

Hemodynamic and Cerebral Effects of Ethanol Sclerotherapy in Pediatric arteriovenous malformations: A preliminary report

Siyuan xie

Capital Center for Children's Health, Capital Medical University

Chi Wang

Capital Center for Children's Health, Capital Medical University,

Qi Di

Capital Center for Children's Health, Capital Medical University,

Chenghao Chen

Capital Center for Children's Health, Capital Medical University,

Yuhao Jiao

Capital Center for Children's Health, Capital Medical University,

Shoudong Pan

Capital Center for Children's Health, Capital Medical University

Gang Shen

Capital Center for Children's Health, Capital Medical University,

Ding Han

hangapeng2009@126.com

Capital Center for Children's Health, Capital Medical University

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Abstract

Background

Ethanol sclerotherapy is a primary treatment for arteriovenous malformations, yet acute pulmonary hypertension remains a life-threatening complication. The hemodynamic dynamics during pediatric AVM embolization are not fully characterized, particularly the dose-response relationship and cumulative effects of repeated injections.

Methods

This prospective observational study included 29 pediatric patients (33 sessions) undergoing ethanol sclerotherapy under general anesthesia with real-time pulmonary artery pressure monitoring via right heart catheterization. Bispectral Index (BIS), regional tissue oxygen saturation (rSO_2), and hemodynamic parameters were recorded at baseline (T0) and after each ethanol injection (T1-T3).

Results

The mean pulmonary artery pressure rose significantly from 21.65 ± 3.84 mmHg at T0 to 26.33 ± 4.48 mmHg at the last injection ($p < 0.001$, Cohen's $d = 1.230$, large effect). A total of 94% (31/33) of patients exhibited an increase in mean pulmonary artery pressure, with 12% (4/33) demonstrating a > 10 mmHg increase. No significant correlation was found between pulmonary artery pressure elevation and total ethanol volume (Spearman $\rho = -0.073$, $p = 0.685$) or ethanol volume per body weight ($\rho = -0.124$, $p = 0.493$). BIS decreased significantly from 56.13 ± 9.53 to 52.19 ± 13.73 ($p = 0.015$, Cohen's $d = -0.477$). rSO_2 decreased from $74.30 \pm 2.54\%$ to $73.19 \pm 3.62\%$ ($p = 0.002$, Cohen's $d = -0.511$). Systemic vital signs (blood pressure, heart rate, SpO_2) remained stable. rSO_2 was preserved in all patients except one with severe pulmonary hypertension.

Conclusion

Acute pulmonary hypertension is frequent and unpredictable in children undergoing ethanol sclerotherapy, occurring even at low doses. Real-time pulmonary pressure monitoring is essential for early detection and intervention. The transient reduction in BIS supports systemic ethanol absorption, though preserved rSO_2 suggests adequate cerebral oxygenation under general anesthesia. No significant linear dose-response relationship was identified.

Introduction

Arteriovenous malformations (AVMs) are congenital vascular developmental abnormalities characterized by the presence of primitive vascular fistulas that rapidly empty into dilated, tortuous drainage veins without an intervening normal capillary bed^[1]. While often clinically silent at birth, AVMs expand synchronously with somatic growth, frequently necessitating intervention during childhood^[2]. Ethanol sclerotherapy, with its unique properties of protein denaturation and endothelial destruction within the nidus, has emerged as a primary therapeutic choice for AVMs in both adults and children^[3]. However, this technique is associated with non-negligible complications, including inflammatory necrotic tissue damage, nerve palsy, and most perilously, acute pulmonary hypertension (PH), which is attributed to ethanol-induced pulmonary arterial vasoconstriction^[4].

The mechanism of pulmonary artery pressure (PAP) elevation during ethanol sclerotherapy for AVMs remains incompletely understood. Several purported mechanisms include ethanol-induced pre-capillary pulmonary artery vascular spasm, pain-mediated sympathetic stimulation, and systemic absorption of ethanol during the procedure^[5–7]. Potential risk factors for PH include ethanol dose, lesion location, diameter, Yakes classification, sex, and age^[5, 8, 9]. Comprehensive perioperative hemodynamic monitoring is therefore indispensable for managing these high-complexity clinical cases.

Recent advances in perioperative monitoring, including bispectral index (BIS) for anesthesia depth assessment and near-infrared spectroscopy (NIRS) for regional tissue oxygen saturation (rSO_2) monitoring, have provided valuable tools for evaluating the systemic effects of ethanol sclerotherapy in real time. BIS monitoring has been shown to reduce anesthetic consumption and improve recovery outcomes in pediatric patients^[10, 11], while NIRS-derived rSO_2 reflects the balance between cerebral oxygen delivery and consumption, furnishing a reliable noninvasive modality for early recognition of regional tissue hypoperfusion^[12].

This study aims to investigate the dynamic changes in PAP, BIS, and rSO_2 during ethanol sclerotherapy in pediatric AVMs by utilizing real-time right heart catheterization combined with multimodal neuromonitoring. We further sought to evaluate whether a dose-response relationship exists between ethanol exposure—quantified both as absolute volume and as body-weight-adjusted volume—and the magnitude of hemodynamic and cerebral effects.

Materials and Methods

The Institutional Review Board of Capital Institute of Pediatrics approved this study (ethics approval number: SHERLL2024112). This trial has been registered on the Chinese Clinical Trial Registry with registration number ChiCTR2500103248. Written informed consent was obtained from the parents of all participants. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Patients

From May 2025 to May 2026, children diagnosed with AVM undergoing ethanol embolization with PAP monitoring under general anesthesia were considered eligible for inclusion. The inclusion criteria were: (1) signed informed consent for the study; (2) age between 6 months and 18 years; (3) diagnosis of vascular malformation confirmed by medical history and imaging examinations. Exclusion criteria were: (1) congenital heart disease; (2) history of pulmonary arterial hypertension; (3) allergy to contrast media or ethanol; (4) cardiac, hepatic, or renal insufficiency; (5) residence at an altitude > 2500 meters.

Procedure

After admission to the operating room, patients were monitored with 3-lead electrocardiography, digital pulse oximetry, non-invasive blood pressure, bispectral index (BIS, Philips, Amsterdam, Netherlands), and regional tissue oxygen saturation (rSO₂, Foresight-Elite, CAS Medical Systems, CT, USA). All procedures were performed under general anesthesia. Anaesthesia was induced with atropine 0.01 mg/kg, propofol 3 mg/kg, rocuronium 0.6 mg/kg, sufentanil 0.1 µg/kg, and methylprednisolone sodium succinate 1 mg/kg. An appropriately sized laryngeal maskairway (LMA) was inserted, and mechanical ventilation was initiated. Ventilator settings: tidal volume 6–8 mL/kg, respiratory rate 18–25 breaths/min, maintaining end-tidal CO₂(EtCO₂) between 35–45 mmHg, with an inspiratory oxygen concentration of 50%. Anesthesia was maintained with remifentanyl 0.1 µg/kg/min, dexmedetomidine at 0.5 µg/kg/h, and expired sevoflurane 1–2%, targeting a BIS value between 40 and 60. After confirming satisfactory anesthesia, the interventional radiologist placed a right heart catheter under digital subtraction angiography (DSA) guidance. The catheter was a 5F Pigtail angiography tube connected to the pressure sensor kit (Angiopointer™, APT Medical, Hunan, China), and the PAP is monitored using a Philips patient monitor.

AVM embolization is performed via femoral artery access and selective catheterization of the supplying vessel with a guiding catheter. After angiography, transarterial or transvenous catheterization with the use of a coaxial catheter and/or percutaneous direct puncture was required to reach the nidus for embolization. The nidus of AVM was accessed by direct puncture, transarterial catheterization, transvenous catheterization, or a combination of these routes. Absolute ethanol sclerotherapy was administered (single injection ≤ 0.5 mL/kg) with close monitoring of PAP. If PH occurred (mean PAP > 25 mmHg), nitroglycerin was administered as a bolus of 1 µg/kg or continuous infusion at 0.3-3.0 µg/kg/min. Angiography was carried out to determine whether the nidus of the AVM was embolized 5 to 10 minutes after each ethanol injection. Repeated ethanol injection was required if the nidus was still noted on angiography, ensuring the total ethanol did not exceed 1 ml/kg. After each bolus injection of ethanol, PAP, rSO₂, BIS and the amount of ethanol used were recorded.

Data Acquisition

Vital signs including PAP, SpO₂, heart rate (HR), blood pressure (BP), BIS, and rSO₂, were recorded at the following points: hemodynamic profiles measured immediately before ethanol injection (T0);

hemodynamic profiles measured within 1 min after each injection at the time of maximum mean PAP value (T1, T2, T3 corresponding to the 1st, 2nd, and 3rd injections, respectively). For patients receiving multiple injections, the last recorded time point (T_{last}) was used for the primary comparison with T0.

Statistical Analysis

Statistical analyses were performed using R software (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria). Normality of paired differences was assessed by the Shapiro-Wilk test. For comparisons of pre- and post-injection values, paired t-tests were applied when the normality assumption was met; otherwise, Wilcoxon signed-rank tests were used. Effect sizes were quantified using Cohen's d: negligible (< 0.2), small (0.2–0.49), moderate (0.5–0.79), and large (≥ 0.8). Correlations were evaluated using Spearman rank correlation. Multivariable analysis was conducted with multiple linear regression, with all continuous independent variables (age in months, body weight, total absolute ethanol dose, ethanol dose per body weight, and number of injections) standardized by Z-score transformation. Temporal trends across multiple injection time points were assessed using the Friedman test (a non-parametric repeated-measures analysis of variance). A two-tailed P-value < 0.05 was considered statistically significant.

Results

A total of 35 patients met the inclusion criteria. Among them, 4 patients were excluded due to guardians' refusal to participate, and another 2 patients were excluded owing to intraoperative modification of treatment plans. Finally, 29 patients were enrolled (13 male and 16 female) with a median age of 114 months (IQR, 37–169 months; range, 14–215 months) and mean weight of 38.5 ± 25.5 kg (range, 10.0 – 96.0 kg), receiving a total of 33 sessions. The flowchart is shown in Fig. 1. All patients were ASA I-II. The AVMs were located in the head and neck (n = 6), upper extremity (n = 9), lower extremity (n = 10), and pelvic cavity and trunk (n = 8). AVMs were classified as type II (n = 23) and type III (n = 10) according to the Yakes classification system^[13]. A total of 33 ethanol sclerotherapy sessions with 53 bolus injections were evaluated [mean frequency of injection per session was 1.6 (range 1–3 times)]. There were 19 sessions (58%) received only one embolization injection and 14 (42%) sessions received two or three injections. Patients' clinical data and AVM details are shown in Table 1.

Table 1
Characteristics of Patients and Interventional Procedures

Parameter	Value
Mean age $\pm$ standard deviation(m)	114 $\pm$ 65(14–215)
Mean weight $\pm$ standard deviation(kg)	38.5 $\pm$ 25.5(10.0–96.0)
M:F ratio	16:13
Location of malformation(n = 33)	
Head and neck	6
Upper extremity	9
Lower extremity	10
Pelvic cavity and trunk	8
Mean no. of ethanol injections per session	1.6 $\pm$ 0.8(1.0–3.0)
Method of ethanol injection(n = 53)	
Direct puncture	18
Transarterial catheterization	29
Transvenous catheterization	6

The mean volume of a single bolus injection was 3.0 ± 4.9 ml (range 0.1–20 ml of absolute ethanol). The amount of ethanol per injection was 0.088 ml/kg (range 0.001–0.426 ml/kg). The total amount of absolute ethanol injected during a session ranged between 0.3 and 30 ml (0.001–0.638 ml/kg) with a mean amount of 4.2 ml (0.121 ml/kg). All patients successfully underwent embolization. Following emergence from anesthesia, the LMA were removed, and all patients were transferred to the ward. Two patients had a systemic response during the intervention, most likely ethanol-induced, manifested by temporary PH and bronchospasms, accompanied by a decrease in SpO₂. In the more severe case, the mean pulmonary artery pressure (mPAP) rose rapidly to a peak of 46 mmHg, coinciding with reductions in SpO₂, rScO₂, and BIS. Despite these events, oxygenation and ventilation normalized gradually with treatment, and there were no consequences for postoperative recovery. All patients had an uneventful recovery. The laryngeal mask was removed before ward transfer, with no instances of postoperative delirium or agitation. According to the angiographic and clinical findings after treatment, therapeutic outcomes were complete or partial response in all patients.

In this study, the average mPAP of the children before injection was 21.65 ± 3.84 mmHg (range 10–31 mmHg), among which the mPAP of 21 cases exceeded 20 mmHg. After the last ethanol injection, the mPAP of 30 patients exceeded 20 mmHg. In 31 patients (94%), the mPAP increased after ethanol injection. Notably, increases of more than 10 mmHg were recorded in 4 sessions (12%) immediately

following ethanol injection. The mPAP at T_{last} was significantly higher than at T₀ ($p < 0.001$, Cohen's $d = 1.230$, large effect size), while BIS ($p = 0.015$, Cohen's $d = -0.477$) and rSO₂ ($p = 0.002$, Cohen's $d = -0.511$) were significantly lower. Changes in PAP, BIS, and rSO₂ were not significantly associated with the injected ethanol volume or delivery method. Although rSO₂ differed significantly before and after ethanol injection, the drop was minimal (74.30 ± 2.54 pre-injection vs. 73.19 ± 3.62 post-injection). Notably, even the patient experiencing severe PH demonstrated only a modest decline in rSO₂, from 71% to 69%. No significant changes were observed in blood pressure, heart rate, or SpO₂ before and after injection. Table 2 shows the comparative results of mPAP, BIS, rSO₂, and hemodynamic parameters.

Table 2
mPAP, BIS, rSO₂, and hemodynamic parameters before and after the last ethanol injection.

Variables	T ₀ (Before)	T _{last} (After Last Injection)	Mean Change (95% CI)	p-value	Cohen's d
mPAP (mmHg)	21.65 ± 3.84	26.33 ± 4.48	+ 4.67 (3.38, 5.97)	< 0.001	1.230 (Large)
BIS	56.13 ± 9.53	52.19 ± 13.73	-3.94 (-6.76, -1.12)	0.015	-0.477 (Small)
rSO ₂ (%)	74.30 ± 2.54	73.19 ± 3.62	-1.11 (-1.85, -0.37)	0.002	-0.511 (Moderate)
Heart rate (beats/min)	86.24 ± 16.50	87.26 ± 17.97	+ 1.02 (-3.39, 5.44)	0.953	0.023 (Negligible)
Systolic BP (mmHg)	87.93 ± 13.70	89.96 ± 9.36	+ 2.03 (-2.12, 6.18)	0.779	0.096 (Negligible)
Diastolic BP (mmHg)	47.39 ± 12.23	50.38 ± 12.79	+ 2.99 (-1.00, 6.97)	0.076	0.304 (Small)
SpO ₂ (%)	99.65 ± 1.98	99.56 ± 2.20	-0.09 (-0.90, 0.72)	1.000	0.000 (Negligible)

Data are presented as mean ± standard deviation. BP, blood pressure; BIS, Bispectral Index; CI, confidence interval; mPAP, mean pulmonary artery pressure; rSO₂, regional tissue oxygen saturation; SpO₂, peripheral oxygen saturation.

Spearman rank correlation analysis revealed no significant correlation between mPAP elevation and total ethanol volume ($\rho = -0.073$, $p = 0.685$) or ethanol volume per body weight ($\rho = -0.124$, $p = 0.493$) (Table 3). Similarly, no significant correlations were found between BIS or rSO₂ changes and either dose metric. The strongest (though still non-significant) correlation was observed between diastolic blood pressure change and ethanol volume per body weight ($\rho = +0.173$, $p = 0.418$)

Table 3

Spearman rank correlation between physiological parameter changes and ethanol dose metrics.

Variables	ρ (Ethanol Total, mL)	p-value	ρ (Ethanol/Weight, mL/kg)	p-value
Δ mPAP (mmHg)	-0.073	0.685	-0.124	0.493
Δ BIS	+ 0.018	0.920	-0.040	0.827
Δ rSO ₂ (%)	-0.054	0.766	+ 0.063	0.726
Δ Heart rate (beats/min)	-0.195	0.331	-0.036	0.858
Δ Systolic BP (mmHg)	+ 0.093	0.666	+ 0.242	0.255
Δ Diastolic BP (mmHg)	+ 0.098	0.649	+ 0.173	0.418

Among the 14 patients who received two or three injections, Friedman test analysis of temporal trends across T0, T1, and T2 revealed no significant cumulative increase in mPAP beyond the initial injection effect ($p > 0.05$). The mean mPAP changes were + 4.80 mmHg after the first injection and + 4.67 mmHg after the last injection, with no statistically significant difference between these values ($p = 0.683$), suggesting that the primary hemodynamic effect of ethanol is established after the first injection and does not significantly intensify with subsequent injections.

Discussion

Ethanol sclerotherapy has been considered a primary therapeutic choice for AVMs because it can cause permanent destruction of the nidus by damaging the endothelium, denaturing proteins, activating the coagulation system, and promoting occlusion^[3]. However, this technique is associated with serious systemic effects, including central nervous system depression, hypoglycemia, hypertension, hemolysis, pulmonary embolism, and most critically, pulmonary vasospasm, cardiac arrhythmias, and electromechanical disassociation^[9, 14, 15].

Acute PH can precipitate right ventricular failure, leading to global hemodynamic collapse if not promptly reversed^[16–18]. Current practice guidelines recommend that the total volume of ethanol injected in a single embolization session was no more than 1 mL/kg^[19]. Notably, ethanol use in children warrants particular caution, maintaining a dose limit of 0.5 mL/kg per procedure is suggested^[20]. In our study, the total amount of absolute ethanol injected during a session ranged between 0.3 and 30 mL (0.001–0.638 mL/kg) with a mean amount of 4.2 mL (0.121 mL/kg). Our study demonstrates that acute PH is a frequent and consistent complication of ethanol sclerotherapy in pediatric patients, occurring in 91% of sessions. The mean mPAP increased significantly from 21.65 ± 3.84 mmHg to 26.33 ± 4.48 mmHg ($p < 0.001$, Cohen's $d = 1.230$), representing a large effect size. Four sessions (12%) exhibited increases exceeding 10 mmHg, with one case reaching a peak mPAP of 46 mmHg. These findings underscore the critical importance of real-time PAP monitoring during the procedure.

No significant correlation was observed between ethanol exposure and the magnitude of PAP elevation. Neither total ethanol volume (Spearman $\rho = -0.073$, $p = 0.685$) nor body-weight-adjusted ethanol volume ($\rho = -0.124$, $p = 0.493$) correlated significantly with mPAP change. This aligns with a subset of previous studies that also failed to demonstrate a linear dose-response relationship^[21]. Conversely, other literature reports, such as Ko et al., indicate that PAP reflects the pulmonary arterial ethanol level and is positively related to the dose^[22]. While previous studies have established a significant correlation between single-injection ethanol dose and pulmonary artery pressure elevation, noting that this relationship is more direct than that with cumulative dose^[22], our study did not demonstrate such a correlation. The absence of a dose-response relationship could be due to several factors: the limited dose range employed in this study (0.001–0.638 mL/kg), a potential threshold effect whereby even minimal ethanol exposure triggers maximal pulmonary vasoconstriction, and substantial inter-individual variability in pulmonary vascular reactivity.

Currently, PH is defined as an mPAP > 20 mmHg (1 mmHg = 0.133 kPa) measured via right heart catheterization under resting conditions^[23]. We observed elevated baseline mPAP at T0 in a portion of pediatric AVM patients before ethanol injection, which could be explained by chronic high-flow shunt overload from congenital fistulas^[24]. Long-term bypass of capillary beds leads to persistent increased cardiac output and repetitive shear stress on immature pediatric pulmonary endothelium, inducing early pulmonary vascular remodeling and elevated resting pulmonary vascular resistance^[25, 26]. This pre-existing pulmonary vascular remodeling may prime the pulmonary vasculature to exhibit exaggerated vasoconstrictive responses to intraprocedural ethanol exposure, offering a mechanistic explanation for the dose-independent acute PH observed in our study.

In this study, BIS monitoring was employed to assess anesthetic depth. Sympathetic stimulation resulting from the intense pain of ethanol injection likely contributes to the elevation in mPAP, whereas supplemental oxygen induces mild pulmonary vasodilation and reduces mPAP^[5]. Consequently, maintaining adequate anesthetic depth and appropriate ventilatory management under general anesthesia is imperative during ethanol sclerotherapy. Prior to ethanol injection, BIS values were maintained between 40 and 60 (mean: 56.13 ± 9.53). This ensured adequate anesthesia, as corroborated by concurrent hemodynamic stability. Immediately following the last injection, BIS values decreased significantly (mean: 52.19 ± 13.73 , $p = 0.015$, Cohen's $d = -0.477$), with a nadir of 29 recorded in one patient. This transient reduction likely reflects the systemic absorption of ethanol and subsequent depression of central nervous system activity, rather than a deepening of anesthesia. The risk of systemic ethanol intoxication following embolization is well-documented in the literature. While clinical experience suggests that a dose of 1.0 mL/kg is generally well-tolerated, Mason et al. demonstrated that even this threshold can induce legal intoxication, reporting a mean dose of 0.87 mL/kg in intoxicated pediatric patients^[9]. Because all patients were under general anesthesia and received postoperative analgesics, the central nervous system depressive effects of ethanol were masked^[7]. Nevertheless, altered mental status was observed in a subset of patients postoperatively. A patient experienced

postoperative irritability after arterial injection, which was considered a phenomenon of drunkenness and resolved within 6 hours^[19].

In our study, BIS decreased following ethanol injection. As BIS is often considered a surrogate indicator for metabolism^[27], this reduction reflects ethanol-induced cerebral suppression and a concomitant decrease in metabolic rate. Concurrently, ethanol exerts a cerebrovascular vasodilatory effect, increasing cerebral blood flow, while rSO₂ typically remained stable or exhibited a slight elevation. Cerebral oximetry remained stable across the cohort following ethanol injection, suggesting that ethanol-induced neurotoxicity was localized and clinically acceptable, without precipitating systemic hypoxia. Furthermore, all patients exhibited an uneventful postoperative recovery, with no instances of delirium or agitation. These findings indicate that the transient cerebral inhibition observed falls within safe clinical thresholds. However, one exception involved a critical event of severe PH complicated by elevated airway pressures and difficult ventilation. In this case, rSO₂ decreased minimally from 71% to 69% concomitant with a BIS reduction from 56 to 45. This transient desaturation was attributable to a precipitous drop in cardiac output secondary to severe PH, leading to inadequate cerebral perfusion. Fortunately, real-time PAP monitoring facilitated the rapid detection of this hemodynamic compromise, allowing for immediate intervention that averted a potentially catastrophic outcome.

Systemic vital signs, including heart rate, systolic blood pressure, and SpO₂, remained stable throughout the procedure, with no statistically significant changes observed. This finding supports the overall safety of ethanol sclerotherapy when performed under general anesthesia with comprehensive monitoring. The stability of SpO₂ (mean change: -0.09%, p = 1.000) is particularly reassuring, indicating that pulmonary gas exchange is preserved even in the presence of elevated PAP.

Based on our findings, we recommend the following safety measures for pediatric ethanol sclerotherapy: (1) mandatory real-time PAP monitoring via right heart catheterization, as PH occurs in nearly all patients regardless of dose; (2) continuous BIS monitoring to detect systemic ethanol absorption and CNS depression; (3) rSO₂ monitoring to ensure adequate cerebral oxygenation; (4) readiness for immediate vasodilator therapy (nitroglycerin) and advanced airway management; (5) adherence to weight-based dosing limits (≤ 0.5 mL/kg per injection, ≤ 1 mL/kg per session) as a safety precaution, despite the lack of a linear dose-response relationship; and (6) maintenance of deep anesthesia (BIS 40–60) throughout the procedure to minimize sympathetic-mediated PAP elevation.

Study Limitations

This study has several limitations. First, the sample size (n = 33) is relatively small, limiting the statistical power to detect moderate dose-response relationships. Second, the dose range in our study was limited (0.001–0.638 mL/kg), and higher doses may reveal a different dose-response pattern. Third, we did not measure blood ethanol concentrations, which would have provided direct evidence of systemic

absorption. Fourth, this was a single-center study, and multicenter validation is needed to confirm our findings.

Conclusion

Our study characterizes the hemodynamics of pediatric AVM ethanol embolization, demonstrating that acute PH is common and independent of absolute ethanol dose, invalidating weight-based limits as sole safeguards. The concomitant drop in BIS confirms systemic ethanol absorption and CNS depression, masked by general anesthesia, while stable rSO_2 suggests adequate cerebral oxygenation. Therefore, continuous PAP monitoring, BIS monitoring, and strict anesthetic depth are mandatory. Given the risk of respiratory collapse, readiness for immediate vasodilator therapy and advanced airway management is essential.

Declarations

Copyright form disclosure: The authors have disclosed that they do not have any potential conflicts of interest.

Conflict of interest:

None.

Ethics approval and consent to participate

This clinical trial was conducted in accordance with the principles of the Declaration of Helsinki (2013 revision), ICH-Good Clinical Practice (ICH-GCP) Guidelines. The Institutional Review Board of Capital Institute of Pediatrics approved this study on 2 December 2024, prior to the commencement of the study (ethics approval number: SHERLL2024112). Written informed consent was obtained from the parents of all participants.

Consent for publication

Not applicable (the manuscript contains no identifiable individual person's data, images, or videos).

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Author Contribution

S.X., D.H. and S.P. designed the study; S.X., C.W., Q.D., C.C., G.S. and Y.J. collected the data; G.S. and D.H. performed the data analysis and critically revised the manuscript; S.X. drafted the manuscript. All authors reviewed the manuscript.

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Figures

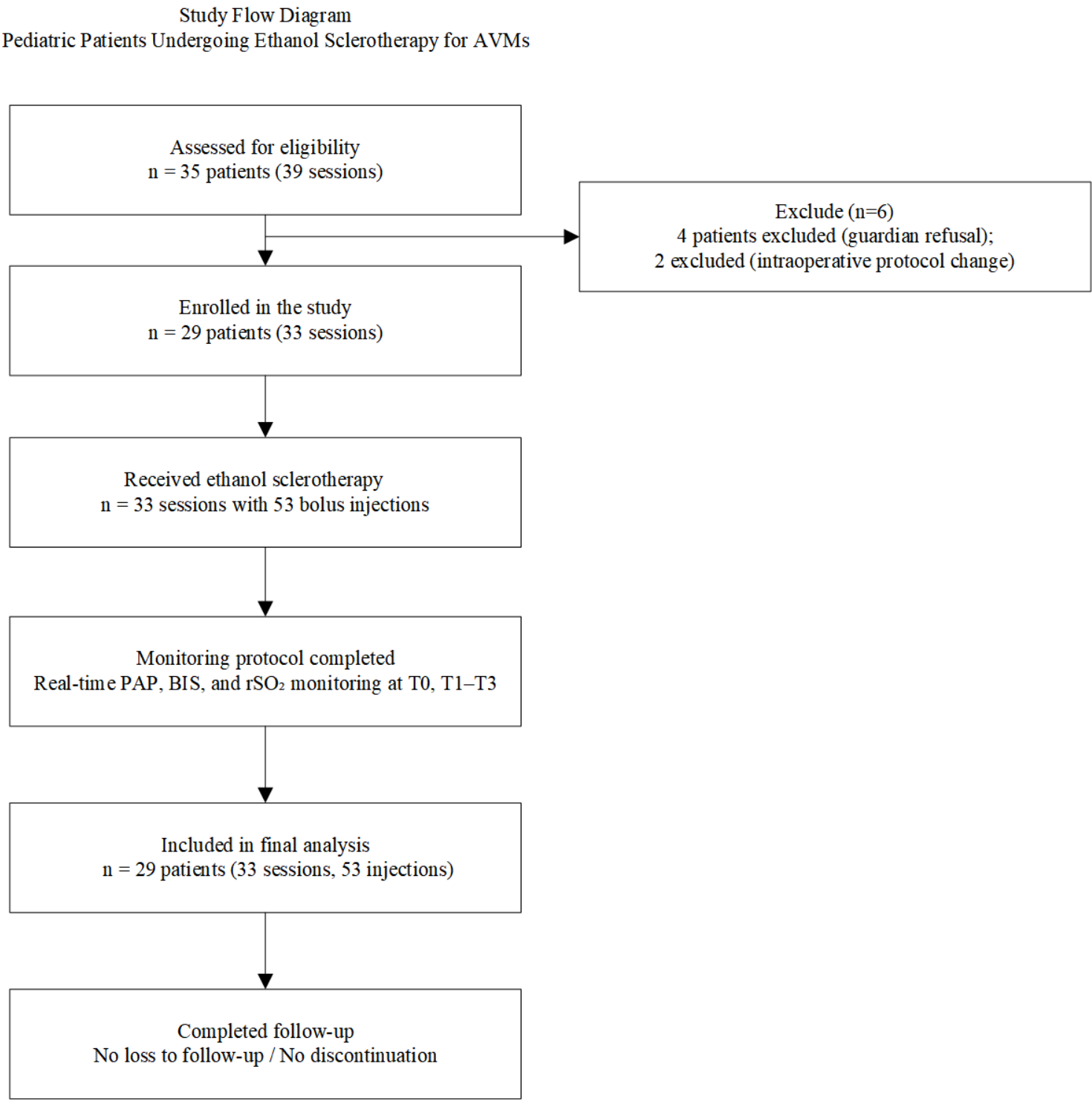


Figure 1

Flow Diagram of Participants