# Is ventricular lavage a novel treatment of neonatal posthemorrhagic hydrocephalus? a meta analysis

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ORIGINAL ARTICLE

# Is ventricular lavage a novel treatment of neonatal posthemorrhagic hydrocephalus? a meta analysis

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## Abstract

**Introduction** Intraventricular hemorrhage (IVH) may produce obliterative arachnoiditis, which disrupts the flow and absorption of cerebrospinal fluid (CSF), resulting in posthemorrhagic hydrocephalus (PHH). PHH gives a high risk of neurofunctional impairment.

Ventricular lavage is the treatment of choice for PHH in neonates with IVH for decades. It is developing with the combination of fibrinolytic therapy, also called drainage, irrigation, and fibrinolytic therapy (DRIFT), and with the use of neuroendoscopic apparatus, also called neuroendoscopic lavage (NEL).

**Methods** This review is a meta-analysis using the PRISMA method guideline, including the clinical studies comparing ventricular lavage (VL) with standard treatment of PHH between 2000 and 2021.

**Results** VL group reduced the shunt dependency compared to standard treatment (OR = 0.22; 95CI 0.05 to 0.97; $p = 0.05$). VL group has less infection risk compared to the standard treatment group (RR = 0.20; 95CI 0.07 to 0.59; $p < 0.05$). The severe neurofunctional outcome is similar between the two groups (OR = 0.99; 95CI 0.13 to 7.23; $p = 0.99$). The early approach treatment group may give better neurofunctional outcomes compared to the late approach (OR = 0.14; 95CI 0.06 to 0.35; $p < 0.05$).

**Conclusion** VL reduce the shunt dependency on the PHH, decreasing the shunt's related infection rate. The early ventricular lavage may give benefit for the neurocognitive outcome.

**Keywords** Posthemorrhagic hydrocephalus · Intraventricular hemorrhage · Neuroendoscopic lavage · Cerebrospinal diversion · Ventriculoperitoneal shunt · Neonates

## Introduction

Intraventricular hemorrhage (IVH) is frequently found in premature babies, with incidence occurring up to 25% to 30% in this group [1]. Large IVHs (grade III/IV) produce obliterative arachnoiditis, which disrupts the flow and absorption of cerebrospinal fluid (CSF), resulting in posthemorrhagic hydrocephalus (PHH) [2].

The presence of a blood clot inside the CSF and the characteristics of the premature newborn prohibit the use of a permanent CSF shunting device. Thus, temporary management of hydrocephalus is required [3].

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The standard management for temporarily alleviate the increasing intracranial pressure (ICP) includes lumbar punctures, ventricular access device, ventriculosubgaleal shunt (VSgS), and external ventricular drain [1–6]. However, the optimal treatment strategy that is effective, has a low complication rate, and provides better cognitive outcome has yet to be found [3].

Ventricular lavage is the treatment of choice for PHH in neonates with IVH for decades. It is developing with the combination of fibrinolytic therapy, also called drainage, irrigation, and fibrinolytic therapy (DRIFT), and with the use of neuroendoscopic apparatus, also called neuroendoscopic lavage (NEL).

NEL is another treatment option for PHH. This procedure was developed following the DRIFT method, aiming to remove intraventricular hematoma in a less invasive and more controlled settings [4]. This method eliminates intraventricular blood clots to reduce brain damage and hydrocephalus. NEL reduces persistent shunting and increases shunt survival/ shunt malfunction [6].

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DRIFT is one of the methods developed to alleviate the rise of ICP. DRIFT is conducted by administering a sub-systemic dosage of tissue plasminogen activator intraventricularly [2, 7]. DRIFT was reported to have better neurodevelopmental outcomes compared to standard management [4]. Basically, the DRIFT and NEL treatment's goal is to eliminate the intraventricular blood clots.

PHH remains a critical illness with a high cognitive, motor, and sensory impairment risk [7]. The ventricular system's increased pressure, distortion, and neurotoxic and inflammatory consequences induce gradual brain damage and consequent neuro-disability, which issometimes severe [8]. In 48% of newborns with a grade 4 IVH and receiving shunt, severe cognitive disability (Mental Development Index [MDI] 50) was identified [7]. It is also the leading risk factor for special educational needs in children of school age [2].

Thus, the main goal of treatment for PHH in neonates with IVH management is to clear the intraventricular hematoma. This meta-analysis was conducted to evaluate the benefits of reducing shunt dependency, infection risk, and neurofunctional outcome in removing the intraventricular hematoma. The recommended treatment should not only be effective, but it should also be capable of reducing severe disability.

## Material and methods

### General information and literature search strategy

The selection of studies was carried out with PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol) method guideline. The data was collected from PubMed, ScienceDirect, Cochrane Library, and Google Scholar.

### Eligibility criteria

Articles included in this review were clinical study comparing ventricular lavage (VL) with standard treatment for neonatal posthemorrhagic hydrocephalus or intraventricular hemorrhage-induced ventricular dilatation, published in English or Bahasa between 2000 and 2021, information regarding the safety and efficacy of ventricular lavage as the first-line therapy for posthemorrhagic hydrocephalus.

Proceeding articles, editorials, commentaries, or publications without a peer-review process were excluded. Congenital, infection, tumor, and spinal dysraphism-related hydrocephalus were excluded.

### Information source and search strategy

We systematically searched the literature to identify relevant articles using PubMed, ScienceDirect, Cochrane Library, and Google Scholar for articles published from January 2000 to December 2021 using keywords in our search strategy below (Table 1). We also performed a hand-search of references listed in relevant articles to identify additional primary studies and minimalize bias.

### Statistical analysis

This meta-analysis utilized Revman version 5.4 from the Cochrane Review. Quantitative data were presented as odds ratio (OR), and risk ratio (RR). The given data were based on a 95% confidence interval (CI). Fixed-effects model (FEM) and Random-effects model (REM) were adopted in the meta-analysis.

## Results

### Data collection

The extracted data included bibliographic data and safety and efficacy results (shunt dependency, infection rate, and neurofunctional outcome). The data extraction was conducted independently by three investigators, and any disputes were resolved by the senior author. The PRISMA flow diagram represents the systematic search (Fig. 1).

**Table 1** Keywords search strategy

| | |
|---|---|
| 1 | (Posthemorrhagic ventricular dilatation) |
| 2 | (Intraventricular hemorrhage) OR (Germinal matrix hemorrhage) |
| 3 | #1 OR #2 |
| 4 | (Ventricular Lavage) |
| 5 | (Neuroendoscopic lavage) OR (endoscopic irrigation) |
| 6 | #4 OR #5 |
| 7 | (Cerebrospinal fluid diversion) OR (Cerebrospinal fluid shunt) |
| 8 | (Ventriculoperitoneal shunt) OR (Ventriculosubgaleal shunt) OR (Lumboperitoneal shunt) OR (Lumbar drainage) OR (Ventriculoatrial shunt) OR (CSF tapping) OR (Ommaya reservoir) OR (Temporary CSF diversion) OR (External ventricular drainage) |
| 9 | #7 OR #8 |
| 10 | (Treatment timing) |
| 11 | (Treatment strategy) |
| 12 | #10 AND #11 |
| 13 | (Outcome) OR (Neurodevelopmental outcome) OR (morbidity) OR (Mortality) OR (Shunt dependency) OR (Shunt conversion) OR (Shunt requiring) |
| 14 | #3 AND #6 AND #9 AND #12 AND #13 |
| 15 | (Infants) OR (Pediatrics) |
| 16 | #14 AND #15 |

## Risk of bias analysis

The result of the bias risk assessment of the included studies was measured using the risk of bias tool developed by the Cochrane Methods Bias Group member risk. For non-randomized studies, we used the risk of bias in non-randomized studies of intervention (ROBINS-I) and version 2 of the Cochrane risk of bias tool for randomized trial (RoB-2) the randomized studies. We have data (not shown) to show normal distribution results with some acceptable deviations. Thus, the eligibility of the literature is high.

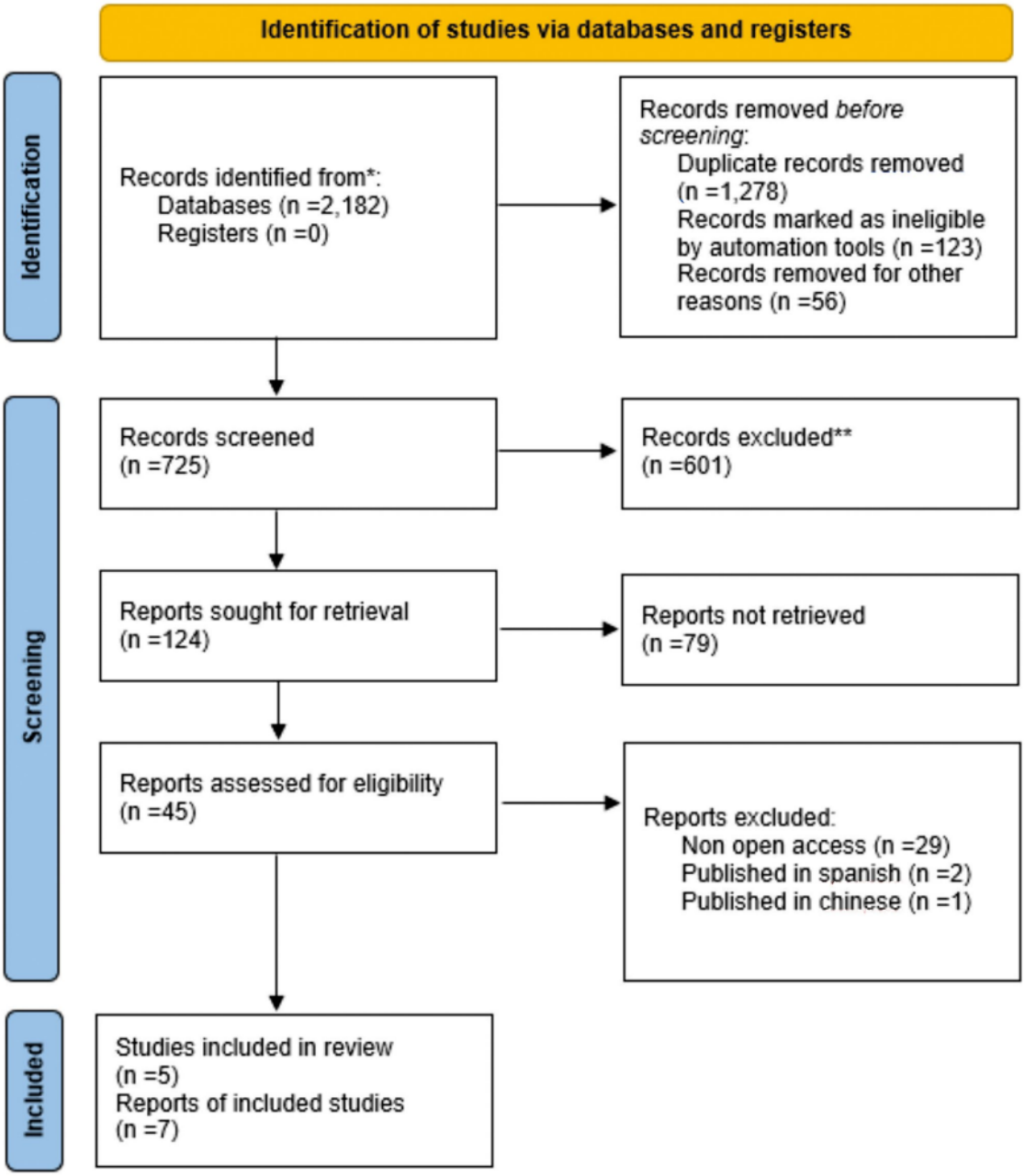


**Fig. 1** PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol) flow diagram

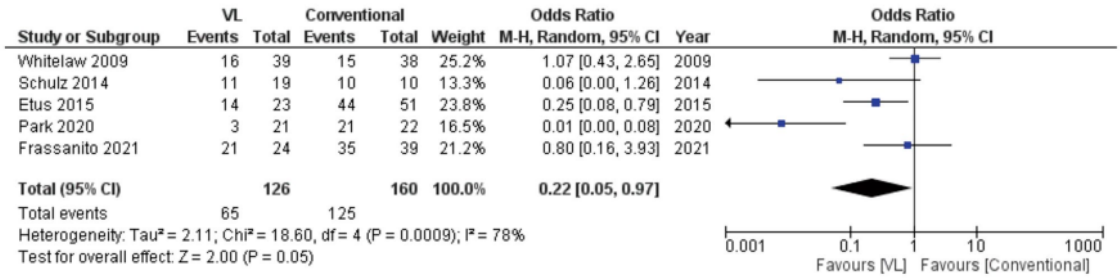


**Fig. 2** Forest plot for shunt dependency after ventricular lavage (VL) compared to standard treatment

## Quantitative analysis

The authors conducted the meta-analysis into several groups of analysis for the specific outcome, which were carried out on homogenous studies for each analysis group (shunt dependency after VL, infection rate after VL, severe neurofunctional outcome after VL, neurofunctional outcome in the early treatment group versus the late treatment group).

The VL treatment group seems to have less need for permanent CSF diversion compared to the standard treatment group (ventriculoperitoneal shunt, ventriculosubgaleal shunt, extra-ventricular drainage, lumbar drainage, lumboperitoneal shunt) during the follow-up and statistically significant (OR = 0.22; 95CI 0.05 to 0.97; $p = 0.05$; Fig. 2).

Regarding the infection rate, the VL treatment group has less risk of infection compared to the standard treatment group (RR = 0.20; 95CI 0.07 to 0.59; $p < 0.05$; Fig. 3).

The VL treatment group seems to have no significant difference compared to the standard treatment group for severe neurofunctional outcome events (OR = 0.99; 95CI 0.13 to 7.23; $p = 0.99$; Fig. 4).

The early approach treatment group is better compared to the late approach treatment group for mitigating severe neurofunctional outcome events (OR = 0.14; 95CI 0.06 to 0.35; $p < 0.05$; Fig. 5).

## Discussion

Since standard management of using lumbar punctures or ventricular drainage had a poor result in functional outcome, other methods are proposed. Ventricular lavage was introduced to decompress early and clear blood clots. The commonly known techniques for ventricular lavage were DRIFT and NEL [6]. The outcomes evaluated in this study were shunt dependency, infection rate, and neurofunctional outcome.

### Shunt dependency

Schulz reported that the period of eventually needing a permanent shunt is longer in the VL group compared to the standard group (temporary CSF diversion: lumbar punctures, a ventricular access device, or an external ventricular drain) [9]. Our data showed that the VL group is significantly less shunt dependent than the standard treatment group (11 of 19 patients vs. 10 of 10 patients). However, in the standard group, repeated CSF removal is required immediately after surgery and on a regular basis [9].

Etus also reported a significantly lower rate of shunt dependency in the VL group compared to those received standard treatment [1]. The discrepancy in the population size between these two groups due to the

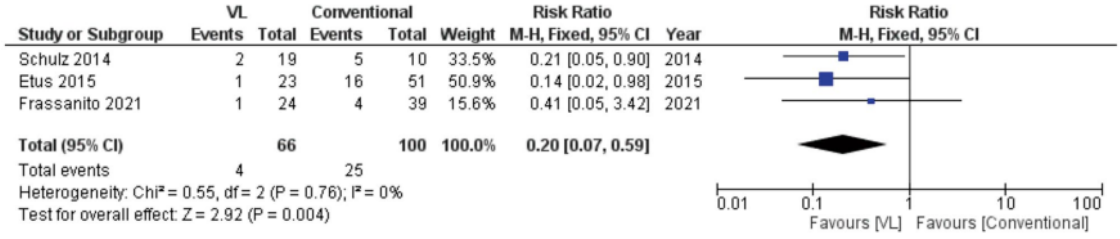


**Fig. 3** Forest plot for infection event after ventricular lavage (VL) compared to standard treatment

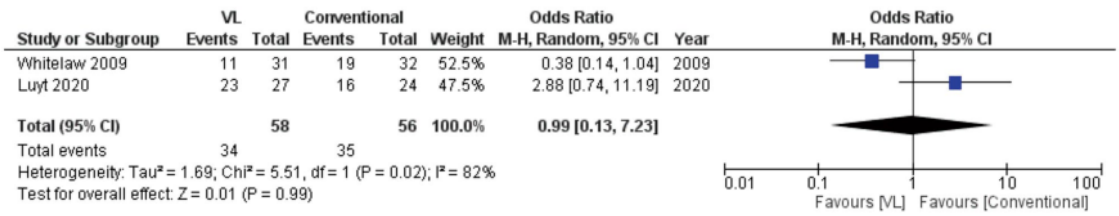


**Fig. 4** Forest plot for severe neurofunctional outcome after ventricular lavage (VL) compared to standard treatment

ventriculosubgaleal shunt being included into the standard treatment together (23 patients vs. 51 patients, respectively) [1] might have a significant impact on the overall quantitative analysis.

Park utilizes ventricular lavage (with a fibrinolytic therapeutic strategy using urokinase) to manage PHH. Eighteen out of 21 patients (86%) receiving VL did not require permanent shunt placement, which was considered a great success [5]. Although this result might cause this group's sample population heterogeneous ($I^2 = 78\%$).

On the contrary, Whitelaw and Frassanito reported that ventricular lavage treatment did not reduce the shunt dependency rate. Whitelaw reported that VL did not reduce the need for permanent shunt with a comparable number between VL and the standard treatment group (16 of 39 patients vs. 15 of 38 patients, respectively) [1]. Frassanito reported that shunt dependency is similar in the group receiving ventriculosubgaleal shunt (VSgS) compared to those receiving VSgS and VL[3], although these results may be caused by the small number of patients, timing of surgery, and other factors [3].

## Infection rate and multiloculated hydrocephalus

Schulz reported a lower infection rate in the VL group. This might be caused by a smaller number of serial CSF punctures in the VL group. The rate of multiloculated hydrocephalus were also lower since this condition is usually precipitated by the previous infection. In a study by Etus et al., the VL group had a significantly lower rate of infection and multiloculated hydrocephalus compared to the group with standard treatment or VSgS [1].

In line with Schulz, Frassanito reported that the group receiving VSgS and VL had a lower infection rate (4.2%) than the group with VSgS only (10.3%). In this study, multiloculated hydrocephalus was also lower in the VSgS and VL group (20.8%) compared to those only receiving VSgS (23.1%). VL was able to lower the rate of multiloculated hydrocephalus since it decreased blood clot and protein load [4].

## Neurofunctional Outcome

In PHH, multiple blood clots initially restrict CSF reabsorption but eventually progress to chronic arachnoiditis of the basal cisterns with extracellular matrix protein deposition [10]. Approximately half of all infants with PHH have an early hemorrhagic infarction of periventricular white matter. However, over the next few weeks, pressure, distortion, free radical generation facilitated by free iron, and inflammation may cause progressive injury to the immature cerebral hemispheres globally [2]. This mechanism leads to the high probability of severe cognitive, motor, and sensory disability in children with PHH.

Decompressing early and clearing the blood clots in the ventricle may lead to a better neurofunctional outcome. This study reported that in 2 years with adjusted gender, birth weight, and IVH grade; the reduction in the primary long-term outcome, death or severe impairment in the VL group attained statistical significance compared to the

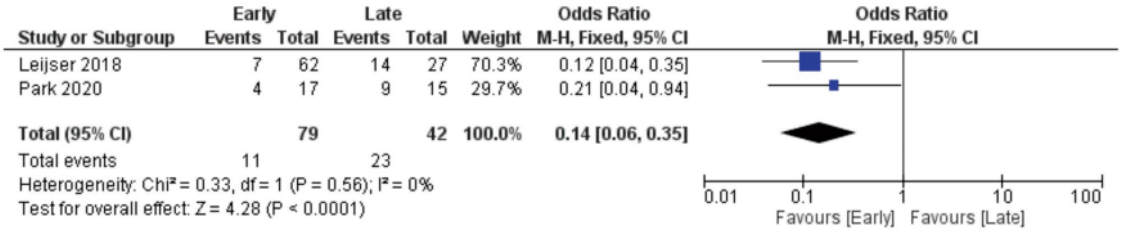


**Fig. 5** Forest plot for neurofunctional outcome in early approach compared to late approach

standard treatment. Furthermore, severe cognitive impairment was substantially halved and was statistically significant, while the sensorimotor outcome was unremarkable statistically. This may be explained by the presence of periventricular white matter infarction, and VL cannot undo this condition [7].

Luyt also conducted a long-term follow-up of 10 years in patients who underwent VL management. It shows that VL in preterm children with PHH after severe IVH enhances cognitive function at a 10-year follow-up when birth weight, IVH grade, and sex are considered. This finding is significant since it follows the patient until middle school age, thus further proving the benefit of VL in the long-term neurocognitive outcome [2].

Leijser and Park conducted a study for the neurocognitive outcome based on the treatment's timing [5, 11].

Park used a ventricular lavage method with urokinase injections and compared the group with early ventricular lavage (within 3 weeks of IVH) and those who had late ventricular lavage (after 3 weeks of IVH onset). A good functional outcome was in patients who underwent early ventricular lavage. The functional outcome evaluated were lower limb function and walking ability; upper limb function and feeding ability; and cognitive function and speaking capacity. All domains were statistically significant better in the early treatment group ($p < 0.05$) [5].

Leijser compared two different timing approaches for PHH, the early approach by using temporary CSF drainage with lumbar punctures or ventricular reservoir followed by permanent shunt; and the late approach by using clinical signs of increased intracranial pressure to start the placement of a permanent shunt. The study shows that, regardless of intervention, infants receiving an early approach have essentially expected early cognitive and motor outcomes, even when a permanent shunt is eventually required. Infants who receive LA, on the other hand, have poor cognitive and motor outcomes if intervention is ultimately required. With the LA, the VP-shunt rate and shunt-related complications were also higher [11].

The poorer neurodevelopmental outcomes in infants who received late intervention suggest that progressive ventricular dilatation and prolonged pressure are harmful to immature white matter. Even if CSF pressure is restored to normal at a later point, the white may no longer be able to heal [12].

Although not included in the meta-analysis, NEL could also improve brain development and avoid secondary damage by reducing triggered inflammation. NEL itself had a similar principle with VL, but less invasive and more controlled settings [6].

Since ventricular lavage is a feasible technique to remove degraded intraventricular blood residual in post-hemorrhage hydrocephalus, this procedure can reduce the shunt dependency risk caused by arachnoiditis-related hydrocephalus due to the high load of degraded blood products. Another substantial burden is the multiloculated hydrocephalus caused by the development of PHH and CSF infection. Our review shows that a well-tolerated ventricular lavage has less risk of infection rate, which may mitigate multiloculated hydrocephalus and may further contribute to reducing shunt dependency rate.

White matter damage due to ventricular dilatation and neurotoxic and inflammatory responses from blood products intraventricular may deteriorate the neuro-disability. On the contrary, our meta data shows that ventricular lavage has no benefit in the neurofunctional outcome. To date, the main goal in treating PHH has been to reduce mortality, shunt dependency, and infection risk. The further mission is to improve neurofunctional prognoses which need further search for a novel treatment for PHH in the future.

## Study limitations

This review includes both DRIFT and NEL as a single treatment group; thus, the treatment's primary goal is similar, to decompress early and clear blood clots of the IVH.

According to the treatment's timing, Leijser and Park had different treatment strategy, but our metadata shows a promising result that the early treatment of the IVH may give benefit the neurofunctional outcome.

## Conclusions

Ventricular lavage may reduce the shunt dependency rate on the PHH in infant patients by mitigating multiloculated hydrocephalus caused by the inflammatory reaction of the IVH. Furthermore, it may decrease the shunt's related infection rate.

The early IVH treatment may benefit the neurocognitive outcome since this treatment aims to eliminate the progressive inflammatory reaction caused by the free iron from the blood clot.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00381-022-05790-3.

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**Author contribution** I.G.M Aswin R. Ranuh contributed to the study's conceptualization, writing, and editing. Muhammad Arifin Parenrengi and Wihasto Suryaningtyas contributed to the conceptualization, reviewing, editing, and finalizing of the manuscript of the study.

**Data availability** Data is openly available in a public repository that issues datasets with DOIs.

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## Declarations

**Ethics approval and consent to participate** Not applicable.

**Consent for publication** Not applicable.

**Conflict of interest** The authors declare no competing interests.

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