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# Efficacy and safety of low dose oral ketamine for controlling pain and distress during intravenous cannulation in children: a double-blind, randomized, placebo-controlled trial

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**Background:** Ketamine is widely used in infants and young children for procedural sedation and anesthesia. The aim of this study was to evaluate the efficacy and safety of low dose oral ketamine to control pain and distress in children during intravenous (IV) cannulation.
**Methods:** This is a prospective, randomized, double-blind study, including children aged between 3 and 6 years requiring a non-emergent IV-line placement. Children were randomly assigned to two groups, treated either with oral ketamine or a placebo. All patients were monitored for vital signs. Pain was assessed using the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) and Wong-Baker Faces Pain Rating Scale (WBFS) scales and sedation using a 5-point sedation score. The facility of IV-line placement was measured by a 3-point scale. Adverse effects were recorded after 1 and 24 hours.
**Results:** A total of 79 and 81 children were entered in the ketamine and placebo groups, respectively. The heart and respiratory rates increased significantly in the placebo group. The median CHEOPS 4 (95% confidence interval [CI]: 3, 4, $P < 0.001$) and WBFS 6 (95% CI: 4, 6, $P < 0.001$) scores decreased statistically in the ketamine group. IV-line placement was 50% easier in the ketamine group (95% CI: 37%, 63%, $P < 0.001$). No serious adverse effects were observed in all cases.
**Conclusions:** Low dose oral ketamine effectively decreased the pain and distress during IV cannulation in children without any significant adverse reactions.

**Key Words:** Administration, Oral; Analgesia; Catheterization; Child; Double-Blind Method; Ketamine; Pain Management; Safety.

## INTRODUCTION

Needle injection for vaccination, medication administration, blood drawing and intravenous (IV)-line placement are some of the frightening and painful procedures for children [1]. Peripheral IV-line placement is also consid-



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ered one of the indications for procedural sedation and analgesia (PSA) in children [2]. In this sense, it has been reported that 50% of children undergoing IV-line placement experienced moderate to severe pain [3]. Ketamine has been widely used around the world for approximately 50 years and its safety profile is demonstrated to be excellent in various settings [4–6]. Reactions such as vivid dreams and hallucinations are less common in children, especially after administration of low doses and when appear they are usually mild [4,7]. Ketamine can be administered intravenously, intramuscularly, orally, buccally, epidurally, nasally, and subcutaneously [8–10]. Previous studies showed that taking oral ketamine alone or in combination with other medications is an effective and safe method for premedication in children, and can lead to calming, reducing anxiety, better separation from parents, easier IV cannulation, easier use of anesthetic facemasks, and induction anesthesia. Moreover, oral ketamine did not have a significant side effect [11–18]. Thus, ketamine could be a good option for PSA in children. Other current uses of ketamine in children are postoperative pain, general anesthesia adjunct, and chronic pain [19,20]. Since oral ketamine has significant advantages compared to other routes of administration (*e.g.*, ease of administration, not invasive, and does not require specialized equipment), it is a recommended agent for PSA. Also, oral ketamine is a good option for analgesia and sedation in combination with other sedative agents such as midazolam for procedures in children such as laceration repair [21].

Children are very sensitive to pain and may require analgesia for painful procedures. Avoiding unnecessary pain is essential in children to avoid sensitization to pain episodes later in life. In this regard, ketamine has a well understood safety profile when administered intravenously and for short periods of time. However, it remains to be determined whether oral, non-invasive ketamine is an appropriate option for children in acute painful procedures, reducing their stress and feelings of discomfort. To the best of our knowledge, a low dose of oral ketamine for controlling pain and distress induced by IV-line placement has not been previously studied in children. Thus, in the present study, we aimed to evaluate the efficacy and safety of low dose oral ketamine for controlling pain and distress during IV cannulation in 3–6-year-old children.

## MATERIALS AND METHODS

This randomized, double-blind, placebo-controlled trial was conducted in the pediatric hospital affiliated with the University of Tehran (Iran). The present prospective study was approved by the research ethics committee of Tehran University of Medical Sciences (IRCT code: 201504251764N3). Patients were recruited from children scheduled for surgery admitted to pediatric wards and requiring an IV cannulation during admission. Diagnoses of children included different surgeries including inguinal hernia repair, undescended testicles, and hypospadias, among others. The inclusion criteria were: children aged 3 to 6, American Society of Anesthesiologists (ASA) class I, ability to tolerate use of the oral route, having no pain at baseline, and not needing emergency IV cannulation. The exclusion criteria consisted of having any medical condition requiring emergency procedures, any contraindication for ketamine use (including but not limited to high blood pressure [BP], high intracranial pressure, high intraocular pressure, heart failure, thyroid disease, respiratory system instability, and patients with established psychosis), taking ketamine or other analgesic in the last 24 hours, abnormal neurological exam, and allergy to orange juice. These patients were chosen to increase the homogeneity of the investigated group.

Children were randomly allocated to one of the two groups, using a computer-generated sequence. A researcher who no longer participated in the study opened opaque sealed envelopes in which random numbers were kept, and then prepared and administered the medication accordingly. For each group a questionnaire including demographic information, age, sex, weight, chief complaint, ASA class, primary diagnosis, concomitant medications taken, and other required information were recorded. Group 1 received 3 mg/kg ketamine mixed with orange juice up to 5 mL and group 2 received 5 mL orange juice alone just before IV-line placement. Also, we used distraction devices like toys, smart phone and tablet for all participants during the IV cannulation. A ketamine concentration of 3 mg/kg has been selected because previous studies have shown that this concentration is adequate as a premedication in children [18,22]. An experienced nurse, unaware of the groups assigned, performed IV cannulation to both groups 20–30 minutes after oral premedication [11–13,23]. The site of cannulation was the dorsum of the hand in all patients. To avoid the accidental exit of the cannula once it had been placed, the cannula was fixed using sterile transparent semi-permeable dressings. All patients were monitored for heart rate, respiratory rate, BP, and oxygen saturation using cardiorespiratory monitoring at baseline and after IV-line placement. The intensity of pain was measured during the insertion of the IV cannula using the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS scale) and the Wong-Baker Faces Pain Rating Scale (WBFS scale). The sedation level was assessed at baseline and before IV cannulation using a five-point sedation score (1: asleep, not readily arousable, 2: asleep,

but arousable, 3: calm but awake, 4: restless [anxious but not clinging to their parents or crying], 5: agitated [clinging to their parents and/or crying]) modified by Horiuchi et al. [24]. The facility of IV-line placement was measured by a 3-point scale (1: unable to insert IV line because patient was agitated, 2: able to insert IV line but patient was uncooperative [severely agitated and crying], 3: able to insert IV line and patient was cooperative). Furthermore, the time required for IV cannulation was defined as the time from inserting the needle through the skin to the blocking of the cap for injection of cannula. The adverse effects were also recorded one hour and 24 hours after intervention. The adverse effects after 24 hours were requested from the children's parents by telephone. The outcome variables were measured by the principal investigator who was unaware of the groups assigned.

In the study, injectable ketamine solution (50 mg/mL) produced by Rotexmedica GmbH company (Trittau, Germany) was used. All the steps were performed under direct observation of a pediatric anesthesiologist and clinical pharmacist.

The main outcome variable of the study was the level of pain during IV cannulation assessed by the CHEOPS and WBFS scales. Secondary outcome variables included changes in the vital signs, sedation level, facility of IV-line placement, length of procedure, and the incidence of adverse effects.

### 1. Statistical analysis

Normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Categorical variables were presented as number (percentage) and were compared using the chi-square test between groups. Continuous variables with and without normal distributions were presented as mean (standard deviation [SD]) and median (interquartile range [25th–75th]) respectively. Continuous variables with and without normal distributions were assessed using the *t*-test and Mann–Whitney test respectively. The analysis of covariance (ANCOVA) test was used to compare mean difference (before and after) of continuous variables between groups. Spearman's correlation coefficient was used to determine the relationship between the pain scales. All statistical analysis was performed in SPSS software ver. 16 (SPSS Inc., Chicago, IL), but the difference in medians between the two groups (ketamine and placebo) and confidence interval (CI) was done using GraphPad Prism ver. 9 (GraphPad Software, San Diego, CA). *P* values less than 0.05 were considered statistically significant.

### 2. Sample size

According to Javid et al. [25], by considering type I and type II error to be 0.05 and 0.2, respectively, and the mean (SD of CHEOPS scale) in the ketamine and placebo groups to be 2.98 (0.9) and 3.37 (0.37), respectively, and the attrition rate to be 15%, the calculated sample size was 80 subjects in each group.

## RESULTS

During the study period, 170 children were eligible to participate in the study. In 10 cases, the parents did not sign the informed consent, thus 160 children were finally included in the study, and were randomly assigned to 2 groups, with 79 and 81 children entering the ketamine and the placebo groups, respectively. The demographic characteristics in the two groups are shown in **Table 1**. There was no significant difference in age, sex, and weight between the two groups. Diagnoses in the two groups were similar without any significant differences between the groups ($P > 0.05$), with inguinal hernia repair being the most common diagnosis. The vital signs of children at baseline and after IV cannulation are presented in **Table 2**.

### 1. Effectiveness measures of ketamine

The median (interquartile range [IQR]) CHEOPS score was 6 (5–8) and 10 (9–11) in ketamine and placebo groups respectively. According to the Mann–Whitney test the difference between groups was statistically significant (95% CI: 3, 4, $P < 0.001$).

The median (IQR) WBFS score was 4 (2–6) for the ketamine group and 10 (8–10) for the placebo group, and the difference was statistically significant (95% CI: 4, 6, $P < 0.001$). The correlation between the pain scales was statistically significant (correlation coefficient = 0.86, $P < 0.001$).

The five-point sedation scores obtained from the ketamine and placebo groups are shown in **Fig. 1**. Baseline sedation scores were not significantly different between the two groups (median [IQR] five-point sedation score for both groups 3 [3–3]; 95% CI: 3, 3, $P > 0.05$). The median [IQR]

**Table 1.** Demographic characteristics of the patients

| Variable | Ketamine (n = 79) | Placebo (n = 81) | *P* value |
|---|---|---|---|
| Age (mo) | 53.26 ± 12.3 | 52.68 ± 14.4 | 0.782[a] |
| Weight (kg) | 17.01 ± 4.17 | 16.84 ± 3.72 | 0.793 |
| Male sex | 59 (74.7) | 66 (81.5) | 0.367[b] |

Values are presented as mean ± standard deviation or number (%).
[a]According to *t*-test. [b]According to chi-square.

**Table 2.** Vital signs in the two groups in baseline and after IV cannulation

| Vital signs | Placebo (n = 81) | | Ketamine (n = 79) | | *P* value[a] |
|---|---|---|---|---|---|
| | Baseline | After IV cannulation | Baseline | After IV cannulation | |
| SpO2 | 97.73 ± 1.06 | 97.67 ± 0.99 | 97.93 ± 1.04 | 97.7 ± 1.25 | 0.639 |
| HR | 105.92 ± 12.8 | 113.3 ± 17.7 | 111.63 ± 13.5 | 113.6 ± 11.08 | 0.021 |
| RR | 24.41 ± 3.56 | 25.86 ± 3.59 | 26.07 ± 4.12 | 25.57 ± 3.67 | < 0.001 |
| SBP | 102.16 ± 11.08 | 105.08 ± 13.9 | 100.56 ± 8.21 | 105.3 ± 9.83 | 0.462 |
| DBP | 65.93 ± 9.11 | 68.67 ± 12.6 | 62.62 ± 6.95 | 68.5 ± 8.5 | 0.117 |
| MAP | 77.95 ± 9.26 | 80.67 ± 12.4 | 75.24 ± 6.72 | 80.64 ± 8.35 | 0.152 |

Values are presented as mean ± standard deviation.
IV: intravenous, SpO2: arterial oxygen saturation, HR: heart rate, RR: respiratory rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure.
[a] Is presented according to analysis of covariance test and compare mean difference (before and after) of vital signs between groups.

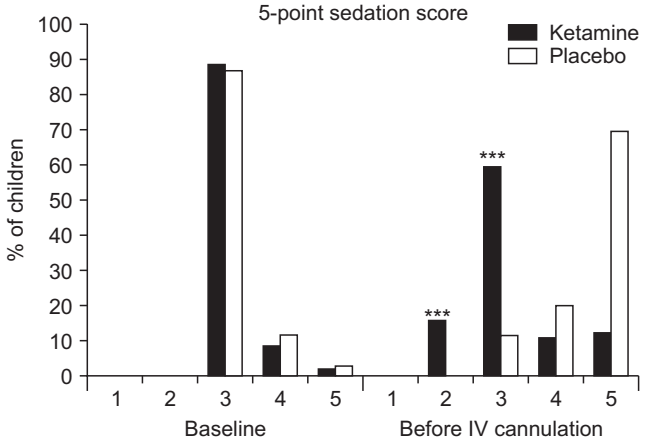


**Fig. 1.** Baseline sedation scores and sedation scores before intravenous (IV) cannulation. X-axis shows sedation scores at the mentioned time interval. ***$P < 0.001$.

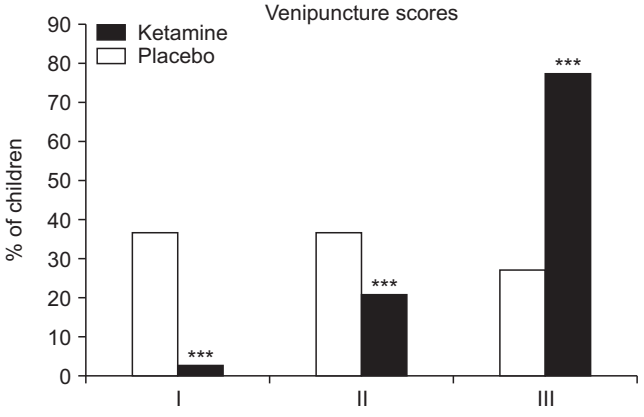


**Fig. 2.** Percentage of patients in each category of intravenous (IV) sedation scale. I: IV cannulation failure, II: uncooperative during IV cannulation, III: cooperative during IV cannulation. ***$P < 0.001$ (according to chi-square test).

five-point sedation score before IV cannulation were significantly different between the groups (3 [3–3] and 5 [4–5] for ketamine and placebo groups respectively), finally, the median score of those in the ketamine group was two points lower than that in the placebo group (95% CI: 1, 2, $P < 0.001$). The incidence of effective sedation (score 2 or 3) was significantly higher (65%) in the ketamine group in comparison with the placebo group (95% CI: 54%, 76%, $P < 0.001$). In addition, in the ketamine group, about 80% of effectively sedated children were calm and awake (score 3). There was no incidence of excessive sedation (score 1) in any case in our study. For IV-line placement (evaluated by a 3-point scale [venipuncture score]) the percentage of children who cooperated in the ketamine group (77.2%) was significantly higher than the placebo group (27.2%) (95% CI: 37%, 63%, $P < 0.001$) (**Fig. 2**).

The average duration of the procedure from the insertion of the needle through the skin to the blockage of the cap for cannula injection were 15 and 30 seconds for the ketamine and placebo groups, respectively ($P < 0.001$).

### 2. Evaluation of adverse effects

Adverse effects were recorded one hour after taking oral ketamine and included nausea (12.4%), vomiting (8.8%), and sialorrhea (2.5%), while no adverse effects were observed in the placebo group. Serious adverse effects such as hemodynamic instability, respiratory depression, and airway complications were not observed in any of the children. All adverse effects were transient and did not compromise the stability of children and there was no need for any interventions. Also, there were no episodes of emergency reactions or abnormal movements in either group. No adverse effects were reported by parents during the follow-up after 24 hours from the procedure.

## DISCUSSION

Medical procedures, including IV cannulation, are problematic in children because of their distress and lack of

cooperation. Parents also get stressed when their children are agitated, and this makes the procedure even more difficult. The present study was designed according to previous studies and the importance of IV cannulation in all children's hospital wards. To the best of the authors' knowledge, this is the first prospective randomized study in which the analgesic effect of low dose oral ketamine (3 mg/kg) was evaluated to control pain and distress in ASA class I children of 3–6 years old during non-emergency IV-line placement.

The use of premedication, due to its potential adverse and side effects should be applied when it is considered necessary and not as a general practice. For this reason, the design of this study can be criticized because it was a controlled trial with a placebo group. Thus, the most challenging part may be really knowing which patients would benefit from the properties of the premedication, taking into account all the potential adverse events associated with the administration of ketamine. Taking into account that premedication is generally not given for pediatric IV cannulation, this study was designed as a double-blind, randomized, placebo-controlled trial. On the other hand, a low dose of oral ketamine for placement of the IV placement in children had not yet been studied, therefore, it is reasonable to assess the efficacy of this agent in a first step with due comparison to a placebo. In case of good efficacy and the lack of serious adverse effects, ketamine can be compared with other medications to develop an ideal premedication in this setting.

PSA are evolving fields practiced by professionals in various clinical settings, and the use of ketamine in this field is gaining popularity [2,19]. The bioavailability of oral ketamine is approximately 20% to 30% [26,27], time to peak in plasma and its onset of analgesic action is 30 minutes, while the sedative activity depends on the administered dose. The half-life of ketamine is short and higher than the half-life of other sedative or analgesic drugs such as nitrous oxide, propofol, and fentanyl [23,28,29]. In comparison to IV administration, orally administered ketamine has fewer adverse effects, and no serious drug interaction has been reported [30,31]. To prepare the oral formulation of ketamine using parenteral dosage form (100 mg/mL IV solution), the appropriate dose is mixed in 0.2 to 0.4 mL/kg of cola, sour cherry juice, or other beverages [12,23,32]. Ketamine has been evaluated as a premedication in several studies [18,23,24,33]. Narendra et al. [34] compared the administration of intranasal ketamine (5 mg/kg) with intranasal midazolam (0.2 mg/kg) for pediatric premedication. In that study, a pain scale used, but the placement of the IV line could not be inserted in 12% of the children [34]. In another study, the effectiveness of rectal midazolam (0.5 mg/kg), rectal ketamine (3 mg/kg), and a combination of them for preoperative sedation was investigated. The facilitation of parental separation and the IV-line placement in young children was also evaluated. The dose of ketamine was similar to that used in the present study and the researchers reported that 56% of the children cried during IV-line placement in the ketamine group. However, the study showed that rectal midazolam with or without ketamine, facilitated parental separation and the cannulation process. Additionally, in the ketamine plus midazolam group, more children slept, and rectal administration may cause distress in children [33]. Motamed et al. [35] compared 3 different sedation regimens in children undergoing upper gastrointestinal endoscopies. The results evidenced that the combination of ketamine (5 mg/kg) and midazolam (0.1 mg/kg) is advantageous by including less sedation failure, faster recovery, decreased benzodiazepine needs, easier IV cannulation, and less pain associated with the cannulation. However, no pain scale was used during and after the procedures. Oral midazolam (0.5 mg/kg), and oral ketamine (5 mg/kg) with oral midazolam (0.5 mg/kg), acetaminophen (10 mg/kg), and codeine (1 mg/kg) to provide sedation and analgesia for painful procedures was also evaluated in burned children. Pain levels were assessed using the CHEOPS scale, and it was reported that a better analgesia was achieved by a combination of ketamine with midazolam [36]. Additionally, the efficacy of oral ketamine (10 mg/kg) was determined as PSA in children between 1 and 7 years of age undergoing laceration repair. It was reported that children treated with ketamine better tolerated local anesthesia and suturing when compared to control children, but no pain scale was used [37]. In another study, the administration of 4, 6 or 8 mg/kg ketamine by mouth was investigated in 80 children (2–8 years) undergoing elective surgery under general anesthesia [23]. The results showed that children receiving 8 mg/kg were significantly calmer and anesthesia induction was more comfortable than those of the other groups. After surgery, in the recovery room, the incidence of nausea and vomiting did not differ between the groups, although the number of patients exhibiting nystagmus was significantly higher in the 8 mg/kg ketamine group. Furthermore, in a study accomplished by Sekerci et al. [18], the results showed the effect of oral ketamine at a dose of 3 mg/kg, as well as a dose of 6 mg/kg, on easier separation from parents, easier acceptance of mask application, and led to an increased level of sedation and a better emotional state during the recovery phase. Also fewer side effects, including nystagmus and vomiting, were reported in this study.

The only published study on oral ketamine during IV cannulation in children compared the efficacy of the combination of ketamine-midazolam with midazolam alone

for reducing stress during IV cannulation in ninety-two ASA I or II children (1–5 years) scheduled for computed tomography imaging. Children were assigned to three groups: midazolam (0.5 mg/kg in 5 mL of honey), midazolam-ketamine (0.25 mg/kg midazolam and 1 mg/kg ketamine in 5 mL honey) and a placebo group receiving honey alone. Sedation and venipuncture scores were recorded; however, no pain scale was used. More children cried during venipuncture in the placebo group when compared to the other two treatment groups. An additional reduced dose of ketamine in the combination group allowed the children to remain awake, calm, and cooperative for IV cannulation [38]. In another study, the combined oral administration of midazolam (0.5 mg/kg) plus oral ketamine (5 mg/kg) resulted in a deeper sedation than midazolam alone, with less children needing IV sedation [21]. Our study showed the same effect for oral ketamine alone as midazolam. Moreover, our study also demonstrated a similar effect for low dose oral ketamine. In the above-mentioned study [38], lidocaine and prilocaine containing cream was applied at the site of IV cannulation, whereas in our study, no topical anesthesia was used.

Like other studies [24,36,37], all the complications reported in our study were transient and did not compromise the stability of the patients. Green et al. [5,6] reported that emesis occurred in 6.7% of 1,022 intramuscular injections of ketamine in children [6] and 3.8% of 156 children treated with IV ketamine suffered from emesis [5]. In the study by Motamed et al. [35] and in the present study in which oral ketamine was used, a 17.6% and 8.8% incidence of vomiting, respectively, was observed. Skeletal muscle hyperactivity including extensor spasms, myoclonus, random movements of the extremities, and fasciculation may be seen after ketamine administration and is often mistaken for seizure activity [39]. According to previous studies [18,37], 13% of children had abnormal movements and tongue fasciculation with ketamine. However, no child presented abnormal movements in the present study. The incidence of emergence reactions like vivid dreams, extracorporeal experiences, hallucinations, delirium, and confusion following ketamine administration, ranging from 0% up to 9%, has been reported [39,40]. Probably due to the low dosage and the oral route of administration, no emergency phenomena were detected in the present study. However, it is important to emphasize the fact that sedation and anesthesia should be avoided if it is not really necessary. In fact, it has been shown that a combination of systematic preparation, rehearsal, and supportive care performed prior to a stressful procedure showed significantly less disgust and more cooperation, and their parents reported significantly greater satisfaction and less anxiety [41].

Oral chloral hydrate can reduce anxiety and postoperative pain, and improve anesthesia induction, but it tastes worse than other oral medications. Furthermore, it requires a higher dose to keep the patients calm and peaceful at the time of mask application for inhalation induction. This medication had a little impact on emergence delirium and postoperative maladaptive behavior, that lead to its reduced use. In a study performed by Schechter et al. [42], the effect of oral transmucosal fentanyl citrate (OTFC) was evaluated for bone marrow aspiration or lumbar puncture procedures. The results showed that OTFC was an effective method of relieving pain in children, but the frequency of vomiting may restrict its clinical usefulness. Another study comparing the effects of dexmedetomidine and midazolam showed that these two drugs are effective as premedicants in calming children, but dexmedetomidine can lead to bradycardia and hypotension [43-47].

A limitation in the present study would be that the existence of side effects in the children following oral ketamine premedication has not been followed long-term. In this sense, it has been reported that ketamine 6 mg/kg induced nightmares, restless sleep, and negative memories in some of the children treated after one week [22]. It would also be beneficial to compare ketamine with oral midazolam or oral fentanyl in terms of its effect on pain and distress during IV cannulation in future studies.

The present study demonstrated that low dose oral ketamine (3 mg/kg) effectively relieved pain and distress during IV cannulation in children, significantly enhanced their cooperation, and also reduced the duration of the procedure when compared to the placebo group. The children experienced some minor adverse reactions after ketamine intake, but none of them was considered serious and none required any additional intervention. Therefore, a low dose of oral ketamine can be considered in pediatric emergency departments and wards to improve venipuncture compliance in highly stressed and uncooperative children.

## DATA AVAILABILITY

The datasets supporting the finding of this study are available from the corresponding author upon reasonable request.

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## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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