

Management of severe spasticity with and without dystonia with intrathecal baclofen in the pediatric population: a cross-sectional study

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ABSTRACT

Objective To investigate the differences in delivery mode, daily dose, and catheter tip location in pediatric patients using intrathecal baclofen (ITB) pumps with spasticity plus dystonia versus spasticity alone.

Methods A single-center, cross-sectional study was performed by collecting retrospective data from electronic medical records. Demographic and diagnostic information was obtained, comparing patients with spasticity with or without dystonia. The data were analyzed for group differences using a two-tailed Student's t-test. Categorical data were analyzed for group differences using Pearson's χ^2 test.

Results A total of 137 patients met the criteria. The majority (114) had spasticity plus dystonia whereas only 23 were documented as spasticity alone. Simple continuous dosing was the most common delivery mode, but flex dosing was used more than twice as frequently with spasticity plus dystonia compared with spasticity alone (42% vs 17%). Patients with spasticity plus dystonia also had more rostral catheter tip locations.

Conclusions While it has been discussed anecdotally, this study confirms the supposition that patients with spasticity plus dystonia have increased dose requirements when compared with those with spasticity alone. Although there are no clear standards of care when managing these patients, they are often on higher daily dosages, are more likely to require flexed dosing method, and have higher catheter placements. Still, there are few studies that demonstrate improvements in dystonia with the use of ITB. In general, these patients would benefit from the development of universal standardizations as well as the confirmation that this is an appropriate treatment.

INTRODUCTION

Intrathecal baclofen (ITB) is one of the main interventions used to manage severe hypertonia; yet there are no standardized recommendations. Hypertonia is increased muscle tone resulting from damage to or abnormal formation of the central nervous system. Spasticity and dystonia are two subtypes of hypertonia frequently seen in pediatric conditions. The classical definitions of hypertonia

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Intrathecal baclofen (ITB) was approved by the Food and Drug Administration for management of spasticity of cerebral origin in children and adults.
- ⇒ ITB is often used off-label for management of secondary dystonia in children, particularly in children with cerebral palsy.
- ⇒ There is large variability in where an intrathecal catheter is placed depending on the child's symptoms and the local practice patterns.

WHAT THIS STUDY ADDS

- ⇒ This study highlights the differences in intrathecal dosing and catheter placement between children with spasticity and those with additional dystonia.
- ⇒ This study shows that children with dystonia often need significantly higher doses of intrathecal management for effective management compared with those with purely spasticity.
- ⇒ This study highlights the great need for future research to better understand the role of ITB in reducing dystonia in children.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

- ⇒ If children with dystonia are being considered for ITB, consider more rostral catheter placement and switching to flex dosing earlier in the titration of baclofen.

were updated in 2003 by an NIH-sponsored Task Force on Childhood Motor Disorders. Spasticity is defined as 'resistance to externally imposed movement that increases with increasing speed of stretch and varies with the direction of joint movement'. In contrast, dystonia is defined as 'involuntary sustained or intermittent muscle contractions [causing] twisting and repetitive movements, abnormal postures, or both'.¹

ITB was initially approved by the Food and Drug Administration (FDA) to treat spasticity of central or spinal origin in 1996.² Direct administration into the intrathecal space

achieves higher efficacy compared with oral baclofen, which poorly crosses the blood–brain barrier owing to limited lipid solubility.^{1,3–5} Increasing evidence suggests therapeutic benefit of ITB in spasticity management in children, and clinical trials support the efficacy and safety of ITB in both children and adults.^{3,4,6,7}

ITB was approved for patients aged 4 years and older.⁸ Goals of treatment include improved mobility and range of motion, prevention of contractures and skin breakdown, reduction of pain and sleep disturbances, as well as promotion of hygiene.^{5–7,9} However, ITB is not currently FDA approved for management of dystonia as there is little evidence illustrating its benefit. Despite this, ITB is regularly used in children with primary (genetic origin) and secondary (brain injury or malformation) dystonia.¹⁰ One randomized clinical trial of ITB in dystonic cerebral palsy (CP), the IDYS trial, suggested efficacy in reducing dystonia, but the findings were not significant.¹¹ Numerous retrospective and prospective cohort studies indicate possible efficacy of ITB at reducing dystonia, but these studies were often underpowered, unblinded, and not randomized.^{12–15}

At this time, there are no standardized ITB dosing recommendations.^{8,9} There is limited evidence supporting specific dosages, but anecdotal agreement is that management of dystonia requires higher doses than spasticity.¹⁶ Albright *et al* reported that mean ITB dosing was 300 µg/day when treating spasticity compared with ~600 µg/day when treating dystonia.¹⁶ Many patients are noted to be at doses above 1000 or even 2000 µg/day.

ITB pumps can deliver baclofen at a simple continuous rate or by flex dosing, which provides scheduled boluses in addition to a basal rate. Again, no standard recommendations for a dosing regimen or titration plan exist. In the Albright *et al*'s study, if the desired results were not evident by 900 µg/day, a trial of flex dosing was initiated.¹⁶ Flex dosing is thought to achieve better baclofen dispersion in the cerebrospinal fluid (CSF), as well as manage predictable variations in tone during the day without increasing total daily dosages.^{2,17} The need for progressive dose increases is thought to reflect a compensatory response of the central nervous system to the changes in neuron excitability with the presence of baclofen, as well as natural changes in spasticity with growth in children. There is no evidence specifying if or when each dosing regimen should be initiated for either spasticity or dystonia. Most clinicians reserve flexed dosing for treating dystonia or more severe spasticity cases that are unresponsive to a simple continuous schedule.¹⁸

The need for high total daily dose (TDD), whether simple continuous or flex patterns, is controversial. Some believe that significant benefits do not occur above 1500 µg/day.¹⁹ As mentioned by physicians at Gillette, ITB may not be beneficial in the management of dystonia, and that perhaps the need for the higher doses required for dystonia illustrates the lack of efficacy in those cases.²⁰

The catheter delivers ITB at the end of the tubing, resulting in a gradient of baclofen concentrations. The

medical team must decide where to place the catheter tip, but there is a paucity of studies characterizing preferred location. One report observed lower daily doses in those with higher catheter tip levels, but the difference was not significant.²¹ Many clinicians tend to determine catheter level according to the patient condition since there is a steep baclofen concentration gradient along the spinal axis with the highest concentration close to the catheter tip location.¹¹ General practice patterns reveal ambulatory diplegics typically have low thoracic or lumbar placements, quadriplegics have high thoracic placements, and those with dystonia have cervical placements. However, recommendations are not standardized, so placement is often based on tradition or surgeon preference.^{22–24}

The objectives of this study are to determine if there are significant differences in the TDD, dosing regimen, and catheter placement between pediatric patients with spasticity plus dystonia versus spasticity alone. Our hypothesis is that children with spasticity plus dystonia will receive higher TDD, flex dosing, and more rostral catheter placement. The results of this study will highlight variations in pediatric ITB management of dystonia and will inform future work to investigate if these variations lead to improved outcomes.

METHODS

Patient selection

This is a single-center, cross-sectional study conducted via chart review at a tertiary pediatric hospital affiliated with an academic institution with a formal ITB pump program. Inclusion criteria included patients with ITB pumps placed before 20 August 2018. Exclusion criteria included patients younger than 4 years of age at the time of data collection, patients with ITB pumps placed on or after 20 August 2018, ITB pumps planned for removal, and patients with incomplete pump data information. Pumps placed after 20 August 2018 were excluded as it was assumed that these patients had not yet reached ideal dosing after pump implantation. At the time of data collection, there were 166 patients with ITB pumps enrolled in the ITB program. Of those, 137 patients met the criteria. As a result of being a single-center study, bias is introduced, as this study reflects local clinical practices and may not be generalizable. Charts were reviewed to determine if the patients had spasticity and/or dystonia. Spasticity was noted when Modified Ashworth Scale scores were listed in the physical examinations and if it was mentioned in the nomenclature used to describe the patient, that is, spastic quadriplegia. Dystonia was noted if the provider noted fluctuating tone with voluntary action or if dystonia was mentioned in the nomenclature describing the patient. In a few charts, a formal Hypertonia Assessment Tool had been completed indicating the presence of spasticity and/or dystonia.

Data collection

Demographic information and medical history elements collected included current age, age at time of pump placement, gestational age, and gender. Diagnostic information obtained comprised documented diagnosis, phenotype, presence of dystonia, and brain imaging findings when available. Pump information included catheter tip level, baclofen concentration, dosing pattern, and TDD. Our institution only used Lioresal, which comes in 500 and 2000 µg/mL concentrations. All data retrieved from the hospital-secured electronic medical records were stored in a hospital-encrypted and password-protected computer.

Statistical analysis

Selected demographic and clinical variables were summarized using descriptive statistics, such as mean or median (IQR) as appropriate for continuous variables and frequency and percentage for categorical variables. TDD was expressed as medians (µg/day) and plotted as a function of presence or absence of dystonia using a notched boxplot. The notch represents the 95% CI around the median, and if two groups' notches do not overlap, there is 95% confidence that their medians differ. The whiskers represent a 95% CI and values outside the whiskers are thought to be outliers.²⁵ Type of dosing schedule and catheter tip location were expressed as frequencies and plotted as a function of presence or absence of dystonia. Quantile-quantile plots were used to verify that data were normally distributed. Data were analyzed for group differences using a two-tailed Student's t-test. Categorical data were analyzed for group differences using Pearson's χ^2 test or Fisher's exact test when $n < 5$ for individual groups. No correction was needed as each data set only had a single comparison. Resulting p values are indicated in each figure. A significance level of $\alpha = 0.05$ was used and a p value < 0.05 was considered statistically significant. R (V.4.0.4) was used for all statistical analyses.

RESULTS

Epidemiology

A total of 137 patients met the criteria for this study. Out of the 137 patients, 114 had spasticity plus dystonia, whereas 23 had spasticity only. While many patients did not have dystonia documented in their problem list, dystonia was described in the patient's history and/or physical examination. These patients were listed as having dystonia for the sake of this study. The patients without and with dystonia did not differ in age, gender, year of ITB pump placement, or distribution of imaging findings (see table 1). The average age of ITB pump placement was approximately 15 years, ranging from 3 to 21 years. Imaging studies, when available, encompassed a spectrum of findings, most consistent with hypoxic-ischemic encephalopathy and periventricular leukomalacia. Others included mitochondrial disease and neurodegeneration with brain iron accumulation, as well as some normal studies (table 1).

Table 1 Demographic characteristics of patients without (–) and with (+) dystonia

Characteristics	Patients without dystonia (n=23)	Patients with dystonia (n=114)	P value
Demographics			
Age (y)	14.7±4.1	15.2±4.4	0.6
Year of ITB pump placement	2015±1.9	2014±2.6	0.3
Gender			0.7
Female	48	52	
Male	52	48	
Primary diagnosis			< 0.001
CP	78	94	
HSP	9	0	
SCI	9	0	
Genetic/other	4	4	
TBI	0	3	
Topographical distribution of CP			0.02
Quadriplegic	61	86	
N/A	22	6	
Diplegic	9	4	
Triplegic	9	4	
Imaging findings			0.5
PVL	35	30	
HIE/encephalomalacia	17	33	
Congenital malformation	17	11	
Unavailable	9	7	
Normal	9	1	
PVL+HIE	4	8	
Non-IVH hemorrhage	4	3	
TORCH/infection	4	2	
Cerebella atrophy	0	2	
NBIA	0	2	
TBI	0	1	
Tumor	0	1	
Kernicterus	0	1	
Microcephaly	0	1	

Age at time of placement and year of ITB placement are reported as mean±SD. The Student's t-test was used to estimate statistical significance for age and year of ITB pump placement. Gender, primary diagnosis, topographical distribution of CP, and baseline imaging findings are reported as percentages with the total number (n) reported in the header of each column. Pearson's χ^2 test was used to estimate statistical significance for gender. Fisher's exact test was used to estimate statistical significance for primary diagnosis and topographical distribution. CP, cerebral palsy; HIE, hypoxic ischemic encephalopathy; HSP, hereditary spastic paraparesis; ITB, intrathecal baclofen; IVH, intraventricular hemorrhage; N/A, not applicable; NBIA, neurodegeneration with brain iron accumulation; PVL, periventricular leukomalacia; SCI, spinal cord injury; TBI, traumatic brain injury; TORCH, toxoplasmosis, other gents, rubella, cytomegalovirus, and herpes simplex.

The distribution of primary diagnoses and topographical distribution in patients with CP significantly differed between the patients without and with dystonia (see table 1). CP was the primary diagnosis in 94% of the patients with spasticity plus dystonia versus 78% in the patients with spasticity alone. Primary diagnoses of hereditary spastic paraparesis and spinal cord injury were found only in the group without dystonia. Patients with dystonia were primarily

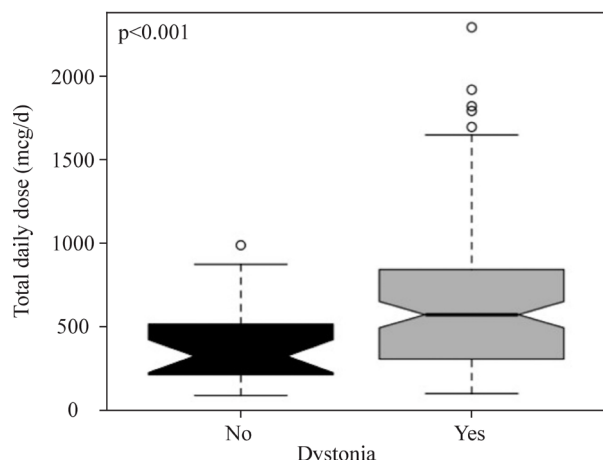


Figure 1 Patients with dystonia use significantly higher daily doses of intrathecal baclofen (ITB). Notched boxplot of total daily dose of ITB ($\mu\text{g}/\text{day}$) as a function of dystonia. The open box shows the IQR (25%–75%) with whiskers representing minimum and maximum values. The narrow portion of the notch represents the median with edges of notch representing the 95% CI of the median. Open circles represent possible outliers. $n=23$ patients without dystonia; $n=114$ patients with dystonia. The Student's t -test was used to estimate statistical significance.

quadriplegic (86%) in terms of the topographical distribution of CP symptoms. Diplegic and triplegic topographical distributions were greater in the group without dystonia (9% without vs 4% with dystonia).

TDD of ITB

Most patients (>80%) used 2000 $\mu\text{g}/\text{mL}$ concentration of baclofen. TDD ranged from 85 to 2298 $\mu\text{g}/\text{day}$, with an overall average of 623 $\mu\text{g}/\text{day}$. Patients with spasticity plus dystonia used significantly higher TDD than those with spasticity alone (figure 1, $p<0.001$). Patients without dystonia had a mean TDD of 389 $\mu\text{g}/\text{day}$ and a median TDD of 321 $\mu\text{g}/\text{day}$. Patients with spasticity plus dystonia had a mean TDD of 670 $\mu\text{g}/\text{day}$ and a median TDD of 570 $\mu\text{g}/\text{day}$. As illustrated in figure 1, the dystonia group had a higher average TDD, a wider IQR of ITB doses, and a greater number of outliers at the high end of the dosing range.

Flex versus simple continuous delivery mode

The most common delivery mode was simple continuous. Eighty-five subjects (62%) used the simple continuous infusion setting, whereas 52 subjects (38%) used flex dosing. Patients with spasticity plus dystonia were significantly more likely to use flex dosing (figure 2, $p=0.03$). Flex dosing was used by 42% ($n=48$) of patients with spasticity plus dystonia versus 17% ($n=4$) of patients without dystonia.

Level of catheter tip placement

Catheter tip placement ranged from the foramen of Monroe to T12. Patients with spasticity plus dystonia tended to have more rostral placements (figure 3, $p=0.0004$). In patients without dystonia, the highest level of catheter tip placement was C6 with modes at T1 and T12. In contrast,

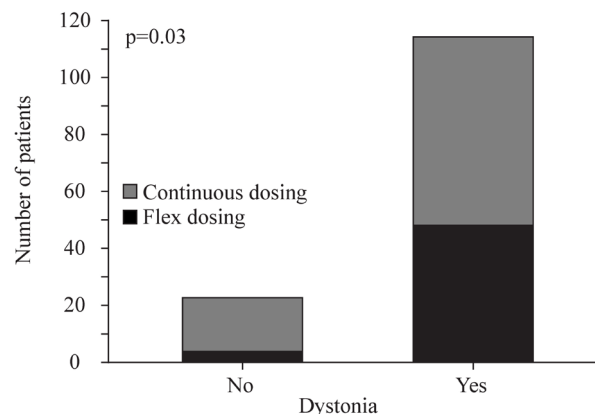


Figure 2 Patients with dystonia are significantly more likely to use flex dosing. Stacked histogram of the number of patients using flex (dark histogram) or continuous (gray) intrathecal baclofen (ITB) pump dosing as a function of the absence (–) or presence (+) of dystonia. Same total n for each group as in figure 1. Pearson's χ^2 test was used to estimate statistical significance.

28% ($n=32$) of the patients with spasticity plus dystonia had catheter tips placed rostral to C6. The most common catheter tip level in patients with spasticity plus dystonia was T1 ($n=38$), followed by C1 ($n=26$).

DISCUSSION

Validity of more aggressive ITB dosing for dystonia management

Patients with spasticity plus dystonia needed significantly higher TDD, were more likely to use flex dosing schedules, and had more rostral catheter levels. Our study supports previous anecdotal expectations with evidence from chart review in a large ITB patient population. This raises the

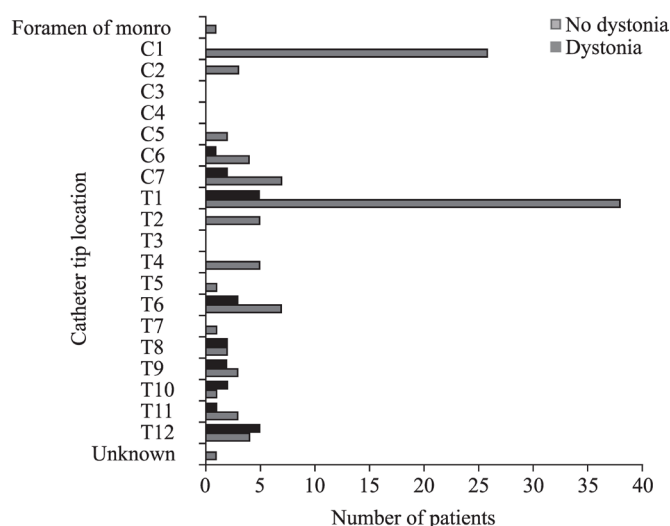


Figure 3 Patients with dystonia tend to have more rostral catheter tip placement. Catheter tip location in intrathecal baclofen (ITB) pump patients with (light gray) and without (dark gray) dystonia. Same total n for each group as in figure 1. Pearson's χ^2 test was used to estimate statistical significance.

question: are these higher doses managing the dystonia or are providers searching for a response by continuing to increase the dose? Perhaps ITB is simply not effective in the treatment of dystonia. In the IDYS trial with severely affected patients with dyskinetic CP, improvements were found in the Goal Attainment Scale (GAS) as individual goals were achieved, including increasing comfort, decreasing pain, and easing caregiving. However, the trial was unable to demonstrate a decrease in the Barry Albright Dystonia Scale (BADs). They did see a significant difference in dystonia as measured by Dyskinesia Impairment Scale (DIS) in the resting subscale, but since dystonia is thought to be triggered by voluntary movements, it is difficult to interpret this finding. The BADs and DIS were also secondary endpoints, meaning that the sample size for this study was powered for the GAS, and as a result, the study may have been underpowered to detect changes in dystonia.¹¹ These results were similarly noted in the recent study by Fehlings *et al*, in which the randomized evidence reported achievements of goals related to pain and comfort with little to no differences in dystonia with ITB.^{13 14} While there were several studies that validated that ITB can reduce dystonia when provided as a single bolus, only two studies demonstrated persistent reductions in dystonia over time.¹⁶ While these goals are important and should be acknowledged, the lack of improvement in the hypertonia and dyskinetic movements provided by ITB should be considered, as there are many risks that are associated with such this intervention.

Flexed dosing regimens

As with proteins and neurotransmitters, ITB has a concentration gradient. Concentration of baclofen at a distance from the catheter tip increased with a single large bolus compared with the simple continuous, which is hypothesized to be attributed to the kinetic energy associated with the faster infusion rates.²⁴

All patients begin with simple continuous dosing, and increasing dosages are trialed before switching to a flex dosing regimen. According to Skalsky and Fournier, this is common practice among providers, as flex dosing is reserved for severe cases or cases of primarily dystonia which seem to be unresponsive to the simple continuous pattern.¹⁸ Here we confirm that individuals with dystonia tend to require the flex regimen more often. Work by Stokic and Yablon in 2012 showed that flex dosing leads to better suppression of the spinal H-reflex, a reflex that directly correlates with spasticity.²⁶ This finding fits with the results of this study and also raises questions as to whether it should be considered more often. Based on the Stokic and Yablon's work, it is possible that the TDD could be reduced with flex dosing, which in turn would lead to fewer refills and less discomfort for the patient.

Rostral catheter placement

There are multiple potential reasons why the use of higher catheter levels has been shown to be more efficacious than caudal placement in several studies. First, there is a known

significant concentration gradient of proteins, neurotransmitters, and metabolites in the CSF, and a similar gradient has been demonstrated with baclofen.^{23 24 27} Second, CSF flow oscillates along a craniocaudal axis without continuous mixing, and the highest flow velocities are in the cervical spine.²⁸ Third, some distinguish between 'phasic' spasticity that is generated by abnormal spinal reflexes and 'tonic' spasticity that is likely produced rostrally by the brainstem. There is some evidence that ITB delivered rostrally may reduce brainstem reflexes in addition to H-reflexes, in turn reducing tonic and phasic spasticity.²⁹

Under-recognition of dystonia

Currently, there is no algorithm to diagnose dystonia.³⁰ Because there are many clinical manifestations and it often coexists with spasticity, dystonia can easily be missed and is likely under-recognized and underdiagnosed. Dystonia was often not included in the formal problem list despite evidence of dystonia in the history and physical examination portions of the documentation. Further, there has been a revival of an old concept, 'spastic dystonia', that was originally proposed by Denny-Brown in 1966.³¹ His work in monkeys showed involuntary sustained muscle activity secondary to lesions in the motor cortices that persisted even with removal of sensory input at the level of spinal cord. Whether or not this is classical dystonia masquerading as spasticity, it may be leading to an over-recognition of spasticity and under-recognition of dystonia. It is possible that 'spastic dystonia' is playing a role in the variations we see in dosing needed for adequate management of hypertonia.

Limitations

The major limitation is that it is a single-center study, which can lead to regional and institutional bias. During the period measured, one neurosurgeon performed the bulk of pump placements, narrowly sampling implantation practices. Catheter placement by the neurosurgeon is guided by patients' presentations with the assistance and recommendations from the physiatrists. Thus, our catheter placement findings may be highlighting individual preferences.

Patients were grouped by their presentation of hypertonia; however, underlying etiologies were not taken into consideration. It is possible we would find differences in ITB management if we further stratified this heterogeneous population.

Future work

Management of dystonia with ITB is predominately anecdotal owing to significant gaps in understanding the pathophysiology of dystonia. Furthermore, ITB's mechanism of action on dystonia is poorly understood. Additional studies are needed to determine whether ITB pumps are truly effective in dystonia management as this could drastically change current practices across the USA and around the world. A blinded randomized controlled trial that directly measures changes in dystonia using validated tools, such as the BADs and DIS, would be beneficial. Of course, ITB may improve

other aspects of a patient's medical care, including motor control, pain, and ease of caregiving. Basic and translational studies to investigate the mechanism of action of ITB on dystonia would be highly important for improving its effective use in practice. Knowing exactly how ITB can assist will allow providers to determine the best candidates and directly target the patient and family's goals.

In conclusion, we document trends within our patient population that illustrate critical differences in ITB use when managing dystonia despite the absence of clearly delineated standards. As such, this study highlights the need for universal standardizations and provides a basis from which to begin the process.

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Contributors JG conceptualized/designed the study, gathered and analyzed the data, helped write and critically revise the manuscript, and reviewed the final article before submission. MS analyzed the data, completed some statistics, created figures and tables, helped write and critically revise the manuscript, and reviewed the final article before submission. HM completed and reviewed the statistics, critically edited the manuscript, and reviewed the final article before submission. DJC helped write and critically revise the manuscript, and reviewed the final article before submission. SPT conceptualized/designed the study, analyzed the data, helped write and critically revise the manuscript, reviewed the final article before submission, and serves as the guarantor of the overall content.

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Data availability statement Data are available upon reasonable request. The authors are willing to share the data discussed in this study upon reasonable request. There are no additional unpublished data from this study.

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