The Diagnosis and Management of Vasovagal Syncope in Pediatric Patients

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Abstract: Vasovagal syncope is the most common cause of syncope in pediatric patients. The present study is aim to provide a comprehensive literature review of the latest advances in the diagnosis and treatment of vasovagal syncope in children. Diagnosis of vasovagal syncope is based on clinical history. For patients with suspected VVS but lack of confident diagnosis after initial assessment, head-up tilt test is helpful. There are four options for treatment of vasovagal syncope: conservative therapy, pharmacologic therapy, pacemaker therapy, and catheter ablation of ganglionated plexi. Conservative therapy (health education, avoidance of triggers, salts and water intake, physical countermeasures and orthostatic training) is recommended for patients with occasional syncope. Pharmacological therapy should be considered for patients with recurrent syncope or for whom conservative therapy has failed. Patients with the predominantly cardioinhibitory response, associated with repeated injury, limited prodromes, and documented asystole may benefit from cardiac pacing. Catheter ablation of ganglionated plexi is a new strategy, its efficacy and safety in pediatric patients should be verified by randomized controlled trials.

Keywords: Diagnosis, Management, Vasovagal syncope, Pediatric patients.

1. INTRODUCTION

Syncope refers to a sudden loss of consciousness due to transient cerebral hypoperfusion associated with an inability to retain postural tone, which is characterized by rapid onset, short duration, and spontaneous and complete recovery. Vasovagal syncope (VVS) is the most common cause of syncope in children [1]. The mechanism of VVS remains incompletely revealed. Excessive activation of vagal tone via dysregulation of Bezold-Jarisch reflex, together with a decreased sympathetic tone, contributes to the pathogenesis of VVS. Prolonged standing or posture change leads to decreased venous return, which results in inadequate ventricular filling and vigorous cardiac contraction. Mechanoreceptors (C fibers) located preferentially in the inferolateral wall of the left ventricle are activated, resulting in hypotension and paradoxical bradycardia due to increased activity of inhibitory receptors and consequent parasympathetic hyperactivity [2]. Though VVS is a functional disease and does not lead to mortality so far, it can result in severe injuries and reduce the quality of life significantly, especially for patients with recurrent episodes [3]. It's very critical to diagnose VVS early so as to optimize the therapeutic option.

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2. DIAGNOSIS

The diagnosis of VVS is based on clinical history. The initial assessment consists of history taking, physical examination, and electrocardiogram (ECG). For patients with suspected VVS but lack of confident diagnosis after an initial assessment, the head-up tilt test is helpful (Figure **1**).

2.1. Clinical History and Physical Examination

VVS frequently occurs in older children aged 11 to 19 years, especially in girls [4]. There are four categories of diagnostic features in VVS: predisposing situations, prodromal symptoms, physical signs, and recovery time and symptoms. 82.5% of VVS in children was provoked by prolonged standing position, emotional stress, pain, heat, venous puncture and dehydration and so on [5]. 85% of children with VVS had prodromal symptoms. Clammy sensation, nausea, light-headedness, or visual changes are strongly suggestive of VVS. Other prodromal symptoms include dyspnea, vomiting, abdominal pain, palpitations, confusion, and auditory changes. After the episode, a portion of patients manifest continuous discomforts, such as fatigue, headache, and dizziness. A report suggested that 3.73% of patients experienced transient aphasia during HUTT and could recover from 3 to 60 minutes [6].

The clinical history should be collected proficiently, and each episode of syncope should be well

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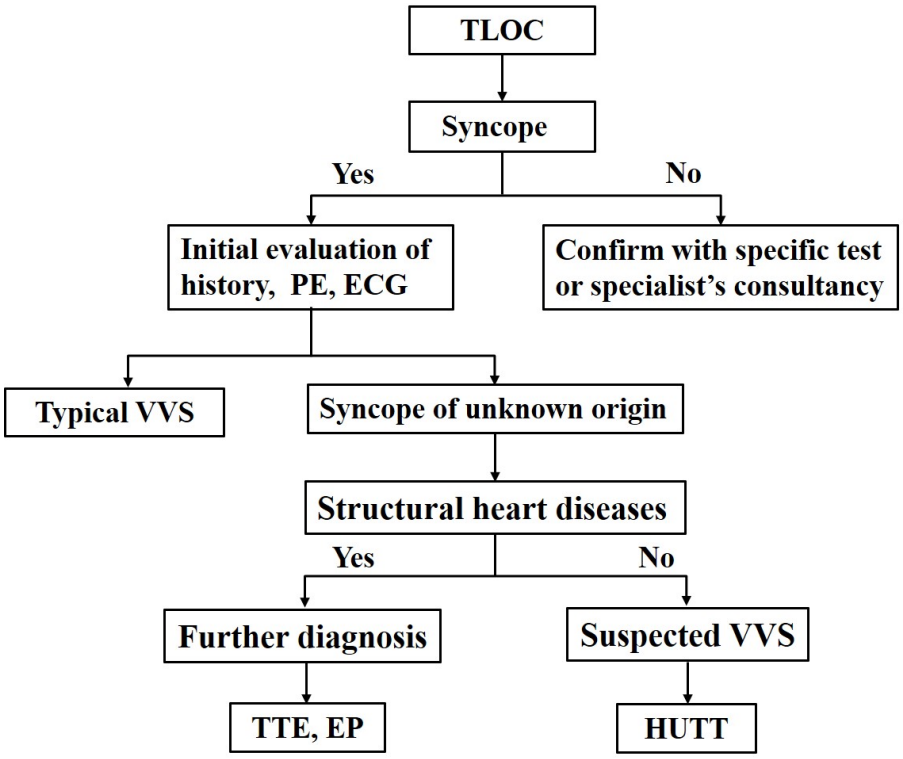

Figure 1: Diagnosis process for vasovagal syncope.

TLOC, transient loss of consciousness; PE, physical examination; ECG, electrocardiogram; VVS, vasovagal syncope; TTE, transthoracic echocardiogram; EP, electrophysiological examination; HUTT, head-up tilt test.

characterized, including the presence of prodromal symptoms, precipitating factors, conditions in which it occurred, the position of the patient and other associated signs such as cyanosis, confusion, sweating, pallor, palpitations, dyspnea, chest pain, nausea, and muscle twitching. Whether there are predisposing factors such as fear, noxious stimuli, environmental heat, or immobilization. Whether the patient has a history of similar recurrent episodes. Whether the episode occurs exclusively when upright or changes in position. Whether the episode is associated with an activity such as urination, defecation, deglutition, hair grooming, or stretch. Whether the episode occurs during or after exercise [7]. Whether the patient takes medications, like beta-adrenergic blockers, calcium channel blockers, and diuretics, which might contribute to syncope. Whether the patient has a medical history of cardiac diseases, seizures, psychiatric or psychological problems. Whether the patient has a family history of sudden death in young [8].

Physical examination should be performed carefully. Measurements of heart rate (HR), blood pressure (BP) in the supine position and within 10 minutes in the orthostatic position, measurements of the BP in both arms are included. Complete cardiac and neurologic examinations should be performed to exclude structural cardiac or neurological diseases. When necessary, baseline laboratory testing, ECG, dynamic ECG, transthoracic echocardiogram, and electrophysiological examination should be performed for differential diagnosis.

2.2. Family History

A positive family history of VVS has been observed and data suggested that VVS clusters in families and have a significant heritable component [9]. A cross-sectional survey identified that 40% (49/126 cases) of subjects with positive tilt-test results had a positive family history of syncope [10]. In our report on 4 pairs of twins, two pairs had a positive family history [11]. There was a trend toward higher casewise concordance rates in monozygous compared with dizygous twins for frequent syncope and syncope associated with typical vasovagal triggers. A study demonstrated that the frequency of ArgArg genotype of alpha1A-adrenergic receptor (ADRA1A) was increased in VVS patients, suggesting Arg347Cys polymorphism was a susceptibility factor of VVS [12]. Gene polymorphisms of beta1 adrenergic receptor gene

(ADRB1) [13], adenosine A2Areceptor gene (ADORA2A) [14], Gs proteinα subunit (GNAS1) were associated with a positive tilt table test [15]. A study reported the association between VVS and gene polymorphism of CHRM2, GNB1, GNG2, KCNJ3, KCNJ5, which are involved in the postsynaptic cardiac parasympathetic signaling pathway. Genetic variations of these genes are not major contributors to the pathogenesis of reflex syncope of vasodepressor or cardioinhibitory types [16]. Until now, candidate gene association studies have only revealed negative or unconfirmed results. To overcome the issues, genome-wide association studies (GWAS) are needed.

2.3. Head-up Tilt Test

Head-up tilt test (HUTT) is used for assessing patients with suspected syncope but lack of confirmed diagnosis after an initial assessment, or a differential diagnosis of convulsive syncope from epilepsy or pseudo-syncope from VVS [17]. The head-up tilt period is performed under two conditions: passive (without any provocative drugs), and pharmacological (with drug challenge). Subjects are tilted at 60° head upward, HR, BP and ECG are recorded continuously until either 45 min duration, or development of syncope or intolerable near syncope symptoms. If syncope occurs, patients are rapidly placed in the supine position. If syncope or presyncope does not occur, tilted posture is maintained, subjects are medicated with adjunctive agents, such as isoproterenol, nitrates, and clomipramine, and HR, BP and ECG are recorded until for 20 min or syncope or presyncope occurs [3].

Syncope or pre-syncope symptom accompanied with one of the following conditions during HUTT is defined as VVS: (1)BP < 80/50 mmHg (10.66/6.67 kPa) or over 25% reduction of mean BP relative to baseline BP; (2)HR < 75 bpm for children aged 4-6 years, < 65 bpm for those aged 6-8 years , < 60 bpm for those aged above 8 years; (3) ECG showing sinus arrest or premature junctional contractions; (4) atrioventricular block, asystole up to 3 s. There are three response types of VVS: vasodepressor type (significant reduction in BP but insignificant change in HR), cardioinhibitory type (significant reduction in HR but insignificant change in BP) and mixed type (significant reduction both in BP and HR) [3].

In a multi-center trial in China, 888 cases children who complained of syncope aged from 5 to 18 years old (male 417 cases, female 471 cases) were enrolled, 283 cases were diagnosed as VVS, among which 61.8% (175 cases) were vasodepressor type, 12.4% (35 cases) were cardioinhibitory type and 25.8% (73 cases) were mixed type [18].

3. DIFFERENTIAL DIAGNOSIS

VVS should be differentiated from cardiac syncope and other reflex syncope. Antecedent structural heart diseases, known arrhythmia or arrhythmia risks such as long QT syndrome, an arrhythmogenic medication history, family history of unexplained death, abnormal cardiac physical examination, abnormal ECG and echocardiogram may suggest cardiac syncope. However, patients with cardiac disease can have VVS and vice versa. It is difficult to elucidate the mechanism of syncope in these patients. Detailed clinical history is important in the differential diagnosis. Syncope during exertion or syncope in the supine position usually suggests cardiac syncope. Plasma brain natriuretic peptide (BNP) may be a sensitive marker to identify cardiac syncope and non-cardiac syncope in children. It suggested a diagnosis of cardiac syncope with 73.5% sensitivity and 70.0% specificity when the plasma BNP was more than 40.65 pg/ml [19].

VVS should be differentiated from other neurally mediated syncope, including orthostatic hypertension (OHT), orthostatic hypotension (OH) or postural orthostatic tachycardia syndrome (POTS). OHT is diagnosed when systolic BP increment≥20 mmHg and/or diastolic BP increment≥25 mmHg in children aged 6-12 years, ≥20 mmHg in adolescents aged 12-18 years from supine to tilted, or tilted BP ≥130/90 mmHg in children aged 6-12 years, ≥140/90 mmHg in children aged 12-18 years, within 3 minutes of HUTT. OH is defined when systolic BP decrement ≥20 mmHg and/or diastolic BP decrement ≥10 mmHg within 3 minutes of standing or tilted test [3, 20]. POTS is defined by day-to-day symptoms of orthostatic intolerance and an increase of HR (HR increment ≥40 bpm or maximum HR ≥130 bpm in children aged 6-12 years, maximum HR ≥ 125 bpm in adolescents aged 12-18 years during a 10-minute tilted test) when upright, without significant change of BP [21]. The predictive value of some markers was reported in substantial studies. Plasma level of hydrogen sulfide was significantly higher in children with POTS than those with VVS (100.9±2.1 vs 95.3±3.8 μmol/L). The receiver operating characteristic curve showed that the hydrogen sulfide plasma level of 98 μmol/L was a cutoff value in the differentiation of VVS from POTS, with 90% sensitivity and 80% specificity [22].

Electroencephalogram, head CT or MRI are used in the differential diagnosis of VVS and loss of

consciousness due to neurological diseases. However, syncope, especially convulsive syncope, is sometimes mistaken for epilepsy. 20%-30% of patients diagnosed with epilepsy are actually VVS [23]. HUTT is necessary for making an accurate diagnosis. The Calgary Score consisting of seven clinical issues is one of the diagnostic tools used in the differential diagnosis between syncope and epilepsy. In our previous study, question 3 in Calgary Score was modified (Table **1**). When the modified Calgary Score≥1 suggested a diagnosis of epilepsy with 92.68% sensitivity and 96.64% specificity [24].

4. MANAGEMENT

Though VVS is not deadly unless the patient is in harm's way, recurrent episodes significantly impair the quality of life. The aim of VVS treatment is to prevent children from accidental injury, reduce recurrence, and improve patients' quality of life. There are 4 options: conservative therapy, pharmacologic therapy, pacemaker treatment, and catheter ablation of ganglionated plexi (Figure **2**).

4.1. Conservative Therapy

Health education is quite a helpful and necessary initial strategy, especially for children with mild VVS or children who experienced only one episode of syncope. It comprises education regarding awareness and possible avoidance of triggers (away from hot crowded environment, cough suppression, sudden posture change, fasting, stressful situation and so on), early recognition of prodromal symptoms, performing maneuvers to abort syncope, increase in water and salt intake, and careful avoidance of agents that lower BP including diuretics [3].

Compensatory physical maneuvers are recommended, even without specific pediatric data. Physical maneuvers can reduce episodes of syncope and increase BP. When faints occur, immediately lying down or squatting, leg crossing, buttocks clenching, fist-clenching may be effective. Patients with more than three episodes of VVS received non-pharmacological treatment including adequate fluid and salt intake, regular exercise, and physical counterpressure maneuvers, the median number of syncopal recurrences was lower in the first year of treatment compared with the last year before treatment (mean 0 vs. 3, P<0.001) [25]. Orthostatic training is supposed to be effective. The training program consists of daily 30-minute sessions of upright standing against a vertical wall, 6 days a week for at least 4 weeks. A study demonstrated that 72.6% of orthostatic trained patients reported no syncopal recurrence after one year of follow-up [26]. However, this program is of greater benefit to patients who are younger or experience frequent episodes of syncope. The acceleration index may be a predictor for the efficacy of orthostatic training in children with VVS [27].

Salt and water supplementation can be encouraged, but a large amount of salt is needed [28-30]. Due to venous pooling, ventricular preload was reduced during the episode. Adequate salt and water intake expand intravascular volume. In our previous study, children with recurrent VVS and positive HUTT received oral

Table 1: Individual Items of the Modified Calgary Score

	Question	Score (If yes)
Q1	Waking with cut tongue?	2
Q2	Prodromaldeja vu or jamais vu?	1
Q3'	Loss of consciousnessduring sleeping?	1
Q4	Head turning to one side during loss of consciousness?	1
Q5	Abnormal behavior noted by bystanders, including witnessed unresponsive, unusual posturing or limb jerking? *(Score as yes for any positive response)*	1
Q6	Postictal confusion?	1
Q7	Any presyncope, such as dizziness, palpitation or nausea?	−2
Q8	Diaphoresis before a spell?	−2
Q9	Loss of consciousness with prolonged sitting or standing?	−2

The Modified Calgary score is derived from Calgary score, to make a differential diagnosis between neurally mediated syncope and epilepsy. All questions were answered as 'yes' or 'no'. If a question was answered as 'yes', points were added or subtracted, depending on whether the answer increased the likelihood of epilepsy. When the modified Calgary Score≥1 suggested a diagnosis of epilepsy.

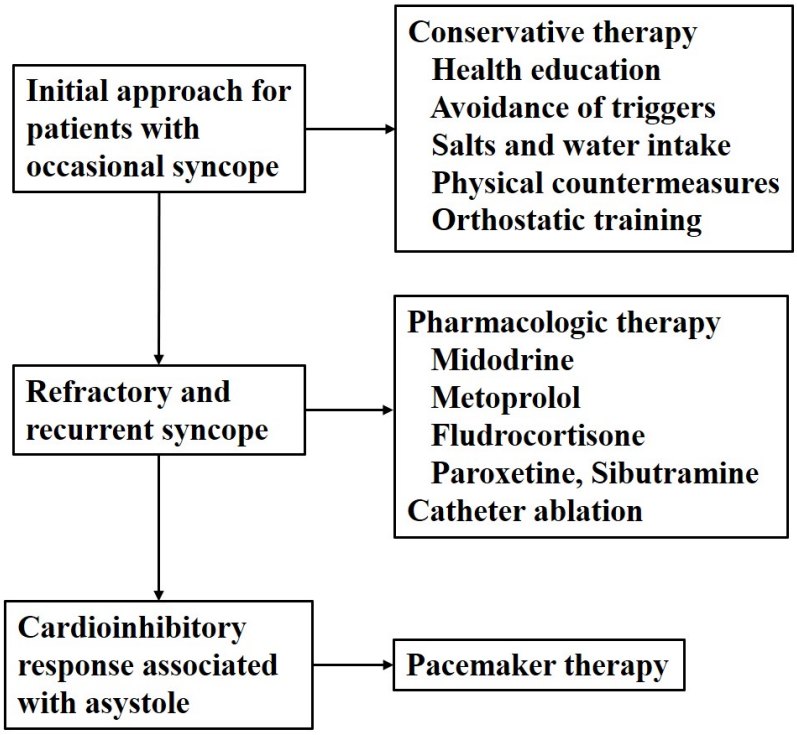

Figure 2: Treatment approach for vasovagal syncope.

rehydration salt, health education and tilt training for 6 months. The episode of syncope was decreased and the proportion of negative HUTT was increased compared with children who underwent health education and tilt training [27]. The total effective percentage of ORS treatment was 63.0%, and the negative conversion rate of HUTT was 48.2% [28]. Compared with children with mixed or cardioinhibitory vasovagal syncope, ORS may be more effective for those with vasodepressor vasovagal syncope, the recommended course of ORS for treatment of VVS in children is 2 months [29,30]. Children with neurally mediated syncope had a higher prevalence of low iron storage (57% vs 17%, P<0.001), and a lower mean value of ferritin (27 vs 46 mg/L, P<0.001) compared with those with other causes of syncope [31]. Another study concluded the same results [32]. These data suggest that iron and even ferritin deficiency aggravates VVS, adequate iron intake may be effective for VVS.

4.2. Pharmacologic Therapy

Pharmacological therapy should be considered in patients with refractory and recurrent syncope. Until now, no single pharmacologic intervention has proven against above the placebo effect in large clinical trials [33].

Alpha-adrenoceptor agonists cause arteriolar constriction as well as venoconstriction, which increases peripheral vascular resistance and cardiac output. In a meta-analysis, alpha-adrenoceptor agonists were significantly effective in the treatment of VVS compared with placebo (OR 0.21, 95% CI 0.06 to 0.77, p=0.02), midodrine is proved to be better than etilefrine [34]. HUTT-based effective rate (75% vs 20%, P<0.05) was increased, and recurrence of syncope (22% vs 80%, P<0.05) was decreased with few side effects in patients treated with midodrine hydrochloride compared with those treated with conventional therapy only [35].

The effects of beta-adrenergic blockers in preventing VVS are controversial. Beta-adrenergic blockers have been postulated to decrease mechanoreceptor activation due to their negative inotropic effects and thus preventing decreased venous return. The effective rate was higher in children treated with metoprolol (a selective beta 1 adrenergic blockers) than those receiving oral rehydration salt treatment. The percentage of negative conversion of HUTT was 60.61% in VVS children receiving metoprolol therapy, and 18.75% in those receiving oral rehydration salt treatment (P<0.01) [36]. However, some studies reported that patients with VVS could not benefit from beta-adrenergic blockers. The Prevention of Syncope Trial was a large, randomized, placebo-controlled,

double-blinded trial that determined the effectiveness of metoprolol in VVS over a 1-year treatment period. Results demonstrated that the likelihood of recurrent syncope was not significantly different between patients receiving metoprolol and those receiving placebo [37]. However recent studies suggested specific VVS patients benefit from metoprolol, the number of previous syncopal episodes before treatment or Poincaré plot can predict the efficiency of metoprolol in the treatment of VVS [38, 39].

The hypothetical mechanism that fludrocortisone is beneficial to VVS would be to increase intravascular volume and decrease the vagal activity. Fludrocortisone is considered to be an addition to dietary salt and water expansion. An uncontrolled study showed that children taking fludrocortisone had significantly decreased syncopal episodes [40]. In the multicenter Prevention of Syncope Trial 2, fludrocortisone significantly reduced the likelihood of syncope (hazard ratio: 0.63, 95% CI: 0.42-0.94, p=0.024), and there was a significant benefit after 2 weeks of dose stabilization [41]. However, in a double-blind, placebo-controlled, randomized study, fludrocortisone and salt couldn't decrease the recurrence of syncope compared with placebo. In this trial, 32 children (20 females, mean age 13.9±2.5 years) were included, 10 of 18 patients had recurrent syncope in fludrocortisone and salt group and 5 of 14 in placebo group after one-year follow-up (P<0.04) [42].

Several other medications are used in the treatment of VVS. Selective serotonin reuptake inhibitor paroxetine and fluoxetine were reported to reduce syncope episodes in patients with recurrent VVS [43]. Sibutramine, a norepinephrine transporter inhibitor significantly decreased syncopal spell frequency in highly symptomatic and treatment-refractory patients [44].

4.3. Pacemaker Therapy

Cardiac pacing should be considered in those patients who experience frequent syncope associated with repeated injury, limited prodromes, and documented asystole. Patients with predominant cardioinhibitory response may benefit from cardiac pacing, while those with predominant vasodepressor response would be less likely to respond to cardiac pacing. A small, single-blind randomized trial demonstrated that permanent cardiac pacing greatly reduced the number of syncopal episodes in pediatric patients with frequent recurrence associated with documented asystole who were refractory to multiple medications [45]. In a recent trial, pacemaker settings were installed in 11 pediatric patients with cardioinhibitory syncope, an entire abolishment of syncope was achieved in 10 patients [46]. However, a double-blind randomized trial in children is needed. Since the vasovagal reflex is both vasodilation and bradycardia, in addition to cardiac pacing antihypotensive measures should be considered when hypotension coexists.

4.4. Catheter Ablation

Endocardial catheter ablation to modify the ganglionated plexi (GPs) in the left atrium was reported as a treatment strategy for refractory VVS. The ablation of GPs reduced mechanoreceptor or chemoreceptor mediated impulses and blocked the afferent pathway of abnormal Bezold–Jarisch reflex. Besides, the efferent vagal inputs to the heart were inactivated by the denervation of the GPs, which prevented bradycardia and hypotension. In a large cohort study, 57 patients with recurrent VVS received high-frequency simulation and anatomically guided GPs ablation in the left atrium, 52 patients (91.2%) remained free of syncope and prodromes were significantly decreased during follow-up of 36.4±22.2 months [47]. A case reported that an adult female patient who presented with recurrent syncope since childhood received cardioneural ablation of atrial GPs, and demonstrate 18-month free of syncope [48]. However, GPs ablation in adolescents and children has not been reported until now. Randomized controlled trials in pediatric patients should be performed to confirm the efficacy and safety of this novel treatment.

5. CONCLUSION

Though VVS is a self-limited disease and does not cause mortality, recurrent syncope impairs the quality of life. To early recognize and effectively prevent VVS is critical. The diagnosis of VVS is based on clinical history, HUTT is useful for patients lack of confident diagnosis after an initial assessment. Management of VVS includes conservative therapy, pharmacological therapy, pacemaker treatment, and catheter ablation. For patients with only occasional syncope, health education, compensatory physical maneuvers, salt and water supplementation are recommended. Alpha-adrenoceptor agonists, beta-adrenergic blockers, fludrocortisone, and other medications are used for patients with recurrent episodes, or in whom conservative therapy has failed, but the data in children are limited. Patients with the predominant cardioinhibitory response, associated with repeated

injury, limited prodromes, and documented asystole may benefit from cardiac pacing. Catheter ablation of ganglionated plexi is a new strategy, randomized controlled trials in pediatric patients are needed to verify its efficacy and safety.

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CONFLICT OF INTEREST

The authors declare no conflict of interests.

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