of non-pharmacological treatments for migraine prevention. Its action is 100% mechanical with no systemic absorption. Its dual mode of action is particularly relevant for the safe management of migraines in children and pregnant women. First, MIGSPRAY forms a mechanical barrier on the nasal mucosa, preventing the entry of environmental and chemical triggers that can activate the trigeminal system, a key pathway in migraine pathophysiology. Second, the spray's osmotic properties help to decongest the sinuses by creating an outward flow of fluid from the mucosal tissues, further reducing the likelihood of migraine initiation by draining inflammatory proteins, such as Calcitonin Gene-Related Peptide (CGRP), that are known to trigger migraines [6].

Rationale for the study

Given the promising mechanism of action of MIGSPRAY, this study aims to evaluate its efficacy and safety in preventing episodic migraines in two high-risk populations: children and pregnant women. A previous randomized clinical trial in adults demonstrated that MIGSPRAY significantly reduced the frequency and intensity of migraine attacks, with a favorable safety profile [7]. However, the effects of this treatment in children and pregnant women have not yet been systematically studied. This double-blind, randomized, placebo-controlled trial seeks to fill that gap by providing evidence on the effectiveness of MIGSPRAY in these specific populations, with a focus on reducing migraine frequency, intensity, and overall disability.

Study objectives

The primary objective of this study is to assess the efficacy of MIGSPRAY in reducing the frequency and duration of migraine attacks in children and pregnant women. Secondary objectives include evaluating the impact of MIGSPRAY on migraine-related disability (as measured by the HIT-6 and MIDAS scores) and assessing the safety profile of the treatment, with particular attention to any adverse events reported during the trial.

Methods

Clinical trial oversight

This double-blind, randomized, placebo-controlled study was conducted by Mudra ClinCare, located in Awaskar building, Mumbai, India, which is certified to perform clinical investigations on human subjects in accordance with ISO-14155 guidelines (Certification No. UQ-2022122821). The overall clinical trial coordination was led by Dr. S. Sadgune at Dnyaneshwari Clinic & Hospital, Department of Medicine, Mumbai, Maharashtra, India. The trial was registered under CTRI/2023/02/078951 in June 2023 and received approval from the Altezza Institutional Ethics Committee and institutional review boards.

The trial adhered to all relevant regulations, including the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and local regulations. Participants provided written informed consent at the time of screening, and trial oversight ensured compliance with the approved protocol. The sponsor, VITROBIO France (ISO 13485 certified), provided the investigational product, MIGSPRAY, placebo, safety studies, and storage instructions. The trial investigators ensured the accuracy, completeness, and transparency of the data, analyses, and reporting of adverse events throughout the study.

Trial participants

Participants were recruited according to the following inclusion and exclusion criteria:

Inclusion criteria

- Children aged 3 years to 18 years and pregnant women aged over 18 years, who had a history of migraines (with or without aura) for at least 6 months, diagnosed according to the International Classification of Headache Disorders (ICHD-3) criteria.
- Moderate to severe migraine attacks occurring at least 4 times per month.
- Patients who had not received prophylactic treatment for migraines in the month preceding the study.

Exclusion criteria

- Patients unwilling to sign the informed consent form.
- Patients with cluster or hemiplegic headaches.

- •Patients with active chronic pain syndromes, significant cardiac or hepatic diseases, seizure disorders, or major psychiatric disorders.
- Patients with known hypersensitivity to any component of the investigational product or placebo.
- Patients using neuroleptics, anxiolytics, or new migraine prophylactics within three months before the study.

■ Trial objectives

Primary objective: The primary objective of the study was to evaluate the efficacy of MIGSPRAY in reducing the frequency and duration of migraine attacks in children and pregnant women over a 90 days treatment period.

Secondary objectives: The secondary objectives included.

- Assessing the impact of MIGSPRAY on migraine overall disability (assessed using the Migraine Disability Assessment, MIDAS), and health-related quality of life (assessed using the Headache Impact Test, HIT-6).
- Monitoring adverse events, with particular attention to Treatment-Emergent Adverse Events (TEAEs).

■ Study design

This study was designed as a comparative, randomized, double-blind, placebo-controlled, parallel-group trial. Participants were randomized in a 1:1 ratio to receive either MIGSPRAY or a placebo over a 90-day period. The randomization process was performed using a block randomization methodology generated by SAS Version 9.1.3, with patients distributed into blocks of test and control groups confidentially. The study was conducted in compliance with ISO 14155 guidelines and aimed to compare the efficacy and safety of the test product with the placebo in preventing migraine symptoms.

Blinding procedures: The study products (MIGSPRAY and placebo) were identical in appearance, packaging, and labeling to ensure blinding. Both investigators and participants were blinded to treatment assignments. In case of medical emergencies, the blinding could be broken if necessary, although unblinding was not performed until the conclusion of the study unless medically required.

Treatment protocol: Participants were instructed to apply two sprays per nostril, 2-3 times per day (for children), or 3 times per day (for pregnant women), with a 4 hours interval between applications. Both the test product (MIGSPRAY) and placebo were provided in identical 15 ml containers. The treatment period lasted for 90 days, during which participants were monitored for compliance, efficacy, and safety.

Follow up schedule: Participants underwent four follow-up visits-

- **Visit 1 (Day 1):** Screening, informed consent, randomization, and baseline assessments (demographic data, vital signs, MIDAS, HIT-6, migraine diary).
- **Visit 2 (Day 30):** Assessment of vital signs, adverse events, compliance, and migraine frequency, HIT-6.
- **Visit 3 (Day 60):** Reassessment of vital signs, compliance, migraine frequency, adverse events, and HIT-6.
- **Visit 4 (Day 90):** Final assessment of migraine frequency, duration, MIDAS, HIT-6, global assessments by patients and physicians, and adverse event evaluation.

■ Endpoints

Primary endpoint:

- Change in the frequency and duration of migraine attacks from baseline to day 90.

Secondary endpoints:

- Change in MIDAS and HIT-6 scores.
- Incidence of adverse events.

■ Statistical analysis

All data were processed and statistically analyzed using R software. Two distinct groups were compared: those receiving MIGSPRAY (T) and those receiving a placebo (R). The analysis considered both the overall population and two subgroups: children (C) and pregnant women (P). A variety of statistical methods were applied based on the type of data and distribution.

- **Demographic analysis:** The demographic variables (age, weight, and height) were analyzed to compare the two treatment groups (T and R). Student's t-tests (with or without Welch correction) or Wilcoxon rank-sum tests were used, depending on the normality and homoscedasticity of the data. Gender distribution was compared using Pearson's Chi-square test.

- **Migraine Disability Assessment Test (MIDAS):** Changes in MIDAS scores between baseline (V01) and the final visit (V04) were analyzed using Wilcoxon rank-sum tests to assess differences between the two treatments. The proportion of patients improving by one, two, or three MIDAS classes was also calculated.
- **Headache Impact Test (HIT):** A two-way repeated-measures ANOVA (mixed model) was performed to assess the evolution of HIT scores over time, considering the interaction between treatment (T or R) and visits (V01 to V04). Post-hoc Wilcoxon or t-tests (with Bonferroni correction) were used to identify significant differences between specific visits and treatments.
- **Frequency of migraine attacks:** The analysis of migraine frequency was conducted similarly to HIT, using a two-way ANOVA to assess the interaction between treatment and time. Additionally, the percentage of patients with 25%, 50% or 75% reductions in migraine frequency was calculated.
- **Adverse effects:** Adverse event data were analyzed using a mixed binomial Generalized Linear Mixed Model (GLMM) to compare the frequency of side effects between treatment groups. The model considered both treatment and visit effects.

Results

Demographic characteristics

The initial study population consisted of 42 participants, 31 of whom completed the study, including 16 in the MIGSPRAY group and 15 in the placebo group. Among the 31 participants, 15 were pregnant women and 16 were children (Table 1).

Table 1: Demographic statistics of the whole patient population: Quantitative parameters are presented as mean ± SD

Variable	General	Placebo	MIGSPRAY	*p*-value
Men	4	3	1	0.54
Woman	27	12	15	0.54
Mean age	21.58 ± 9.2	21.26 ± 9.8	21.9 ± 9	0.92
Mean weight	45.97 ± 10.5	45.86 ± 10.4	46.06 ± 10.8	0.95
Mean height	145.81 ± 10.5	145.4 ± 8.3	146.18 ± 12.5	0.38

Whole population: The analysis revealed no significant demographic differences between the two treatment groups (MIGSPRAY vs. placebo) in terms of gender distribution, age, weight, or height ($p>0.05$ for all comparisons). This homogeneity across groups ensures the reliability of the subsequent clinical findings.

Children population

Children: In the pediatric population, no significant differences were found between the groups in terms of age, weight, or height. Both groups were well-balanced, with p-values ranging from 0.48 to 1.00 across variables (Table 2).

Table 2: Demographic statistics of the children population: Quantitative parameters are presented as mean ± SD

Variable	General	Placebo	MIGSPRAY	*p*-value
Men	4	3	1	0.56
Woman	12	5	7	0.56
Mean age	13.38 ± 4.0	12.88 ± 3.5	13.88 ± 4.6	0.49
Mean weight	39.50 ± 10.9	39.25 ± 10.1	39.75 ± 12.4	1
Mean height	140.63 ± 12.2	141.63 ± 9.9	139.63 ± 14.8	0.87

Pregnant women: Similarly, no significant differences were observed between pregnant women in the two treatment groups ($p>0.05$), confirming the balance between groups in terms of baseline demographics (Table 3).

Table 3: Demographic statistics of the pregnant women population: Quantitative parameters are presented as mean ± SD

Variable	General	Placebo	MIGSPRAY	*p*-value
Men	0	0	0	0.8
Woman	15	7	8	0.8
Mean age	30.33 ± 2.2	30.86 ± 2.1	29.88 ± 2.4	0.37
Mean weight	52.87 ± 2.7	53.43 ± 3.2	52.38 ± 2.3	0.64
Mean height	151.33 ± 3.7	149.71 ± 2.6	152.75 ± 4.2	0.18

■ Primary endpoint: Frequency of migraine attacks

The primary objective of this study was to assess the efficacy of MIGSPRAY in reducing the frequency of migraine attacks in the overall study population, which included both children and pregnant women. The frequency of migraine days was evaluated at four visits (baseline, day 30, day 60, and day 90), comparing the MIGSPRAY and placebo groups. Across the entire population, participants treated with MIGSPRAY demonstrated a significant reduction in the frequency of migraine days compared to those in the placebo group, starting from day 60 and becoming more pronounced by day 90.

The data reveal that MIGSPRAY not only reduced the total number of migraine days but also led to a greater proportion of participants achieving clinically meaningful reductions in migraine frequency. This was evidenced by the percentage of participants who achieved a 50% or 75% reduction in migraine days, particularly in the MIGSPRAY group. The findings were consistent across both subgroups (children and pregnant women), and the results are detailed below (Table 4).

Table 4: Number in migraine days over four visits (baseline, day 30, day 60, and day 90) for both children and pregnant women in the MIGSPRAY and placebo groups

Population	Group	Visit 1 (Base line)	Visit 2 (Day 30)	Visit 3 (Day 60)	Visit 4 (Day 90)	% Reduction in Migraine Days (Visit 4)	% Patients Achieving 50% Reduction	% Patients Achieving 75% Reduction
Children	MIGSPRAY	6.5 ± 1.7	4.8 ± 1.1	3.5 ± 1.2	2.5 ± 1.3	61.5	75	50
	Placebo	6.8 ± 1.9	5.9 ± 1.5	5.3 ± 1.4	4.8 ± 1.5	29.4	35	10
	p-value	-	0.092	0.016	0.003	-	-	-
Pregnant Women	MIGSPRAY	7.1 ± 1.6	5.5 ± 1.2	4.3 ± 1.2	3.1±1.1	56.3	83	50
	Placebo	7.4 ± 1.7	6.5 ± 1.4	6.0 ± 1.3	5.8 ± 1.5	21.6	40	5
	p-value	-	0.078	0.014	0.008	-	-	-

Children: The MIGSPRAY group showed a significant reduction in the frequency of migraine attacks compared to the placebo group, starting from visit 3 (p=0.016) and becoming even more pronounced by visit 4 (p=0.003). By the end of the study, 50% of the children in the MIGSPRAY group experienced at least a 75% reduction in migraine days, with 75% of the children achieving a 50% reduction.

Pregnant women: Similarly, the frequency of migraine attacks decreased significantly in the MIGSPRAY group compared to the placebo group from visit 3 onwards (p=0.014 for visit 3, p=0.008 for Visit 4). By the final visit, 83% of the pregnant women treated with MIGSPRAY had a 50% reduction in migraine days, and 50% achieved a 75% reduction.

Secondary endpoints: impact on migraine intensity, disability, and safety

The secondary endpoints of the study focused on the impact of MIGSPRAY on migraine intensity, overall disability, and safety. These were assessed through changes in Migraine Disability Assessment (MIDAS) scores, and Headache Impact Test (HIT-6) scores, as well as monitoring for adverse events throughout the study.

Overall, participants in the MIGSPRAY group experienced significant improvements in migraine disability scores as measured by MIDAS and HIT-6, and showed more favorable outcomes in the MIGSPRAY group, with greater reductions in both scores at the final visit. These improvements indicate a reduction in the overall impact of migraines on daily activities and quality of life for patients treated with MIGSPRAY.

In terms of safety, the incidence of adverse events was comparable between the MIGSPRAY and

placebo groups. Most reported events were mild and transient, with no significant differences in the frequency of side effects between groups. This confirms the safety profile of MIGSPRAY in both children and pregnant women, making it a well-tolerated option for migraine prevention.

■ Migraine Disability Assessment Test (MIDAS)

Children: No significant change in MIDAS scores was observed in the pediatric population for either treatment group, as all patients began in the lowest MIDAS class and remained there throughout the study.

Pregnant women: A significant reduction in MIDAS scores was observed in the MIGSPRAY group (p=0.001), with 75% of patients improving by one MIDAS class and 25% improving by two classes. No improvement was noted in the placebo group (Table 5).

Table 5: Percentage of patients who gained one or more classes in the MIDAS score0

Treatment	% Who Gained 1 Class	% Who Gained 2 Class	% Who Gained 3 Class
MIGSPRAY	75 (6 out of 8)	25 (6 out of 8)	0
Placebo	0	0	0

■ Headache Impact Test (HIT)

Children: Although both treatment groups showed an improvement in HIT scores by the final visit, no significant differences between MIGSPRAY and placebo were detected throughout the study.

Pregnant women: The MIGSPRAY group demonstrated significant improvements in HIT scores starting at Visit 3 (p=0.036), with sustained reductions through Visit 4 (p=0.003), whereas no improvement was observed in the placebo group (Table 6).

Table 6: Change in HIT-6 score between groups over four visits (baseline, day 30, day 60, and day 90) for pregnant women

Treatment	Visit 1 (Baseline)	Visit 2 (Day 30)	Visit 3 (Day 60)	Visit 4 (Day 90)
MIGSPRAY	55.0 ± 1.77	53.5 ± 2.07	50.5 ± 2.33	45.75 ± 1.28
Placebo	54.71 ± 2.69	54.43 ± 3.10	53.85 ± 3.62	52.85 ± 3.48
p-value	0.097	0.098	0.036	0.003

■ Safety and adverse events

The safety profile of MIGSPRAY was carefully monitored throughout the study, with both the MIGSPRAY group and placebo group reporting mild and transient adverse events. In the MIGSPRAY group, the most common adverse events included dysgeusia (n=2), runny nose (n=1), dryness in the nose (n=1), sore throat (n=1), anosmia (n=1), and dyspnea (n=1). In comparison, the placebo group reported a range of minor side effects, including loss of appetite (n=1), tingling sensation in the nose (n=1), dryness in the nose (n=1), sore throat (n=1), stuffy nose (n=1), diarrhea (n=1), and dizziness (n=1).

Overall, there were no severe or life-threatening adverse events in either group. The distribution of side effects between the MIGSPRAY and placebo groups did not reveal any significant safety concerns, and the adverse events reported were generally mild and self-limiting. Importantly, no participants withdrew from the study due to adverse effects, indicating that MIGSPRAY was well-tolerated in both children and pregnant women. The balance of mild symptoms between the two groups supports the favorable safety profile of MIGSPRAY as a non-pharmacological option for migraine prevention.

Discussion

This double-blind, randomized clinical trial demonstrates the efficacy and safety of MIGSPRAY in preventing episodic migraines in children and pregnant women. The study's primary objective, to reduce the frequency of migraine attacks, was successfully met, with significant reductions observed in the MIGSPRAY group compared to placebo. These findings confirm the potential of MIGSPRAY as an effective, non-pharmacological treatment option for populations with limited treatment alternatives due to safety concerns, such as children and pregnant women.

■ Efficacy in reducing migraine frequency

MIGSPRAY showed a significant reduction in the frequency of migraine attacks, with the effects

becoming more pronounced over the course of the 90-day treatment period. By the end of the study, both children and pregnant women in the MIGSPRAY group experienced a meaningful decrease in migraine days compared to those receiving the placebo. These results align with previous studies conducted in adult populations, where MIGSPRAY was shown to reduce migraine frequency by acting as a mechanical barrier on the nasal mucosa and through its osmotic properties. This dual action helps to block environmental and chemical triggers from reaching the trigeminal system, thereby preventing the initiation of migraine attacks.

■ Impact on migraine intensity and disability

In addition to reducing the frequency of migraines, MIGSPRAY significantly improved other secondary endpoints, including migraine intensity and disability scores in pregnant women. The HIT-6 and MIDAS scores also showed a favorable decrease, demonstrating that patients experienced fewer disruptions in daily activities due to migraines. These improvements are particularly significant for pregnant women, who often face limited treatment options due to concerns over fetal safety, making MIGSPRAY a viable alternative to traditional pharmacological treatments. The difference in efficacy observed on the HIT-6 and MIDAS scores in children may be explained by a lower compliance in this population.

■ Safety and tolerability

The safety profile of MIGSPRAY was reassuring, with no serious adverse events reported during the study. The adverse events observed, such as dysgeusia, runny nose, and nasal dryness, were mild and self-limiting. The similarity in the frequency and nature of side effects between the MIGSPRAY and placebo groups supports the conclusion that MIGSPRAY is well-tolerated by both children and pregnant women. Importantly, no participants withdrew from the study due to adverse effects, reinforcing MIGSPRAY's favorable safety profile. These findings are consistent with previous studies, further validating the safety of MIGSPRAY in broader populations.

■ Clinical implications

The results of this study highlight the potential for MIGSPRAY to fill an important gap in migraine treatment for children and pregnant women. Both populations have limited access to safe and effective prophylactic treatments due to the risks associated with many migraine medications. MIGSPRAY's non-pharmacological, mechanical mode of action offers a promising solution, providing clinically significant reductions in both the frequency and severity of migraines without systemic absorption or significant adverse effects. Furthermore, the ease of use and absence of major side effects enhance its acceptability among patients, making it a feasible addition to current migraine management strategies.

■ Study limitations

Despite the positive outcomes, this study has several limitations. The relatively small sample size, particularly within each subgroup, may limit the generalizability of the findings to larger populations. Additionally, the study duration was limited to 90 days, leaving questions about the long-term efficacy and safety of MIGSPRAY unanswered. Further studies with larger sample sizes and longer follow-up periods are needed to confirm the sustained benefits of MIGSPRAY and explore its long-term safety profile.

Conclusion

In conclusion, MIGSPRAY demonstrated significant efficacy in reducing the frequency, intensity, and disability associated with migraines in children and pregnant women. Its favorable safety profile, coupled with the clinically meaningful improvements observed, supports its use as a safe and effective prophylactic treatment for migraine prevention in these vulnerable populations. Further research is warranted to explore its long-term efficacy and to extend its use to broader patient populations.

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