Treatment of Posthemorrhagic Ventricular Dilatation

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Contributor: Gengying Liu, Chuan Nie

Volpe IV is defined as intraventricular hemorrhage combined with venous infarction) and probably lead to posthemorrhagic ventricular dilatation (PHVD). Severe IVH and subsequent PHVD have become the leading causes of brain injury and neurodevelopmental dysplasia in preterm infants. Researchers reviewed the literature on the diagnosis and therapeutic strategies for PHVD and provide some recommendations for management to improve the neurological outcomes.

Keywords: preterm infant ; intracerebroventricular hemorrhage ; posthemorrhagic ventricular dilatation

1. Drainage Intervention Fibrinolytic Therapy (DRIFT)

Drainage intervention fibrinolytic therapy (DRIFT) involves inserting a catheter into the ventricle and injecting recombinant tissue plasminogen activator (RT-PA), after which artificial cerebrospinal fluid is used, repeatedly flushing the ventricle until the drainage-recovered fluid is not colored [1]. The purpose of DRIFT is to remove harmful substances such as pro-inflammatory cytokines, free iron, and blood components from the ventricle and reduce secondary damage to brain cells. Whitelaw et al. [2] randomly divided 70 PHVD preterm infants born at gestational ages of 24 to 34 weeks into two groups: one group was treated with DRIFT and the other with standard treatments (lumbar punctures or treatment using a ventricular access device), finding out that there was no statistically significant difference in the VPS rates and mortalities between these two groups. However, compared with the standard treatment group, the rates of severe disability and mortality in the DRIFT group were significantly reduced after two years of follow-up [3]. After ten years of follow-up, the cognitive quotient (CQ) of the DRIFT group was 69.3, which was significantly higher than that of the standard-treatment group (53.7) [4]. This result indicated that DRIFT positively affects long-term cognition, but does not improve motor function. The authors speculated that DRIFT could reduce secondary neurotoxicity and damage to the cerebral cortex but could not promote the regeneration of key motor bundles after severe cerebral hemorrhagic infarction. Park et al. [5] also reported that intraventricular drainage combined with urokinase injections every 3 to 6 h could reduce the VPS rate and improve the neurological prognosis. However, it has been verified that DRIFT can improve the long-term cognitive ability of preterm infants with PHVD, which is beneficial for long-term neurological outcomes, but also can bring infection, secondary bleeding, and rapid fluctuations of intracranial pressure. Whitelaw's above study also found that 35% of infants treated with DRIFT developed a recurrent IVH, which was higher than the 8% in infants managed with standard treatment.

2. Ventricular Access Device (VAD)

When continuous cranial ultrasound monitoring indicates progressive dilation or the ventricle dilation does not stop after two to three lumbar punctures, a VAD is often temporarily placed to drain cerebrospinal fluid [6]. The most common VAD device is the Ommaya reservoir [7]. The Ommaya reservoir is a VAD used for repetitive access to the intrathecal space. It consists of an indwelling ventricular catheter with a collapsible silicone reservoir port. The distal end of the catheter is surgically placed into the ipsilateral anterior horn, with the proximal end connected to the reservoir [8]. Ommaya reservoir insertion can not only reduce the frequency of lumbar punctures, but it can also repeatedly extract cerebrospinal fluid based on intracranial pressure. When there are manifestations of intracranial hypertension such as a bulging fontanel, head circumference growth > 2 cm/week, skull suture separation, feeding difficulty, and apnea, a VAD is the first choice, and the drainage volume can be increased to 15 mL/kg/day [9]. It is noteworthy that a rapid decrease of VI should be avoided to avoid secondary bleeding caused by violent intracranial hemodynamic changes. Peretta et al. [10] investigated 17 preterm infants with PHVD after implanting an Ommaya reservoir and reported that it could reduce VPS's dependence. Lin et al. [11] reported that 3 to 5 weeks after implanting an Omamaya reservoir in 15 infants, the levels of protein, glucose, and red blood cells in their cerebrospinal fluids returned to normal. After a follow-up of 18 to 36 months, one infant required a VPS; one had died, two developed spastic paralyzes of both lower limbs, and another eleven did not have any complications (73%). However, some studies have reported the opposite results. Richard et al. [12] studied 64 infants with PHVD treated with an Ommaya reservoir, and after six months to four years of follow-up, the final VPS rate was 69%. The

incidence of severe sequelae was 39%, suggesting that the Ommaya reservoir does not provide good outcomes with respect to mortality, VPS rate, and neurological function.

3. Ventriculosubgaleal (VSG)

The subgaleal space is the fibroareolar layer of the scalp between the galea aponeurotica and the periosteum of the cranial bones. Due to its elastic and absorptive capabilities, it can be used as a shunt to drain excess cerebrospinal fluid from the ventricles. A VSG consists of a shunt tube with one end in the lateral ventricles and another inserted into the subgaleal space [13]. The placement of the drainage tube is simple, and could even be completed in the neonatal intensive care unit (NICU). Sil et al. [14] found that a VSG could delay or even avoid the placement of a VPS, according to a retrospective study in 2020, effectively reducing the dependence on a permanent shunt. A multi-center study conducted in the United States showed that 31 of 36 (86%) preterm infants treated with a VSG required a VPS, while 61 of 88 (69%) treated with a VAD needed a VPS [15]. The difference was statistically significant, indicating that a VAD's effect is better than that of a VSG. Notably, there was no significant difference in the incidence of infection between these two groups. However, another study indicated that infection and shunt blockage were the most common complications, and *Staphylococcus aureus* and *Staphylococcus epidermidis* were the most common pathogens [13]. Both VAD and VSG are temporary drainage measures for PHVD. Compared with VAD, VSG reduces the daily aspiration of cerebrospinal fluid [16], and cerebrospinal fluid is resorbed through the space under the galea aponeurotica. No additional puncture or aspiration are required, and the time the device can be used is prolonged. The longest time a VSG was used is reported to be 2.5 years [17]. Fountain et al. [18] systematically reviewed the literature on the outcomes of a VAD and VSG and found no statistical differences in infection rates, catheter blockage rates, VPS rates, or mortalities.

In addition to VAD and VSG as temporary interventions, endoscopic third ventriculostomy (ETV) combined with choroids plexus cauterization [19][20], the intraventricular or venous infusion of bone marrow mesenchymal cells [21][22][23], and the iron chelator deferoxamine have been shown to prevent the progression of PHVD [24]; all of these methods require further study before being widely used clinically, however.

4. Ventriculoperitoneal Shunt (VPS)

A VPS device comprises a ventricular catheter connected to a valve and a distal catheter in the peritoneal cavity. It is a cerebral shunt that can transfer excess cerebrospinal fluid from the lateral ventricles into the peritoneum when the normal outflow is blocked or there is a decrease in fluid absorption [25]. A VPS is usually the first choice for the treatment of PHVD and hydrocephalus in adults [26]. However, preterm infants, especially extremely low birth weight infants, are prone to infections due to poor immune function. Furthermore, it is common for mechanical obstructions caused by the inadequate peritoneal development and the insufficient absorption capacity of preterm infants. The protein in cerebrospinal fluid is high in the acute stage [27][28]. In addition, evidence suggests that roughly one-third of newborns experienced spontaneous resolution of ventricular dilatation [29]. For these reasons, it is recommended to postpone VPS in preterm infants [30]. VPS is considered a radical treatment for PHVD. A VPS transfers the excess cerebrospinal fluid from the ventricle to the peritoneal cavity, where it is absorbed. However, there are strict indications for the placement of a VPS. (1) After a lumbar puncture, the implantation of a VAD, or the drainage of cerebrospinal fluid by a VSG, the ventricle still shows a progressive dilation, and after four weeks the continuous drainage of cerebrospinal fluid is required to maintain VI < 97th centile + 4 mm. (2) Weight > 2 kg. (3) Cerebrospinal fluid protein < 1.5 g/L. (4) Red blood cell count of cerebrospinal fluid < 100/mm^3 [31]. Although VPS is an effective treatment, it also increases the risk of infection in preterm infants [32]. A multi-center study performed in the United States and Canada indicated that the infection rates of a VPS placement during the first year ranged from 8% to 10% [33]. Infection and device malfunction are the most critical complications [34][35]. The symptoms of infection included abdominal pain, positive peritoneal irritation sign, and fever. If those who carry the shunt device develop a persistent fever, they are most likely infected. Additionally, using antibiotics alone usually has no impact, necessitating the removal of the implanted shunt device.

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