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# Multimodal oral analgesia for non-severe trauma patients: evaluation of a triage-nurse directed protocol combining methoxyflurane, paracetamol and oxycodone

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## Abstract

Insufficient analgesia affects around 50% of emergency department patients. The use of a protocol helps to reduce the risk of oligoanalgesia in this context. Our objective was to describe the feasibility and efficacy of a multimodal analgesia protocol (combining paracetamol, oxycodone, and inhaled methoxyflurane) initiated by triage nurse. We performed a prospective, observational study in an emergency department (Grenoble Alpes University Hospital, France) between December 2017 and April 2018. Adult non-severe trauma patients with a numerical pain rating scale (NRS) score ≥ 4 were included. The primary efficacy criterion was the proportion of patients with an NRS score ≤ 3 at 15 min. Pain intensity was measured for 60 min and during radiography. Data on adverse events and satisfaction were recorded. A total of 200 adult patients were included (median [interquartile range (IQR)] age: 32 [23–49] years; 126 men (63%)). Sixty-six patients (33%) reported an NRS score ≤ 3 at 15 min. The time required to achieve a decrease of at least 2 points in the NRS score was 10 (5–20) min. The median [IQR] pain intensity was 4 [2–5] before radiography and 4 [2–6] during radiography. Adverse events were frequent ($n = 128$, 64%). No serious adverse events were reported. The patients and caregivers reported good levels of satisfaction. The administration of a nurse-driven multimodal analgesia protocol (combining paracetamol, oxycodone, and methoxyflurane) was feasible on admission to the emergency department. It rapidly produced long-lasting analgesia in adult trauma patients.
**Trial registration:** NCT03380247

**Keywords** Analgesia · Trauma · Emergency · Nurse-driven protocol · Methoxyflurane

## Introduction

The prevalence of pain on admission to the emergency department is estimated at between 60 and 78%, and constitutes the main reason for attendance [1, 2]. However, the insufficient use of analgesics (referred to as oligoanalgesia) affects about 50% of patients with pain in this setting [2-4]. There are many reported barriers to effective analgesia. Physicians and other medical staff may be poorly trained, and pain may be poorly evaluated [5, 6]. The physician's attitude to opioid use (i.e. safety, and the risk of subsequent addiction) can also be a barrier to analgesia [5]. This lack of trust in opioids is also observed in patients [7]. Overcrowding in the emergency department can also delay the administration of effective analgesia [8].

Some emergency departments have implemented a nurse-directed protocol that enables the triage nurse to administer appropriate analgesics (as a function of the pain intensity) as soon as a patient is admitted; this approach increases the proportion of patients receiving an analgesic and shortens the time to analgesia [9-12]. These protocols are generally based on the oral administration of immediate-release analgesics because the use of the intravenously administered compounds would lengthen the triage time [13]. Most

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analgesia protocols combine paracetamol with step 2 or 3 analgesics, depending on the pain intensity. In the best of cases, the administration of oral analgesics produces effective analgesia after 30 min [14]. Hence, a significant proportion of trauma patients do not achieve rapid analgesia, despite the implementation of a nurse-directed pain management protocol [15, 16].

Methoxyflurane is a halogenated ether. It was initially used as an anaesthetic agent but this indication was quickly abandoned because of serious adverse events, mainly renal failure [17]. Methoxyflurane was further used for its analgesic properties at much lower doses and during short time exposition [17]. Furthermore, it is easy to administer, and is well suited to use in the emergency department [18]. The gas produces a significant reduction in pain levels within minutes of administration; the estimated median time to first pain relief is 5 min [19, 20]. Methoxyflurane's analgesic effect lasts for about an hour. It is administered via an inhalation device containing 3 mL of methoxyflurane. The maximal quantity of methoxyflurane per 24 h is 6 mL and 15 mL per week. In Europe, the indication for methoxyflurane selected by the health authorities is the relief of moderate-to-severe trauma pain.

The aim of this study was to describe the feasibility and to evaluate a triage-nurse directed protocol combining methoxyflurane, paracetamol and oxycodone. Special interest was focused on the change in pain intensity during the first hour of treatment of non-severe trauma patients.

## Methods

### Study design and settings

We performed a prospective, observational study in the emergency department at the Grenoble Alpes University Hospital (Grenoble, France) from December 2017 to April 2018. Grenoble Alpes University Hospital is the trauma reference centre for the French Alps. Its emergency department admits about 60,000 patients a year, 40% of whom are consulting for trauma. The study was approved by the local independent ethics committee (*CPP SudEst*, Grenoble, France; reference: 38RC17.157) and was registered at ClinicalTrial.gov (NCT03380247). All patients gave their written informed consent.

Patients could be included between 8 a.m. and 6 p.m. on weekdays because of the availability of clinical research staff to monitor the outcomes. On arrival in the emergency department, the patient's name and vitals were recorded by a nurse. If the patient was eligible, he/she was given written and verbal information on the study by one of the investigators. If the patient did not choose to opt out and if he/she signed the consent, he/she was included in the study. The patient then received multimodal analgesia as a function of the pain intensity (measured as the Numerical pain Rating Scale (NRS) eleven-point score) on inclusion (Table 1). If patient experienced moderate pain, triage nurse gave him paracetamol and oxycodone 5 mg and methoxyflurane 3 mL. The rational of half dose oxycodone in moderate pain is to avoid the use of codeine and tramadol at least at triage. In case of more severe pain (NRS $\geq$ 6), the dose of oxycodone was increased to 10 mg. Only one vial of 3 mL Methoxyflurane could be administrated during the whole stay in the ED. Non-pharmacological treatments (cryotherapy and immobilisation) were also offered. The patient was then taken to a treatment area. Pain intensity and the occurrence of adverse events and NRS were monitored during the first hour in the emergency department.

### Methoxyflurane inhalation

Inhalation of Methoxyflurane according to the formulation guidelines requires to (1) verify that the activated carbon cartridge is inserted into the diluent port on the top of the inhaler; (2) pour the entire contents of the Methoxyflurane vial into the base of the inhaler while rotating to make sure the wick it contains is well saturated; (3) ask the patient to inhale through the mouthpiece of the inhaler to achieve the analgesic effect. The patient should exhale in the inhaler so that the expired vapor passes through the activated carbon cartridge to adsorb any expired portion of Methoxyflurane. If more analgesia is needed, the patient may cover the dilutor orifice with the finger on the activated charcoal cartridge during inspiration. The patient should be advised to inhale intermittently for adequate analgesia (auto administration). Continuous inhalation will reduce the duration of use to 30 min (approximately 60 min with intermittent inhalation).

**Table 1** Triage-nurse directed protocol as a function of pain intensity on admission to the emergency department

| Numerical rating scale score | 4–5 | ≥6 |
|---|---|---|
| Trauma patient aged 18 or over | Paracetamol 1 g + oxycodone 5 mg + methoxyflurane 3 mL | Paracetamol 1 g + oxycodone 10 mg + methoxyflurane 3 mL |

### Study population and data collection

The main inclusion criterion for adult patients (aged 18 or over) was consultation at the emergency department after trauma. The other inclusion criteria were moderate-to-severe pain (a NRS score ≥ 4), and the absence of contraindications to the compounds used in the analgesia protocol (paracetamol, oxycodone, and methoxyflurane). Contraindications of paracetamol were hypersensibility to paracetamol and severe hepatic insufficiency. Contraindications of oxycodone were hypersensitivity to oxycodone or to any of the excipients; severe chronic obstructive pulmonary disease; severe bronchial asthma; severe respiratory depression with hypoxia; high levels of carbon dioxide in the blood; paralytic ileus; chronic right ventricular failure; combination with buprenorphine, nalbuphine, pentazocine, naltrexone and nalmefene/. Contraindication of methoxyflurane were hypersensitivity to the active substance or any other fluorinated anesthetic or other excipient; history of malignant hyperthermia; history of serious adverse events in the patient or family after administration of inhaled anesthetics; history of signs of liver damage after use of methoxyflurane or after halogenated hydrocarbon anesthesia; clinically significant renal impairment; altered level of consciousness regardless of cause, including head trauma, drug or alcohol use; clinical evidence of cardiovascular instability; clinical evidence of respiratory depression. These contraindications are in accordance with the guidelines of French authorities.

The main exclusion criterion was confirmed or suspected multiple trauma, as defined by the presence of trauma to the thorax (apart from broken ribs with a $SpO_2 \geq 98\%$), abdomen or pelvis trauma; suspected severe head injury; a Glasgow coma score < 15; intake of analgesics other than paracetamol in the 4 h preceding admission (except for nitrous oxide in the hour preceding admission); any contraindication to the molecules used in the protocol; or the immediate need for peripheral venous access on admission. This latest exclusion criterion was chosen because patient requiring immediate IV access (antibiotic administration in open fracture for example) would benefit more from IV analgesic treatments than multimodal oral analgesics. In accordance with French legislation, patients had to have social security coverage. Pregnant or breastfeeding women, prison inmates, and persons under legal guardianship were not included.

The data were collected on a study-specific case report form by a research physician, a research nurse and/or the study's clinical research assistant in the emergency department. These research people were not involved in patient care.

The case report form was used to gather data on the patient's characteristics (age, gender, weight, height, admission time, and reason for admission), clinical data on admission (the NRS score, the pain site, the triage level on admission, and vital signs), and clinical data in the treatment area (the NRS scored every 5 min for 30 min, and then after 45 and 60 min, the NRS score during the radiographic assessment, the occurrence of adverse events, the implementation of peripheral venous access, and drugs administered). The patient's and caregivers' level of satisfaction were measured on a 100 mm visual analogue scale at 60 min. Lastly, the patient's outcome and final diagnosis were recorded.

### Statistical analysis

The study's primary objective was to describe early changes in pain levels in patients receiving multimodal analgesia on admission to the emergency department. The primary efficacy criterion was the proportion of patients with an NRS score ≤ 3 within 15 min of analgesic administration.

The secondary objectives were to assess the analgesic efficacy of this multimodal analgesia protocol (defined as the time to first pain relief, i.e. a decrease of at least 2 points in the NRS score, and the proportion of patients with a 30% reduction in the NRS score at 15, 30 and 45 min); the level of pain before and after the radiographic assessment (when performed during the first hour); the patient's and medical staff's levels of satisfaction with pain management in general and with each component of the multimodal analgesia protocol in particular); and the analgesia protocol's feasibility and safety (non-completion of the protocol, and the frequency of adverse events, including the Ramsay Sedation Scale score [21]).

A sample size of 200 patients gave a two-sided 95% confidence interval of ± 5.5%; we estimated that 80% of patients would have an NRS score ≤ 3 within 15 min of the first pain score (i.e. measured on inclusion, prior to any analgesic treatment). The study's power was a priori calculated using nQuery® Advisor software (version 7.0, Statsols, Boston, MA, USA).

Qualitative variables were described as the number (percentage), and quantitative variables were described as the median [interquartile range (IQR)]. Dichotomous variables were compared using a chi-squared test or (as appropriate) Fisher's exact test. Quantitative variables were compared using a Mann–Whitney test. The data were analyzed using SPSS software (version 20, IBM, Armonk, NY, USA).

## Results

A total of 580 patients were screened between December 22nd, 2017, and April 10th, 2018. Of these, 275 met at least one non-inclusion criterion, 70 refused to take analgesics on admission, and 27 refused to participate in the study. Ten other patients were not invited to participate in the study,

**Table 2** Characteristics of the study population

| | $N=200$ |
|---|---|
| Age (years) | 32 (23; 49) |
| Gender (male, %) | 126 (63) |
| Parameters on admission | |
| Body mass index (kg/m$^2$) | 23.8 (21.7–26.9) |
| NRS score | 7 (6–8) |
| Triage score[a] | 4 (4–4) |
| Time interval between trauma and consultation (min) | 120 (60–840) |
| $SpO_2$ (%) | 98 (96–99) |
| Respiratory rate (per min) | 16 (14–18.5) |
| Heart rate (per min) | 81 (72–89) |
| Systolic blood pressure (mmHg) | 129 (119–144) |
| Glasgow Coma Score | 15 (15–15) |
| Ramsay Sedation Scale | 2 (2–2) |
| Length of stay in the emergency department (min) | 148 (103–227) |
| Patient outcome | |
| Discharge to home (*n*, %) | 183 (92) |
| Final diagnosis (*n*, %) | |
| Fracture | 46 (23) |
| Contusion, sprain | 103 (52) |
| Wound, burns | 28 (14) |
| Dislocation | 9 (5) |
| Other | 12 (6) |

Data are quoted as the number (%) or the median (IQR). NRS: numerical pain rating scale

[a]Triage score: nurse-rated triage score for emergency department patient, scale out of 5, 1 being vital distress

although the reason was not recorded. In all, 200 patients were included in the study. 87 (44%) patients were referred to the ED by ambulance. The characteristics of the study population are summarized in Table 2.

## Evolution of pain intensity

The proportion of patients with an NRS score ≤ 3 after 15 min of patient care was 33% ($n=66$). The time interval to a reduction of at least 2 points in the NRS score was 10 min (5–20). The NRS score fell significantly from minute 5 of follow-up onwards ($p<0.001$), and there was a significant decrease in the NRS score over the first hour of patient care ($p<0.001$) (Fig. 1). Further administration of analgesics, i.e. rescue medication, during the first hour of care was necessary in 12 cases (6%), and 15 patients (8%) required peripheral venous access during their stay. One hundred and two (51%) patients were classified as analgesia responders (a decrease of at least 30% in the initial NRS score) at minute 15, with 147 (74%) responders at minute 30 and 153 (77%) responders at minute 45 (Fig. 2). When patients were

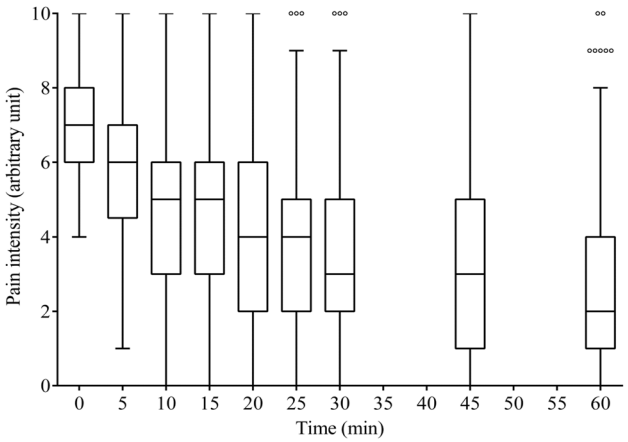


**Fig. 1** The change in pain intensity during the first hour of patient care. Data are represented as Tukey boxplots

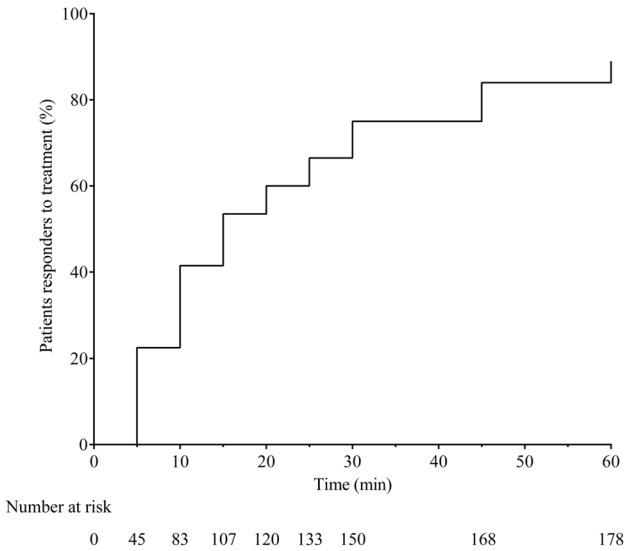


**Fig. 2** The cumulative proportion of responders (i.e. patients with at least a 30% decrease in the NRS score, relative to admission) during the first hour of follow-up

**Table 3** Pain intensity evolution at 15 min into different patients' groups according to Numerical Rating Score at baseline

| Numerical rating scale score | 4–5, $N=40$ | 6–7, $N=86$ | 8–10, $N=74$ |
|---|---|---|---|
| NRS score ≤ 3 | 23 (58) | 27 (31) | 16 (22) |
| NRS difference from baseline | 1.75 (±2.0) | 2.49 (±1.72) | 3.07 (±2.36) |

*NRS* numerical rating scale

divided into groups according to NRS at baseline (post hoc analysis at the request of reviewers), pain reduction at minute 15 was significant ($p<0.001$) in all groups (Table 3).

When X-rays were performed during the first hour of care, the NRS score before the radiographic assessment [4 (2–5)] and the NRS score during the assessment X-rays [4 (2–6)] were not different ($p = 0.15$).

### Safety of use

One or more adverse events were reported by 128 patients (64%). Among a list proposing symptoms, dizziness was the most frequent adverse event, and was reported by 64 patients (32%). Although drowsiness was also frequently reported (by 49 patients, i.e. 25%), the Ramsay Sedation Scale score did not change significantly different over the first hour [2 (2–2) at all time points]. Four patients (2%) presented a Ramsay Sedation Scale score of 3 or 4 during the first hour of follow-up. The other reported adverse events were the unpleasant odour of methoxyflurane ($n = 32$, 16%), nausea ($n = 12$, 6%), headache ($n = 10$, 5%), and vomiting ($n = 2$, 1%). No serious adverse events were reported.

Seventeen patients (9%) stopped using methoxyflurane in the first hour of care. This was variously due to adverse events ($n = 10$ cases, i.e. 59% of the non-completions), difficulty using the device ($n = 2$, 12%), and the absence of pain ($n = 5$, 29%). The time to cessation was 30 (20–40) min.

### Satisfaction

The patients and medical staff reported good levels of satisfaction (> 80 on a 100 mm visual analogue scale) for all aspects of the protocol (Fig. 3).

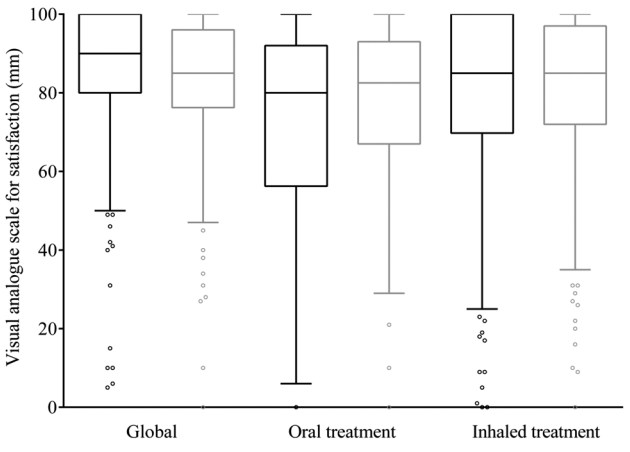


**Fig. 3** Levels of satisfaction reported by the patients (in black) and medical staff (in grey), for the multimodal analgesic protocol in general and for oral and inhaled treatments in particular

## Discussion

The present study is the first to have assessed the feasibility of a multimodal analgesia protocol (combining inhaled methoxyflurane, paracetamol, and oral oxycodone) upon nurse triage at the time of admission to the emergency department. The results of this observational study evidenced a significant reduction in pain in non-severe trauma patients during the first five to ten minutes of care. The pain level continued to fall during the hour following admission to the emergency department. Although a large number of adverse events were reported by the patients, these events did not appear to decrease the patients' and medical staff's levels of satisfaction with the analgesia protocol.

Rapid, effective analgesia is essential in the emergency department. In a patient with trauma, it is not possible to envisage rapid treatment without providing the patient with effective analgesia in the first minutes of care [15]. At present, there is no consensus on the ideal analgesia protocol for this context. Several studies have evaluated the value of various analgesics alone or in combination: paracetamol, paracetamol combined with a nonsteroidal anti-inflammatory drug, and paracetamol combined with an oral opioid [12, 14, 22]. Only few studies have evaluated the performance of intranasal opioids administration in adult emergency departments [23]. Nevertheless, intranasal opioids administration is not recommended in moderate pain and the preparation of the product is a limiting factor. We chose to combine paracetamol, oxycodone and, above all, methoxyflurane. In a placebo-controlled trial of methoxyflurane, the reduction in pain intensity (on a visual analogue scale) was 23.1 mm in the methoxyflurane group vs. 11.3 mm in the placebo group ($p < 0.001$) [20]. In the present study, we observed a statistically significant reduction in pain from minute 5 onwards (Fig. 1). It is nevertheless probable that the decrease in pain intensity is clinically significant between 5 and 10 min, i.e. the median time to achievement of a 2-point reduction in the NRS score.

During the use of our multimodal protocol, the decrease in pain intensity seemed to be greatest at minute 30, and analgesia was maintained until minute 60. Eleven percent of the patients did not respond to multimodal treatment, versus 18% for the use of methoxyflurane alone [20]. In contrast to most literature data, the performance of a radiographic assessment during the first hour was not associated with a clinically significant increase in pain [9]. By combining a "starter analgesic" (methoxyflurane) with slower-onset but long-acting compounds, the multimodal protocol therefore provided our trauma patients with stable analgesia. It is also noteworthy that the pain intensity at

1 h in our study was lower than the values published by other studies in similar populations [22]. We also observed that a low proportion (6%) of patients required another analgesic during the first hour of care. These findings emphasize the efficacy of the multimodal analgesia protocol but, paradoxically, call the choice of the compounds into question. In fact, the use of opioids in the emergency department and its impact on addiction and misuse are subject to intense debate [24, 25]. Oral opioids do not seem to be superior to a combination of anti-inflammatory drugs and paracetamol [12, 22]. The adjunction of a non-opioid molecule could be even associated with a shorter length of stay in the emergency department [26]. The use of a multimodal analgesia protocol might thus help to reduce the prescription of opioids—notably for moderate pain [27]. It would doubtless be of value to study the pertinence of a multimodal analgesia protocol combining paracetamol and methoxyflurane in the relief of moderate pain, with the adjunction of oral opioids only for severe or even very severe pain (i.e. an NRS score $\geq 8$). The value of anti-inflammatories as part of this combination also remains to be assessed (12).

In the emergency department, the safety of analgesia protocols is a critical factor. The occurrence of adverse events can considerably limit the clinical value of an analgesia protocol. In our cohort, adverse events were frequent (affecting 66% of patients) but benign. They were responsible for the cessation of treatment (with methoxyflurane) in only 5% of cases, which is similar to the frequency reported for the use of equimolar nitrous oxide/oxygen [18]. Moreover, patients and caregivers reported good levels of satisfaction, despite the frequency of adverse events. This probably emphasizes the multimodal analgesia protocol's advantageous efficacy/safety ratio. One of the protocol's major strengths relates to the possibility of analgesia self-management by the patient, thanks to the use of methoxyflurane. Another strength of this type of analgesia is its ease of initiation, immediately upon admission of the patient to the emergency department by the triage nurse.

The main limitation of the present study is, of course, its purely observational nature. Before definitively concluding that the multimodal analgesia protocol is efficacious, it will be necessary to perform a blinded, comparative study. In analgesia studies, the placebo effect can be very large [28, 29]. The pharmacokinetics of the molecules used here prompt us to think that the rapid efficacy observed in our cohort can probably be ascribed to methoxyflurane, whereas the stability of the analgesia is doubtless due to paracetamol and the opioid. Moreover, a bias due to the intake of extended-release analgesics cannot be excluded even if patients who absorbed any analgesics other than paracetamol in the 4 h preceding admission were not included. Lastly, the study population was highly selected. It was mainly composed of young patients presenting with benign limb trauma during daytime. Although this type of patient constitutes the majority of trauma cases seen in the emergency department, our results cannot be extrapolated to patients presenting with more severe trauma or multiple trauma or during night with potential cofounders such as intoxication. The population in this study was similar to those observed in other multicentre studies [22, 30].

In conclusion, multimodal analgesia (combining inhaled methoxyflurane, paracetamol, and an oral opioid) initiated on admission to the emergency department effectively reduces pain in non-severe trauma patients within the first 15 min. The analgesia lasted for at least the first hour of care. The high levels of satisfaction reported by both the patients and medical staff, and the low incidence of serious adverse events argue in favour of this type of safe, pharmacokinetically logical management.

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## Compliance with ethical standards

**Conflict of interest** MM and CMD received fees from Mundipharma (MM and CMD) and Purdue (MM), two pharmaceutical companies that market methoxyflurane. We confirm that the remaining authors have no known conflicts of interest associated with this publication.

**Research involving human participants** The study was approved by the local independent ethics committee (*CPP SudEst*, Grenoble, France; reference: 38RC17.157) and was registered at ClinicalTrial.gov (NCT03380247).

**Informed consent** Signed informed consent was obtained from all individual participants included in the study.

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