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PEDIATRIC ORIGINAL

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Clinical effects of adding fludrocortisone to a hydrocortisone-based shock protocol in hypotensive critically ill children

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Abstract *Background:* Adult studies evaluating corticosteroids have found varied efficacy. One study showing mortality benefit utilized fludrocortisone (FLU) and hydrocortisone (HC) (Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 288:862–871, 2002). Use of FLU in children has not been described. We developed a protocol using HC for systemic inflammatory response syndrome (SIRS) and shock with optional addition of FLU. *Hypothesis:* Addition of FLU to a HC-based steroid protocol is associated with decreased vasopressor duration without adverse effects in hypotensive children with SIRS. *Methods:* Retrospective review of low-dose HC and FLU supplementation in children with SIRS and fluid refractory shock. Patients receiving FLU in addition to HC were compared with patients receiving HC alone. *Results:* Ninety-seven children with SIRS and shock received steroids. Sixty of 97 (62%) received FLU in addition to HC. Seventy-three children required dopamine (DA) infusion, and 56 received norepinephrine (NE). Overall mortality was 7/97 (7%), with 5/7 (71%) nonsurvivors receiving HC + FLU. Fifty of 97 (52%) children with SIRS met definition for sepsis. Septic children who received HC + FLU required NE for significantly shorter duration than those receiving HC alone ($p = 0.011$). Nineteen of 60 HC + FLU patients (32%) developed nonsymptomatic hypokalemia. Hypokalemia was significantly more common in HC + FLU patients compared with those receiving HC alone ($p = 0.05$). *Conclusions:* Overall, addition of FLU in children with SIRS was not associated with decreased vasopressor duration or vasopressor score. However, HC + FLU was associated with shorter duration of NE support in the septic subgroup. Hypokalemia was a frequent adverse finding with HC + FLU ($p = 0.05$). Use of FLU should be considered in further studies evaluating the role of steroids in refractory pediatric septic shock.

Keywords Adrenal insufficiency · Pediatric · Critical care · Cortisol

Introduction

The role of corticosteroids in management of shock and hypotension remains a controversial topic. Previous multicenter studies employing high-dose corticosteroids empirically in septic adults showed no benefit and potential harm [1–4]. However, interest was renewed by encouraging results using lower doses of corticosteroids in critically ill adults with relative or absolute adrenal insufficiency [5–9]. A randomized trial of low-dose

steroid supplementation demonstrated mortality benefit in adults with relative adrenal insufficiency [1]. More recent multicenter studies, most notably the CORTICUS trial, showed some physiologic benefits, but have not been able to duplicate improvements in survival [10, 11]. Potential reasons for differences in trial results are myriad, but one suggested possibility is related to the steroid regimen employed in treatment protocols. The Annane study utilized the mineralocorticoid fludrocortisone (FLU) in addition to HC. The rationale for FLU addition includes the potential benefits of enhanced volume retention and vascular tone related to FLU [12]. However, use of FLU is hampered by its formulation only as an enteral preparation, and the degree of absorption through the gastrointestinal tract of hypotensive patients on vasopressors remains uncertain [13–15].

Experience with use of FLU as a supplement to HC has not been described in pediatric shock. In 2005, our center developed a standardized protocol-based approach to empirically initiate dosing of HC, with a provision for use of FLU supplementation, in children with SIRS, shock, and hypotension not responsive to fluid resuscitation and requiring vasopressors. We reviewed our experience with HC and FLU supplementation in these children, hypothesizing that addition of FLU to supplement HC would be associated with shorter vasopressor duration compared with HC use alone.

Materials and methods

We performed a retrospective review of patients receiving protocolized low-dose glucocorticoid and mineralocorticoid supplementation in a quaternary-care pediatric intensive care unit (PICU) at Children's Healthcare of Atlanta at Egleston in Atlanta, Georgia, between July 2005 and July 2007. The study was approved by the institutional review board at Children's Healthcare of Atlanta, and a waiver of informed consent was granted.

Patients included for review were children up to 18 years of age admitted to the PICU for, or who subsequently developed, systemic inflammatory response syndrome (SIRS) with associated hypotension requiring fluid resuscitation and vasopressors [16, 17].

Hypotension was defined as mean arterial pressure less than fifth percentile for age [17]. Septic shock was defined and classified according to American College of Critical Care Medicine (ACCM) definitions of cardiovascular support [17]. SIRS without sepsis was defined as a pathophysiologic shock state that was attributable to noninfectious etiologies.

Vasopressor requirement was defined as $\geq$10 mcg/kg/min dopamine and/or $\geq$0.1 mcg/kg/min norepinephrine following at least 60 cc/kg fluid resuscitation. Patients were excluded if they had preexisting neuroendocrine disorder, had received steroids for other indications, were being treated with or had recent history of antipsychotic medication use, were human immunodeficiency virus (HIV) positive, or had received etomidate in the week prior to admission. Patients were further excluded from review if violations in the management protocol occurred, including inappropriate discontinuation of steroids, or for protocol violations (i.e., not fluid resuscitated, not started on steroids or vasopressors, steroids stopped prematurely).

Steroid supplementation protocol

We developed a steroid supplementation protocol at our center which was modified from a previous standard steroid management protocol for adult septic shock patients developed by Annane et al. [1]. Children with hypotension or shock unresponsive to fluid resuscitation and receiving vasopressors received a loading dose of 100 mg/m^2 (maximum 200 mg) hydrocortisone, followed by 25 mg/m^2/dose given every 6 h. The dosing was continued for 7 days, and then discontinued without taper [17]. Additionally, based on attending physician discretion, children could also be initiated on enteral fludrocortisone once daily for 7 days at dose of 50 mcg PO/NG/GT for children <35 kg and 100 mcg PO/NG/GT for children $\geq$35 kg (Fig. 1). Recommended FLU dosing range for primary adrenal insufficiency in children is 100 mcg daily [1]. Children with primary adrenal insufficiency require higher doses of 9-alpha-fludrocortisone in infancy and childhood [18]. Empirically, a FLU dose of half of primary adrenal insufficiency dosing was chosen in protocol development for children <35 kg.

Data collection

Demographic information was obtained, including age, gender, ethnic group, admission diagnosis, and history of chronic disease. Volume of fluid resuscitation, duration of mechanical ventilation, length of PICU stay (LOS), amount/duration of medication used, development of secondary infections, and duration of shock were also a few of the parameters examined.

Severity of illness was measured by calculation of Pediatric Risk of Mortality III (PRISM III) score and pediatric logistic organ dysfunction (PELOD) score. Rebound hypotension was determined, defined as development of low blood pressure within 24 h of discontinuing steroids. The number of vasopressor-free days at day 7 after protocol initiation was determined. Vasopressor scores at day 1 and 7 of protocol institution were also calculated [19].

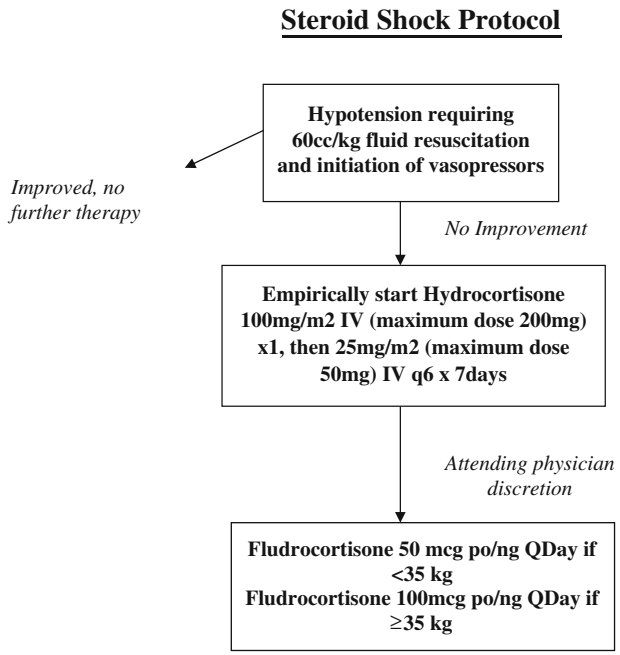

Fig. 1 Algorithm for glucocorticoid and mineralocorticoid supplementation. Steroids were continued for 7 days and discontinued without any taper. Use of fludrocortisone was left to physician discretion

Statistical analysis

Patients' demographic, clinical, and laboratory data were collected in an electronic database (Excel 2007; Microsoft Redmond, WA, USA). Summary statistics were compiled to allow description of the patient population, and all analyses were performed using Software Predictive Analytics software and solutions (version 17, 2009; SPSS Inc., Chicago, IL, USA). Comparisons made between HC + FLU and HC alone groups, as well as septic and nonseptic patients, were performed using chi-square test or Fisher's exact test.

Results

Ninety-seven children with SIRS and shock who received steroids by protocol were identified (Table 1). Fifty of 97 (52%) were septic and 47 of 97 (48%) were nonseptic. Primary diagnoses in nonseptic SIRS patients included but were not limited to closed head injury (10), aspiration (6), cardiac failure (6), seizures (6), or near drowning (3). Median patient age was 72.5 months (range 0.5–295 months). Median PRISM score was 15 (range 13–31) and did not differ between septic and nonseptic SIRS patients (Table 2). Median fluid resuscitation was 60 cc/kg (range 40–140 cc/kg) at 1 h and 100 cc/kg (60–200 cc/kg) at 6 h, and did not differ between groups (Table 3). Seventy-three children required dopamine (DA) infusions, and 56 required norepinephrine (NE). Ten patients required epinephrine, and four received vasopressin. Overall mortality was 7/97 (7%).

Sixty of 97 patients (62%) received both HC + FLU. Median PRISM III and PELOD scores were not significantly different between HC + FLU and HC groups. Children who received HC + FLU in this cohort were significantly younger (Table 1). Clinical outcomes between the two groups were compared (Tables 1, 3). No differences were seen in length of stay, incidence of ventilator-associated pneumonia (VAP), catheter-associated bloodstream infections (CA-BSI), or rebound hypotension. Five of seven (71%) patients dying received HC + FLU, compared with 2/7 (29%) HC alone, but this was not statistically significant.

Complications included nonsymptomatic hypokalemia after 7 days of therapy in 19/60 FLU patients (32%) with potassium <3 mmol/l in 12 (20%). Hypokalemia was significantly more common in HC + FLU patients compared with those receiving HC alone ($p = 0.05$). No significant difference in serum sodium at 7 days was seen.

No difference in age was seen between septic and nonseptic SIRS children receiving protocol treatment. Hypokalemic events did not differ between septic versus nonseptic children (p = NS). Incidence of hypokalemia in septic HC + FLU was 9/50 (18%) versus 2/50 (4%) in septic HC alone (p = NS).

Vasopressor duration did not differ between nonseptic SIRS patients receiving HC + FLU (median 26 h, range 2–1,082 h) and those with HC alone (median 34.5 h, range 1–1,050 h) (Fig. 2a). No difference in vasopressor score was seen overall or in the subset of septic patients with FLU. For the subset of septic patients who received NE, those with HC + FLU required NE for significantly shorter duration (median 5 h, range 1–168 h) than those with HC alone (median 16 h, range 1.5–140 h) ($p = 0.011$) (Fig. 2b). Duration of DA use did not differ between the HC + FLU and HC groups in septic children (Table 4).

Discussion

Use of FLU in treatment protocols distinguishes studies evaluating use of corticosteroids in septic shock [1, 13]. Potential benefit from addition of FLU could accrue from its reported effects on fluid volume and vascular tone, or its role as an anti-inflammatory agent [12]. Studies have shown that transient hyperreninemic hypoaldosteronism is common in patients with septic shock [20]. Abnormal aldosterone levels are associated with greater sodium and fluid depletion and are followed by increased incidence of acute renal failure requiring renal replacement therapy and prolonged length of stay in ICU [20]. Fludrocortisone

Table 1 Demographic and clinical care characteristics of all hypotensive patients with comparison by FLU + HC and HC alone

	All patients	HC + FLU patients	HC alone	*p*-Value* (HC + FLU versus HC alone)
Total patients	97	60	37	0.02
Median age in months (range)	72.5 (0.5–295)	111 (1–263)	27 (0.5–295)	0.045
Septic	50	31 (52%)	19 (51%)	NS
Nonseptic	47	29 (48%)	18 (49%)	NS
Median PELOD (range)	23 (22–42)	27 (22–42)	22 (21–41)	NS
Median PRISM III	15 (13–31)	15 (12–27)	15 (13–31)	NS
Length of ICU stay (days)	11 (1–104)	9.5 (1–53)	14 (2–104)	NS
Length of hospital stay (days)	20 (2–226)	19 (2–226)	21 (2–127)	NS
Mechanical ventilation (%)	68/97 (70%)	40/60 (67%)	28/37 (76%)	NS
Ventilator days (range)	8 (0–90)	7.5 (0–50)	11 (0–90)	NS
Mortality	7/97 (7%)	5 (8%)	2 (5%)	NS

* Statistical significance between HC + FLU and HC alone by chi-square analysis

Table 2 Demographic and clinical care characteristics of all hypotensive patients with comparison by septic and nonseptic

	All patients	Septic SIRS	Nonseptic SIRS	*p*-Value* (septic versus nonseptic)
Total patients	97	50	47	NS
Median age in months (range)	72.5 (0.5–295)	90 (0.5–295)	29 (1–215)	0.024
Median PELOD (range)	23 (22–42)	23 (20–40)	23 (20–42)	NS
Median PRISM III (12–31)	15 (13–31)	15 (12–30)	15 (13–31)	NS
Length of ICU stay (days)	11 (1–104)	8 (1–104)	13 (2–101)	NS
Mechanical ventilation (%)	68/97 (70%)	32/50 (64%)	36/47 (77%)	NS
Ventilator days (0–90)	8 (0–90)	7.5 (1.5–87)	9.5 (3–90)	NS
Mortality	7/97 (7%)	4/50 (8%)	3/47 (6%)	NS

* Statistical significance between septic and nonseptic state by chi-square analysis

Table 3 Vasopressor and hemodynamic characteristics of all patients with comparison by HC + FLU and HC alone

	All patients	HC + FLU	HC alone	*p*-Value (HC + FLU versus HC alone)
Vasopressor-free days at 7 days	6.2 (0–6.8)	6 (0–6.8)	6 (0–6.8)	NS
Vasopressor score hour 0	15 (10–120)	16 (10–120)	14 (9–70)	NS
Vasopressor score hour 4	5 (0–50)	6 (0–50)	5 (0–30)	NS
Vasopressor score hour 24	0 (0–78)	0 (0–78)	0 (0–78)	NS
Vasopressor score day 7	0 (0–80)	0 (0–10)	0 (0–80)	NS
Duration on DA (h)	24 (2–1,082)	23.5 (2–1,082)	24 (2–432)	NS
Duration DA from introduction of steroids (h)	8 (1–1,050)	9 (1–1,050)	6 (1–200)	NS
Duration on NE (h)	28 (2–566)	28 (2–566)	23.25 (5–173)	NS
Duration NE from introduction of steroids (h)	10 (1.5–545)	12.5 (1.5–140)	6 (1.5–545)	NS
Rebound hypotension	20/97 (21%)	11/97 (11%)	9/97 (9%)	NS

Values represent median for the respective groups. All patients received steroids; see "Methods" for definitions. No significant differences were seen between FLU and non-FLU patients by chi-square analysis. No differences were noted between septic and nonseptic subsets

would provide a more focused and potent therapy for hyperreninemic hypoaldosteronism. The physiologic effect of FLU would provide benefit to conditions causing the spectrum of SIRS, such as sepsis [12, 20, 21].

Critics of FLU inclusion in a steroid protocol argue that supraphysiologic levels of HC should obviate the need for FLU supplementation, because HC acts on FLU receptors [12, 14]. One study noted that the 11β-hydroxysteroid dehydrogenase type II enzyme activating cortisol is upregulated in certain conditions such as sepsis, and thus prevents its binding to mineralocorticoid receptors [22]. A review of FLU in critically ill adults noted a significant decrease in mortality, with 74% of patients in the HC alone group dying compared with 46% of patients in the HC + FLU group ($p = 0.018$) [23]. No adverse effects were noted in these studies.

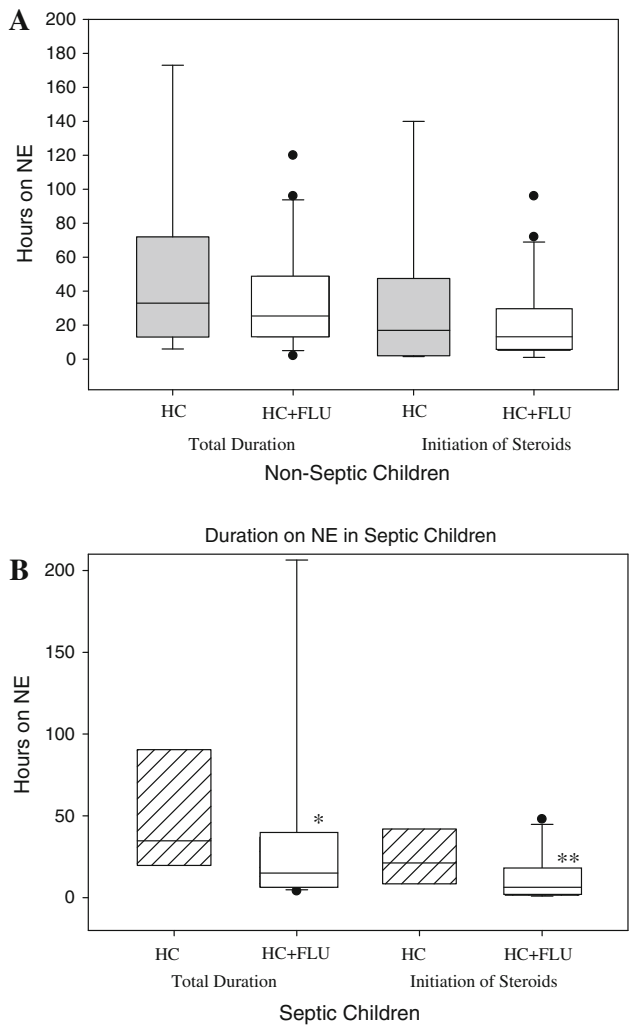

Fig. 2 **a** Duration of norepinephrine (NE) infusion in children with SIRS and vasopressor-dependent shock receiving fludrocortisone (FLU) in addition to hydrocortisone (HC) compared with HC use alone. No significant differences were seen between groups. *Box plot* of NE duration in nonseptic children. Values in hours are represented by *box*, with *boundary* closest to zero indicating 25th percentile, *line* within *box* marking the median, boundary farthest from zero indicating 75th percentile, *whisker bars* indicating 10th and 90th percentiles, and *dots* representing outliers. **b** Duration of NE dosing in SIRS children with vasopressor-dependent septic shock. *Box plot* of NE duration in septic children. Values in hours are represented by *box* with *boundary* closest to zero indicating 25th percentile, *line* within *box* marking the median, boundary farthest from zero indicating 75th percentile, *whisker bars* indicating 10th and 90th percentiles, and *dots* representing outliers. $*p = 0.011$ for total duration of NE infusion, and $**p = 0.009$ for duration following initiation of steroids in septic children

This is the largest reported cohort of children receiving FLU as part of a protocol for treatment of vasopressor-dependent shock. Overall, in children with SIRS, vasopressor duration was not reduced with addition of FLU. However, reduction in NE duration was seen with addition of FLU in the cohort of septic patients. These data are consistent with findings by Annane suggesting that vasopressor-dependent septic patients may indeed benefit from addition of FLU. Although severity of illness was not significantly different between patients in the HC + FLU and HC groups, septic patients receiving HC + FLU had significant reduction in vasopressor duration of NE (Fig. 2b). These findings suggest that FLU provided an additive mineralocorticoid effect compared with HC alone. Neither dose nor duration of dopamine use was significantly reduced with FLU addition (Table 3). It is possible that no difference was seen because approximately half of patients required both NE and dopamine. In our PICU, weaning of NE likely occurred first, resulting in a large number of patients who remained on an unchanged dose of dopamine pending weaning off norepinephrine. This would have artificially prolonged DA in those patients receiving both infusions.

Hypokalemia was frequent and more likely to occur with FLU use. Treatment of hypokalemia in these patients was individualized, and replacement was unnecessary in most patients. This finding of increased hypokalemia, while of uncertain clinical significance, does suggest that FLU, even given enterally, has adequate bioavailability. This quality of FLU physiologic effects, even in "underperfused" states, has been speculated [13].

A recent follow-up study from the corticosteroid therapy and intensive insulin therapy for septic shock (COIITSS) study investigators [24] did not demonstrate outcome benefit with addition of FLU to HC in adults. In contrast to our cohort, the study was performed in elderly adults with high mortality (over 45%). In this study, no difference in mortality was seen between the FLU (42.9%) treated and HC alone (45.2%) groups. The study also noted "the direction of the point estimate may favor use of fludrocortisone, but size of the effect was small" [24].

All SIRS patients with vasopressor-dependent shock received therapy utilizing our center's steroid protocol. Preliminary studies from our center suggest benefit of steroid protocol use on vasopressor duration in both nonseptic and septic patients [25]. However, in our study, association of benefit on vasopressor response was only seen in septic patients receiving HC + FLU, suggesting further studies should be focused on septic SIRS patients.

Several factors limit the interpretation of our study, including its retrospective design, lack of randomization, absence of routine adrenocorticotropic hormone (ACTH) stimulation testing, lack of criteria guiding timing of steroid initiation and of FLU addition, and small sample size. Timing of steroid initiation was at physician discretion, leading to a potential difference in duration of vasopressor requirement before steroids were chosen.

Further studies are needed to determine if FLU response correlates with adrenal insufficiency. Further

Table 4 Demographic, clinical, vasopressor, and hemodynamic characteristics of septic patients with comparison by HC + FLU and HC alone

	All septic patients	Septic HC + FLU	Septic HC alone	*p*-Value (HC + FLU versus FLU)
Total patients	50	31	19	NS
Median age in months	90 (0.5–295)	132 (1–263)	28 (0.5–295)	0.04
Median PELOD	23 (20–40)	30 (20–40)	22 (20–34)	NS
Median PRISM III	15 (12–30)	15 (12–24)	15 (12–31)	NS
Length of ICU stay (days)	8 (1–104)	6 (1–53)	14 (2–104)	NS
Mechanical ventilation (%)	32/50 (64%)	17/31 (59%)	15/19 (79%)	NS
Ventilator days	7.5 (1.5–87)	6 (1.6–26)	12 (2–87)	NS
Mortality	4/50 (8%)	2/31 (6%)	2/19 (11%)	NS
Vasopressor-free days at 7 days	6.22 (0.5–6.9)	6.1 (0.5–6.7)	6.5 (4–6.9)	NS
Vasopressor score hour 0	15 (10–100)	14.5 (10–100)	18.5 (10–50)	NS
Vasopressor score hour 4	5	5	4	NS
Vasopressor score hour 24	0	0	0	NS
Duration on DA (h)	17.5 (2–432)	17.75 (2–345)	21.5 (2–432)	NS
Duration DA from introduction of steroids (h)	9 (1–288)	9.5 (1–228)	6 (1–200)	NS
Duration on NE (h)	25.5 (4–560)	13 (4–360)	34.75 (6–560)	0.02
Duration NE from introduction of steroids (h)	11 (1–168)	5 (1–168)	16 (1.5–140)	0.01

Values represent median with ranges below for the respective groups. Fludrocortisone is associated with decreased NE requirement but not vasopressor score over time

evaluation of the efficacy of ACTH stimulation is underway at our center using a standard ACTH stimulation test in all patients meeting study criteria noted in this series.

While this report provides the largest published cohort of children receiving FLU as part of a steroid protocol, sample size in this study limits the applicability of the results to practice. Data from such a sample size can be used, however, to power future studies in children. Continued application of data from adult studies to children is hampered by differences in comorbidities, pathophysiologic processes of sepsis, and mortality outcomes specific to children [26, 27]. Dynamic and evolving developmental differences in the hypothalmopituitary axis of a growing child make comparisons difficult and necessitate more pediatric-specific study [27–29].

Conclusions

Addition of FLU to HC in a corticosteroid protocol for pediatric shock was not associated with shorter vasopressor duration in children with SIRS. However, in a smaller cohort of septic children, FLU addition was associated with decreased NE requirement, but not vasopressor score over time. Patients receiving FLU had increased incidence of hypokalemia. This highlights the need for a randomized trial evaluating addition of FLU to steroid protocols in children with septic shock.

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Conflict of interest The authors have declared no conflicts of interest.

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