# **Comparative Efficacy of NASO B12 (Methylcobalamin Nasal Spray) and Methylcobalamin Sublingual Tablet in Vitamin B12 Deficiency: A Prospective, Randomised, Open-Label Study**

**ABSTRACT**

**Background:** Vitamin B12 is crucial for DNA synthesis, haematological and neurological functions. Conventional Vitamin B12 supplementation methods, including intramuscular and oral routes have their own limitations. The intramuscular injections are painful, and their dosing schedule is inconvenient. Methylcobalamin oral tablets do not provide a predictable absorption of Vitamin B12. NASO B12 (Methylcobalamin nasal spray) offers a painless and novel alternative; however, there is no data to compare it directly with Methylcobalamin sublingual tablets.

**Objective:** To evaluate the efficacy of NASO B12 (Methylcobalamin 250 mcg/spray) versus Methylcobalamin sublingual tablet (1500 mcg) in Vitamin B12-deficient patients.

**Methods:** In a randomised, open-label study, 30 patients with confirmed Vitamin B12 deficiency (<200 pg/ml) were administered either NASO B12 (500 mcg every alternate day) or Methylcobalamin sublingual tablet available on the market (1500 mcg every alternate day). Vitamin B12 levels in the blood were measured at baseline, 30 minutes after administration of the first dose, and on Day 6 (a total of three doses of each product).

**Results:** NASO B12 achieved significantly higher Vitamin B12 levels in the blood, 30 minutes after administration of first dose (1397.3 ± 369.03 pg/ml vs. 197.9 ± 29.7 pg/ml, *p* < 0.001) and on Day 6 (839.5 ± 163.02 pg/ml vs. 267.6 ± 37.61 pg/ml, *p* < 0.001). All patients in the NASO B12 group achieved a Vitamin B12 ≥ 400 pg/ml level as recommended by the American Academy of Family Physicians (AAFP), whereas none of the patients in the Methylcobalamin sublingual tablet group achieved the same. Both treatments were well tolerated.

**Conclusion:** NASO B12 exhibited rapid, predictable and superior absorption, along with sustained therapeutic Vitamin B12 levels (>400pg/ml), as compared to the Methylcobalamin sublingual tablet. This highlights the potential of NASO B12 as an effective and patient-friendly alternative for the rapid and assured correction of Vitamin B12 deficiency.

**Key words**

*NASO B12, Methylcobalamin Sublingual tablet, Methylcobalamin nasal spray, Vitamin B12 deficiency*

1. **INTRODUCTION**

Vitamin B12 is considered an important element for methylation processes in Deoxyribonucleic acid (DNA) and the metabolism of cells.[[1]](#endnote-1) Deficient levels of Vitamin B12 can result in megaloblastic anaemia, neuropsychological problems and other medical conditions. Known risk factors include gastrointestinal disease, taking metformin over a time exceeding four months, taking proton pump inhibitors or H2 blockers for a period of time exceeding twelve months, vegetarianism, and age more than 75 years.[[2]](#endnote-2)

The epidemiology of Vitamin B12 deficiency worldwide is estimated to be 40% in adolescents and adults in Latin America. In African and Asian nations, the overall incidence of Vitamin B12 deficiency is significantly higher—for instance, it is 70% among school-going children in Kenya, 80% among pre-schoolers in India, and 70% among Indian adults.[[3]](#endnote-3) The prevalence of Vitamin B12 deficiency among vegetarians ranges from 21 to 85%, irrespective of age, location, or demography.[[4]](#endnote-4) The clinical manifestations of Vitamin B12 deficiency lead to different haematological, neurological, and neuropsychiatric disorders. The clinical presentation of Vitamin B12 deficiency may include decreased haemoglobin, hyper-segmented neutrophils, a lack of proportion of platelets and neutrophils. Vitamin B12 deficiency may also lead to peripheral neuropathy, erectile dysfunction, depression, delirium, mania, and spinal cord degeneration.[[5]](#endnote-5)

Vitamin B12 supplementation is administered through different routes like intramuscular, oral and sublingual.[[6]](#endnote-6),[[7]](#endnote-7) However, these routes have their own limitations. Besides causing Injection site pain, the intramuscular route also poses the additional financial burden on the patient since the patient is frequently required to visit healthcare professionals. While Oral formulations offer convenience, the absorption of Vitamin B12 from such formulations is highly variable and suffers from low bioavailability. Sublingual route has been considered to bypass the gastrointestinal tract, however, confirmatory studies about its effectiveness are lacking.[[8]](#endnote-8),[[9]](#endnote-9),13

Recently, a novel intranasal formulation of Methylcobalamin (NASO B12) has been made available by Troikaa Pharmaceuticals Ltd. The nasal route of drug delivery is appealing because it provides a substantial surface area, high vascularisation, and a porous endothelial basement membrane. As a result, it provides higher systemic bioavailability of Vitamin B12 than the oral route of administration.[[10]](#endnote-10),[[11]](#endnote-11),12 The efficacy and safety of this novel formulation have been demonstrated in multiple clinical studies. A bioavailability study reported that the absorption of Vitamin B12 from NASO B12 was rapid and comparable to that of intramuscular injection. NASO B12 exhibited a similar pharmacokinetic profile, was well-tolerated, and proved to be a safe and effective alternative to existing Vitamin B12 delivery methods.[[12]](#endnote-12) In a clinical trial, it was noticed that rapid correction of Vitamin B12 deficiency by NASO B12 resulted in an elevation in the haemoglobin levels in Vitamin B12-deficient patients.[[13]](#endnote-13) In another comparative efficacy study on diabetic patients consuming metformin (known for the risk of developing Vitamin B12 deficiency), it was demonstrated that NASO B12 increased significantly higher Vitamin B12 levels in the blood as compared to Methylcobalamin oral tablets.[[14]](#endnote-14)

We could not find any study comparing the efficacy and safety of the nasal formulation of methylcobalamin and Methylcobalamin sublingual tablets. Thus, the objective of this study was to compare the efficacy and safety of a nasal formulation of methylcobalamin, NASO B12 (Methylcobalamin nasal spray) with marketed Methylcobalamin sublingual tablets for the treatment of Vitamin B12 deficiency.

**2. MATERIALS AND METHODS**

**2.1 Investigational Products**

The test product included NASO B12 nasal spray (Methylcobalamin 250 mcg/spray – marketed and manufactured by Troikaa Pharmaceuticals Ltd., Ahmedabad, India), and the comparator product used was a currently marketed Methylcobalamin sublingual tablet (1500 mcg).

**2.2 Overview of the study design**

The study was a prospective, randomised, open-label, parallel-group, comparative clinical study. The study site for the research conducted was Dia Care Research (Gandhi Park 1 & 2, Nehru Nagar Circle, Opp. BRTS, Ambawadi, Ahmedabad, Gujarat – 380015). Patient enrolment was initiated on April 30, 2024 and concluded on May 29, 2024. 30 patients with Vitamin B12 deficiency wereenrolled in the study. The patients were randomly assigned to the test and the reference group equally. After randomisation, Group I comprised patients administered NASO B12 and Group II comprised patients administered Methylcobalamin sublingual tablet. Both groups were administered with the respective doses as planned on day 1, 3 and 5 (on alternate days for a total of 3 doses only). After completion of the treatment, patients were followed up on Day 6. This study was conducted following the IEC/IRB-approved protocol, adhering to the Declaration of Helsinki (2013, Brazil), the New Drugs and Clinical Trial Rules (2019), ICMR Ethical Guidelines (2006), and ICH E6 Good Clinical Practice guidelines.

**2.3 Study population**

**2.3.1 Patient eligibility**

30 patients were enrolled in the research for approximately 6 days (excluding the screening period) for the study. Adult patients (age >18 years) of either gender having a Vitamin B12 level less than 200 pg/ml were included. The female patients with non-childbearing or childbearing potential were included after a negative urine pregnancy test confirmation. Individuals with known hypersensitivity or cobalt allergy or any background illness were excluded. (More details about Protocol DCR/IIS/NASOB12, are available on the Clinical Trial Registry: CTRI/2024/04/066019).

**Randomized, Parallel group Trial**

**30 patients having Vitamin B12 deficiency enrolled**

**NASO B12 group**

**(Methylcobalamin 250 mcg/ spray in each nostril, a total dose 500 mcg)**

**(Test group) (n=15)**

**Methylcobalamin sublingual tablet group**

**(each tablet containing**

**Methylcobalamin 1500 mcg)**

**(Reference group) (n=15)**

**Patients of both the groups received either NASO B12 (Methylcobalamin nasal spray) or currently marketed Methylcobalamin Sublingual tablet on day 1, 3 and 5 (on alternate days for a total 3 doses only). Post-treatment, each patient was followed up on Day 6**

**Figure 1: Study chart**

The patients with allergies and hypersensitivity to Vitamin B12, Nasal pathology, chronic nasal symptoms, nasal allergies and upper respiratory tract infection were excluded from the study. The patients having illnesses where Vitamin B12 was contraindicated, severe renal/hepatic impairment or failure, or pregnant or lactating women were excluded.

**2.4 Study Procedures**

The Patient Information Sheet and Informed Consent Form were used to get informed written consent before the patient's enrolment. The patients were informed about the protocols and specifically the steps that they needed to follow. Each recruited patient received a patient diary to write down the date and time of administration of both medications as well as to report any discomfort experienced thereafter.

Administration of NASO B12, 250 mcg per spray in each nostril or Methylcobalamin sublingual tablet 1500 mcg was planned every alternate day on Day 1, Day 3 and Day 5 as per the randomisation of patients in test group and reference group depicted in Fig. no.1. The first dose of the investigational product (NASO B12) and comparator product (1500 mcg of Methylcobalamin sublingual tablet) was started immediately after completion of the enrolment procedure. The patients were administered the 1st doses in the presence of the investigator. The blood sample for Vitamin B12 level evaluation was collected at the site 30 minutes after administration of the first dose. The subsequent two doses on Day 3 and Day 5 were administered by the patient independently at home. On Day 6 (i.e. approximately 24 hours after the last dose), the patient visited the study site and blood samples for the estimation of levels of Vitamin B12 were collected. The record was maintained of the concomitant medications administered to the patients during the study. Any nutritional/dietary supplements or fixed-dose combinations containing Vitamin B12 supplementation were not permitted during the study period.

**Outcomes**

The primary outcome of this study was to compare the change in Vitamin B12 levels in the blood 30 minutes after administration of the first dose on Day 1. Secondary outcomes were a comparison of change in Vitamin B12levels on Day 6 [i.e. after 03 doses], and the proportion of patients achieving Vitamin B12 levels ≥ 400 pg/ml 30 minutes after administration of the dose, on Day 1 and Day 6 (i.e. 24 hours after the last dose on Day 5).

**Statistical Analysis**

The blood Vitamin B12 levels between the test and reference groups were compared using Student’s t-test.

**3. RESULTS**

**3.1 Patient characteristics and demographic information**

30 patients who met the inclusion criteria participated in the study. All the patients who were enrolled for administration of the test product and the comparator product completed the study. The data of 30 patients in the study were considered for analysis. Demographic characteristics and the baseline Vitamin B12 levels in the blood are mentioned in Table 1.

**Table 1: Demographic characteristics at Baseline in the NASO and Methylcobalamin sublingual tablet groups**

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| DEMOGRAPHIC CHARACTERISTICS AT BASELINE |
| Baseline characteristics  | **Group 1 (n=15)****(NASO B12)** | **Group 2 (n=15)****(Methylcobalamin Sublingual Tablet)** |
| Age(years), mean(sd) | 50.4(13.7) | 50.2(12.2) |
| Gender: |
| Female, n (%) | 11(73.3%) | 7(46.6%) |
| Male, n (%) | 4(26.6%) | 8(53.3%) |
| Race | Asian | Asian |
| Baseline Vitamin B12 (pg/ml), mean(sd) levels in blood | 177.7(14.3) | 173.2(24.4) |

**Efficacy Outcomes**

The baseline level of Vitamin B12 (mean ± SD) for the test product, NASO B12 was 177.7 ± 14.327 pg/ml, and that of the comparator product, Methylcobalamin sublingual tablet was 173.2 ± 24.44 pg/ml, which was almost at a similar level.

**3.2 Comparison of Vitamin B12 levels, 30 minutes after the first dose of NASO B12 vs the first dose of Methylcobalamin Sublingual Tablet**

Comparison of Vitamin B12 levels, 30 minutes after administration of the first dose on Day 1 reveals that NASO B12 produced there were significantly higher levels of Vitamin B12 (1397.3 ± 369.03 pg/ml) in comparison with the marketed Methylcobalamin sublingual tablet (197.9 ± 29.7 pg/ml) (Fig. 2). Notably, the blood levels of Vitamin B12 in patients administered NASO B12 surpassed the 400 pg/ml threshold recommended by the American Academy of Family Physicians (AAFP), whereas in the case of the marketed Methylcobalamin sublingual tablet, the blood levels of Vitamin B12 remained way below this benchmark. Also, the mean change of blood levels of Vitamin B12 from the baseline in the NASO B12 group was 1219.7 pg/ml, compared to only 24.7 pg/ml observed with the Methylcobalamin sublingual tablet (*p* < 0.001) (Fig. no. 3) These findings suggest that at 30 minutes after administration of the dose, NASO B12 depicted faster and superior systemic absorption of Vitamin B12 as compared to the Methylcobalamin sublingual tablet.

**3.3 Comparison of Vitamin B12 levels on Day 6 (i.e. 24 hours after the last dose of NASO B12 or Methylcobalamin Sublingual Tablet)**

This comparison of Vitamin B12 levels reveals that NASO B12 administration resulted in significantly (*p*<0.001) higher levels of Vitamin B12 (839.5 ± 163.02 pg/ml) in comparison to the marketed Methylcobalamin sublingual tablet (267.6 ± 37.61 pg/ml) (Fig. 2). Furthermore, by Day 6 the mean change in Vitamin B12 levels from baseline remained significantly higher in the NASO B12 group (661.8 pg/ml) versus the Methylcobalamin sublingual tablet group (94.4 pg/ml), reconfirming the superior systemic delivery and sustained efficacy of the intranasal formulation (*p* < 0.001) (Fig. 3).

**Figure 2: Comparison of Vitamin B12 levels achieved in NASO B12 and Methylcobalamin sublingual tablet groups**

**Figure 3: Mean change in Vitamin B12 levels in the NASO B12 and Methylcobalamin Sublingual Tablet groups.**

**3.4 Proportion of patients achieving Vitamin B12 levels ≥ 400pg/ml with NASO B12 or Methylcobalamin Sublingual Tablet**

Results of the study revealed that 100% of patients in the NASO B12 group achieved >400 pg /ml level of Vitamin B12, 30 minutes after first dose on Day 1 and Day 6 (i.e. 24 hours after the last dose) (Fig. 4). In the Methylcobalamin sublingual tablet group, none of the subject achieved a level of >400 pg/ml at any of the time points, demonstrating significantly high (*p*<0.001) improvement of Vitamin B12 levels with NASO B12 compared to the Methylcobalamin sublingual tablet.

***p*<0.001**

**Figure 4: Percentage of patients achieving Vitamin B12 levels of >400 pg/ml in the NASO B12 and Methylcobalamin groups**

No adverse reactions were reported in the NASO B12 and Methylcobalamin sublingual tablet groups. Both NASO B12 and Methylcobalamin sublingual tablets were found to be well tolerated.

**4. DISCUSSION**

For a long time, intramuscular and oral formulations of Vitamin B12 supplementation have been the cornerstone for treating Vitamin B12 deficiency. The administration of intramuscular injections of Vitamin B12 is inconvenient for patients, primarily due to the pain at the injection site and the necessity for frequent visits to healthcare professionals. Oral Vitamin B12 formulations do not consistently raise the amount of Vitamin B12 in the body, even after extended treatment. To overcome the limitations of current Vitamin B12 supplementation options, alternative formulations like NASO B12, a novel Methylcobalamin nasal spray and Methylcobalamin sublingual tablet have been made available. NASO B12 has been extensively studied in clinical studies, and many published articles are available to support its efficacy.12,13,14,[[15]](#endnote-15) The published efficacy studies for the marketed Methylcobalamin sublingual tablets are lacking. To the best of our knowledge, no study has compared the efficacy of the nasal formulation of Methylcobalamin (NASO B12) and Methylcobalamin sublingual tablet, therefore, we compared their efficacy and safety in our study.

In this study, 30 minute time point after administration of first dose for the assessment of Vitamin B12 levels was chosen, to evaluate the expected fast absorption by both nasal and sublingual route, however the time point on Day 6 (i.e. 24 hours after the last dose) was selected to evaluate the comparative retention of Vitamin B12 by the body after multiple dose administration. The study results indicated that the NASO B12 is quickly and significantly absorbed after intranasal administration, while the absorption from the Methylcobalamin sublingual tablet is very low. Vitamin B12 is stored in the liver, and adequate levels therein decrease the likelihood of Vitamin B12 deficiency. However, in Vitamin B12-deficient patients, liver stores get depleted, and to replenish the stores, high levels of Vitamin B12 are required.[[16]](#endnote-16),[[17]](#endnote-17) In this context, highVitamin B12 levels achieved by NASO B12 are adequate to replenish the liver stores and correct the deficiency, as well as provide sustained levels.12

This is even more evident when we compare the amount of Vitamin B12 being administered by both formulations. While the Methylcobalamin sublingual tablet provides a dose of 1500 mcg, the NASO B12 spray offers a dose of 500 mcg (250 mcg/ml per spray).

Despite the three times higher dose being administered via Methylcobalamin sublingual tablet, NASO B12 (test product) has demonstrated superior therapeutic efficacy compared to Methylcobalamin sublingual tablet as depicted by the increase in Vitamin B12 levels at 30 minutes after administration of first dose (1219.7 pg/ml vs 24.7 pg/ml) and on Day 6 (661.8 pg/ml vs 94.4 pg/ml), respectively.

It was also remarkable to note that in the NASO B12 group, all the treated patients achieved the Vitamin B12 levels >400 pg/ml, whereas not a single patient in the Methylcobalamin sublingual tablet group achieved the same, even after 3 doses. This observation shows that NASO B12 provides consistent efficacy in all patients. The above observations become more significant when we consider the normal Vitamin B12 level (i.e. ≥400 pg/ml) recommended by the American Academy of Family Physicians.2 Also, published studies suggest that maintaining Vitamin B12 levels in the blood at or above 400 pg/ml is essential for optimal haemoglobin production, healthy red blood cell indices, in preventing cognitive decline and dynapenia.[[18]](#endnote-18),[[19]](#endnote-19),[[20]](#endnote-20) Methylcobalamin nasal spray, NASO B12, effectively addressed this critical benchmark by reaching the ≥ 400 pg/ml level, a target which the Methylcobalamin sublingual tablet could not achieve.

There we no adverse event complaints reported during the study, and both treatments were well tolerated.

This data gives us a tremendous therapeutic overview of both the NASO B12 and Methylcobalamin sublingual tablets. The study highlights NASO B12 as a superior alternative for managing Vitamin B12 deficiency, ensuring rapid and consistent absorption. Unlike Methylcobalamin sublingual tablet, NASO B12 help effectively achieve the optimal Vitamin B12 level of ≥400 pg/ml in the blood. From a clinical and policy perspective, NASO B12 reduces the need for frequent clinic visits, improves compliance, and offers a cost-effective, self-administered solution, making it a valuable advance in Vitamin B12 therapy.

Although the study had a limited patient group, the results were extremely significant, revealing a clear and consistent superiority for NASO B12 over Methylcobalamin sublingual tablets. It is also worth noting that this study largely focused on correcting low blood Vitamin B12 levels rather than looking into the underlying causes of deficiency. Future studies may evaluate the effect of different food patterns and etiological subtypes on treatment response. Furthermore, because elderly patients, pregnant and lactating women, and children were excluded from this trial, additional research may evaluate the efficacy and safety of NASO B12 in these specific populations.

**5. CONCLUSION**

NASO B12 demonstrated rapid and predictable absorption of Vitamin B12 required to replenish liver stores and hence effectively treats Vitamin B12 deficiency. NASO B12 is superior to the Methylcobalamin sublingual tablet available in the market and should be the logical choice for treating Vitamin B12 deficiency.

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