Effects of Cerebrospinal

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Submission date: 16-Jan-2024 05:49PM (UTC+0800)
Submission ID: 2271811952
File name: Effects_of_Cerebrospinal.pdf (3.31M)
Word count: 5452
Character count: 30973

Pharmacogn J. 2024; 16(1):
A Multifaceted Journal in the field of Natural Products and Pharmacognosy
www.phcogj.com

Original Article

Effects of Cerebrospinal Fluid Drainage on Pro-Inflammatory and Anti-Inflammatory Cytokines Expression in the Subventricular Zone of Kaolin-Induced Hydrocephalic Rats

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ABSTRACT

Background: To determine the neuroprotective effect of CSF drainage by analyzing its impact on the expression and the ratio of pro- and anti-inflammatory cytokines in the subventricular zone in kaolin-induced hydrocephalic rats. **Method:** Sprague-Dawley rats of 23 weeks of age (n=36) were used in this study. The rats were randomly divided into normal control, hydrocephalus, and CSF drainage-treated groups. Hydrocephalus was obtained by injecting 0,05 cc of 20% kaolin suspension into the cisterna magna. The CSF drainage-treated group had ventricular tapping seven days after kaolin induction. The rats were sacrificed 7, 14, or 21 days after kaolin induction. The brain was removed and prepared for immunohistochemistry analysis to detect IL-1 β, IL-6, TNF-α, and IL-10 cytokines expression. **Results:** Immunohistochemistry analysis revealed that the expression of pro-inflammatory cytokines was significantly increased in hydrocephalus groups than in the control group. In contrast, the expression of anti-inflammatory cytokine was significantly decreased. CSF drainage had a neuroprotective effect by reducing pro-inflammatory cytokine expression and increasing anti-inflammatory cytokine expression. In the hydrocephalus group, the ratios of IL-1 β/IL-10, IL-6/IL-10, and TNF-α/IL-10 increased toward a pro-inflammatory status. After CSF drainage, the ratios of IL-1 β/IL-10, IL-6/IL-10, and TNF-α/IL-10 shifted toward an anti-inflammatory status. **Conclusion:** CSF drainage protects the brain from excessive neuroinflammatory processes in kaolin-induced hydrocephalic rats. Additional investigation is warranted to ascertain the use of inflammatory cytokines expression as a valuable biomarker for hydrocephalus. Furthermore, research on anti-inflammatory drug administration in clinical settings is required.

Keywords: Kaolin-induced hydrocephalus, neuroinflammation, cytokines, subventricular zone, cerebrospinal fluid drainage, neuroprotective.

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History

- Submission Date: 16-10-2023;
- Review completed: 09-12-2023;
- Accepted Date: 02-01-2024.

DOI : 10.5530/pj.2024.16.

Article Available online

http://www.phcogj.com/v16/i1

INTRODUCTION

Hydrocephalus, a complex condition characterized by dilatation of the ventricular system, can cause brain injury via mechanical and biochemical mechanisms. Damage mainly occurs in the subventricular zone.[1-2] This area is a significant region on the outer wall of the lateral ventricles because it contains neural stem/progenitor cells, which play a crucial role in neurogenesis.[3-4] Due to the proximity of this area to the lateral ventricles, ventriculomegaly directly impacts healthy neurological development.

Damage to the ependymal lining of the ventricular wall, compression of small vessels and damage to axons in the periventricular white matter area, proliferation/activation of astrocytes and microglial cells, and disruption of neuronal connections are signs of mechanical injury caused by hydrocephalus.[5] Cerebral blood flow disruption of periventricular white matter induces cellular change, hypoxic-ischemic cascade, and neuroinflammatory response.[6]

Neuroinflammation in the central nervous system (CNS) is the body's response to pathological conditions, including chemical, physical, and biological factors.[7] This damage activates astrocytes and microglia. Activated microglia release numerous oxidants and activate multiple genes and proteins, including pro-inflammatory cytokines (e.g., interleukin 1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin 6).[8] This pro-inflammatory response will have a protective effect during the acute phase. However, if this pro-inflammatory response is sustained, it will have a neurotoxic effect that causes neuronal dysfunction and cell death.[9] Therefore, the body develops anti-inflammatory response systems (e.g., interleukin 10 cytokine) to suppress the inflammatory process. The body must balance pro- and anti-inflammatory responses to reach the resolution phase, characterized by tissue repair and homeostasis.[10]

The standard treatment for hydrocephalus is the placement of a ventriculoperitoneal shunt (VP shunt) or endoscopic third ventriculostomy (ETV) to divert CSF. To determine the neuroprotective effect of CSF drainage on hydrocephalus, we examined whether CSF drainage can decrease the expression of pro-inflammatory cytokines and increase the expression of anti-inflammatory cytokines in the subventricular zone of hydrocephalic rats. Additionally, the ratio of pro-inflammatory to anti-inflammatory cytokines was investigated.

Cite this article: Parenrengi MA, Dariansyah AD, Suryaningtyas W, Fauziah D, Sudiana IK, Utomo B, Gunawn PI. Effects of Cerebrospinal Fluid Drainage on Pro-Inflammatory and Anti-Inflammatory Cytokines Expression in the Subventricular Zone of Kaolin-Induced Hydrocephalic Rats. Pharmacogn J. 2024;16(1):.

MATERIAL AND METHODS

Animal

Sprague-Dawley rats of 23 weeks of age (n=36) were used in this study. The rats were obtained from the Experimental Laboratory of Universitas Gajah Mada, Yogyakarta. The rats were randomly divided into normal control, hydrocephalus (H-7, H-14, and H-21), and CSF drainage-treated groups (D-14 and D-21), with the number of replications for each group being 6 mice. The rats were placed in individual cages, provided adequate food and water, and received 12 hours of light and dark cycles.

The rats in the hydrocephalus groups were sacrificed on the 7th, 14th, and 21st days, while the rats in CSF drainage-treated groups were sacrificed on the 14th and 21st days after kaolin induction. The Institutional Animal Care and Use Committee of the Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, approved this experiment's protocol (No. 2.KE.062.06.2020).

Hydrocephalus induction and CSF drainage procedure

The hydrocephalus model was obtained by injecting kaolin suspension into the cisterna magna. The procedure was performed under anesthesia. The anesthesia used in this experiment is a mixture of 2 cc of Ketamine, 1,25 cc of Xylazine, 0,33 cc of Acepromazine, and 6,41 cc of normal saline, with a dosage of 0,3 cc multiplied by the gram of body weight and divided by 100. The rats were placed on a soft sponge mattress in a prone position. The neck was flexed at the end of the sponge pad to open the foramen magnum. The neck area of the rat was shaved and cleaned with 70% ethanol and 10% povidone-iodine. A 0,05 cc of 20% kaolin suspension was injected slowly through the foramen magnum. The rats were attentively monitored until they recovered from the effects of the anesthetic. Hydrocephalus was estimated to occur seven days after kaolin induction. The rats were examined for clinical signs of hydrocephalus, such as changes in eating behavior, enlarged head circumferences, bumping of the neck, gait changes, and hind limb weakness.

CSF drainage was performed on the 7th day after kaolin induction. CSF drainage is performed according to the methodology established by previous research. The rats were under anesthesia. The cranial region of the rat was shaved and sterilized. CSF drainage was performed by tapping through the lateral ventricle of the rats. The anatomical landmark in our study is located 1 cm anterior and 1 cm lateral to the bregma, with a depth of approximately 1.5 cm perpendicular to the bone.[11]

Euthanasia of the Rats

The rats were euthanized with the decapitation method to preserve the brain tissue. Several efforts have been made to prevent stress before decapitation. For example, the rat was moved individually from its cage to the decapitation area, anesthesia was performed before the decapitation, and the procedure was performed rapidly with a sharp blade to reduce the suffering. After each decapitation procedure, the blade was cleaned and sterilized.

Immunohistochemistry staining and cytokines evaluation

The harvested rat brain was fixed for 48 hours at room temperature in 4% paraformaldehyde. The rat brain was processed into a paraffin block and sliced into 5-µm sections. Paraffin sections were stained with monoclonal antibodies (Santa Cruz Biotechnology, USA) for immunohistochemistry (IHC) to detect individual cytokine expression. The dilution for cytokines IL-1β (sc-12742), IL-6 (sc-32296), TNF-α (sc-8436), and IL-10 (sc-365858) was 1:100. Cells with a brownish color showed positive expression of each cytokine. The expression of cytokines was determined quantitatively by calculating the mean positive expression of 20 fields of view in the subventricular zone using a microscope with a magnification of 1000x.[12] The ratios were calculated by dividing the absolute expression of pro-inflammatory cytokines by the expression of anti-inflammatory cytokine.[13]

Statistical analysis

The analysis of the data was presented as mean±S.D. The Shapiro-Wilk test was used to analyze data for normality. Statistical analysis for group comparison was performed using ANOVA for normally distributed data. For distributions that are not normal, the Kruskal-Wallis test is applied. To find any significant differences between the groups, a post-hoc test was conducted. Statistical significance was considered for a P value of 0.05 or less with 95% CI. The data analysis was conducted using SPSS statistical software version 25 (IBM Corp., Armonk, NY, USA).

RESULTS

Effect of CSF drainage on IL-1β cytokine expression

Immunohistochemical studies to examine the expression of cytokines IL-1β, IL-6, and TNF-α in the subventricular zone are illustrated in Figure 1. Table 1 displays the absolute cytokine expressions in the subventricular zone.

The expression of IL-1β cytokine (Figure 2) was significantly higher (p<0,05) in all hydrocephalus groups than in the normal group (3.16±0.75). IL-1β cytokine expressions increased in the hydrocephalus group from day 7 (6.50±1.37) to day 21 (6.66±1.63). On the seventh day after CSF drainage, the IL-1β cytokine expression in the CSF drainage-treated group was still significantly higher (p=0,030) than in the normal group (5.00±0.89). On the fourteenth day following CSF drainage, the IL-1β cytokine expression decreased (3.00±0.63).

Effect of CSF drainage on IL-6 cytokine expression

The expression of IL-6 cytokine (Figure 3) was significantly higher (p<0,001) in the hydrocephalus group on days 14 and 21 than in the normal group (4.50±1.37). IL-6 cytokine expression increased in the hydrocephalus group from day 7 (6.16±0.75) to day 21 (11.16±1.47). On the seventh day after CSF drainage, IL-6 cytokine expression was significantly higher (p=0,002) in the CSF drainage-treated group than in the normal group (7.50±1.04). On the fourteenth day following CSF drainage, the IL-6 cytokine expression decreased (2.83±0.75).

Effect of CSF drainage on TNF-α cytokine expression

The expression of TNF-α cytokine (Figure 4) in the hydrocephalus group on days 14 and 21 was significantly higher (p<0,001) than in the normal group (3.33±1.21). In the hydrocephalus group, TNF-α cytokine expressions increased from day 7 (6.33±2.80) to day 21 (10.50±1.87). On the seventh day after CSF drainage, TNF-α cytokine expression was higher in the CSF drainage-treated group than in the normal group (4.33±1.03). On the fourteenth day following CSF drainage, the TNF-α cytokine expression was decreased (1.66±0.81).

Effect of CSF drainage on IL-10 cytokine expression

To investigate the effect of CSF drainage on tissue repair and homeostasis, immunohistochemical analysis of IL-10 cytokine expression was performed (Figure 1).

The expression of IL-10 cytokine (Figure 5) in the hydrocephalus group on days 14 and 21 was significantly lower (p<0,05) than in the normal group (4.83±1.47). The IL-10 cytokine expression in the hydrocephalus group decreased from day 7 (3.50±1.04) to day 21 (1.66±0.81). On the seventh day (8.66±1.86) and the fourteenth day (10.83±1.47), IL-10 cytokine expression was significantly higher (p<0,001) in the CSF

drainage-treated group than in the normal group. The expression of anti-inflammatory cytokines (IL-10) demonstrates that CSF drainage can have a neuroprotective effect by enhancing the anti-inflammatory response.

The ratio of pro-inflammatory to anti-inflammatory cytokines

The ratio of pro- to anti-inflammatory cytokines is presented in Table 2. The IL-1β/IL-10 ratios were significantly higher ($p<0.05$) in all hydrocephalus groups than in the normal group (0.69±0.20). On the fourteenth day following CSF drainage, the ratio of IL-1β to IL-10 was significantly lower ($p<0.05$) in the CSF drainage-treated group (0.28±0.06) than in the normal group. The ratio of IL-6/IL-10 was significantly higher ($p<0.05$) in the hydrocephalus group on days 14 and 21 compared to the normal group (1.03±0.54). In the CSF drainage-treated group, the ratio of IL-6 to IL-10 was lower than in the normal group. The TNF-α/IL-10 ratios were significantly higher ($p<0.05$) in the hydrocephalus group on day 14 compared to the normal group (0.75±0.37). The ratio of TNF-α to IL-10 was lower in the group treated with CSF drainage than in the normal group.

Table 1. Absolute cytokines expressions in the subventricular zone (mean±S.D).

Cytokines	Groups						p Value
	N	H7	H14	H21	D14	D21	
IL-1β	3.16±0.75	6.50±1.37*	8.50±1.51*	6.66±1.63*	5.00±0.89*	3.00±0.63	<0.001
IL-6	4.50±1.37	6.16±0.75	9.50±1.51*	11.16±1.47*	7.50±1.04*	2.83±0.75	<0.001
TNF-α	3.33±1.21	6.33±2.80	7.33±1.03*	10.50±1.87*	4.33±1.03	1.66±0.81	<0.001
IL-10	4.83±1.47	3.50±1.04	1.83±0.75*	1.66±0.81*	8.66±1.86*	10.83±1.47*	<0.001

IL interleukin, *TNF* Tumor Necrosis Factor, *N* normal control, *H7* hydrocephalus day 7, *H14* hydrocephalus day 14, *H21* hydrocephalus day 21, *D14* CSF drainage day 14, *D21* CSF drainage day 21
*p<0.05, significantly different from the normal control group by ANOVA, followed by post hoc analysis

Table 2. Ratios of pro-inflammatory and anti-inflammatory cytokines (mean±S.D).

Ratios	Groups						p Value
	N	H7	H14	H21	D14	D21	
IL-1β/IL-10	0.69±0.20	2.04±0.99*	5.50±3.03*	4.83±2.38*	0.60±0.21	0.28±0.06*	<0.001
IL-6/IL-10	1.03±0.54	1.90±0.65	6.00±2.77*	8.00±3.57*	0.89±0.18	0.26±0.06	<0.001
TNF-α/IL-10	0.75±0.37	1.93±1.02	4.52±1.66*	7.80±4.14	0.52±0.16	0.15±0.08	0.001

IL interleukin, *TNF* Tumor Necrosis Factor, *N* normal control, *H7* hydrocephalus day 7, *H14* hydrocephalus day 14, *H21* hydrocephalus day 21, *D14* CSF drainage day 14, *D21* CSF drainage day 21
*p<0.05, significantly different from the normal control group by ANOVA or Kruskal-Wallis, followed by post hoc analysis

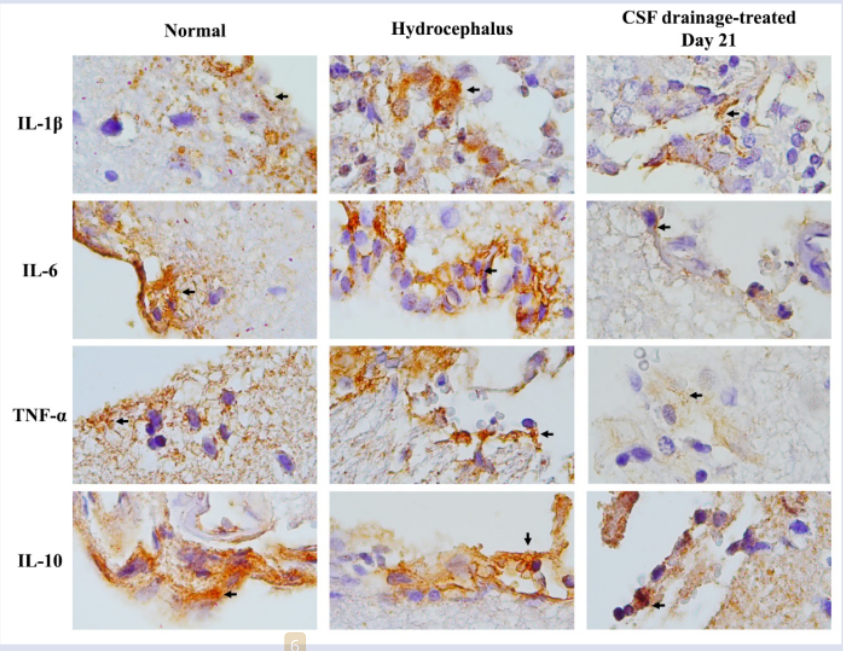

Figure 1. The representative images of IL-1β, IL-6, TNF-α, and IL-10 cytokines expression in subventricular zone.

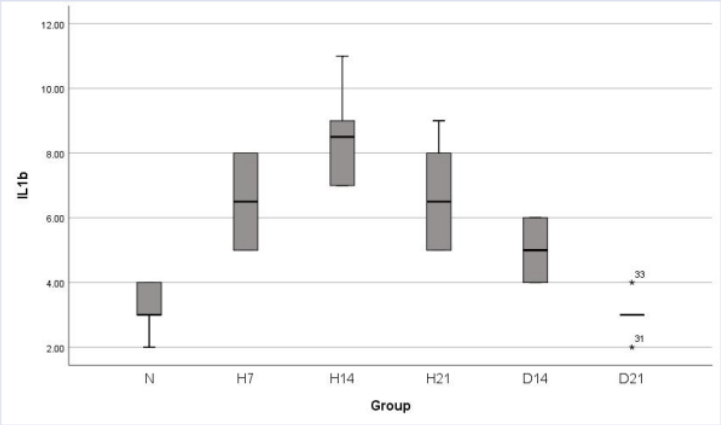

Figure 2. The expressions of IL-1β cytokine in the subventricular zone *IL-1β* interleukin IL-1β, *N* normal control, *H7* hydrocephalus day 7, *H14* hydrocephalus day 14, *H21* hydrocephalus day 21, *D14* CSF drainage day 14, *D21* CSF drainage day 21.

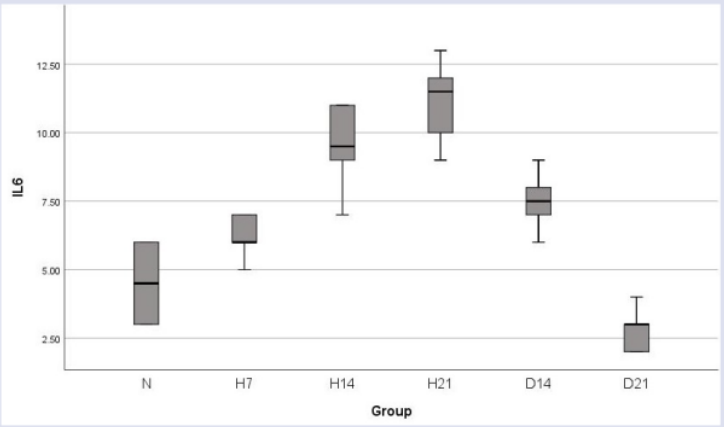

Figure 3. The expressions of IL-6 cytokine in the subventricular zone *IL-6* interleukin IL-6, *N* normal control, *H7* hydrocephalus day 7, *H14* hydrocephalus day 14, *H21* hydrocephalus day 21, *D14* CSF drainage day 14, *D21* CSF drainage day 21.

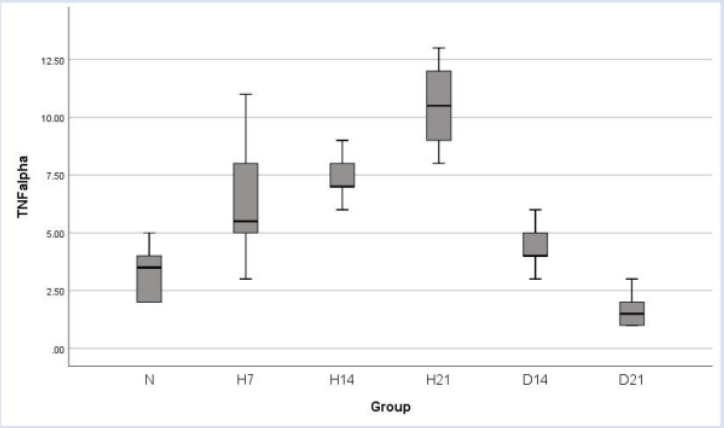

Figure 4. The expressions of TNF-α cytokine in the subventricular zone *TNF* Tumor Necrosis Factor, *N* normal control, *H7* hydrocephalus day 7, *H14* hydrocephalus day 14, *H21* hydrocephalus day 21, *D14* CSF drainage day 14, *D21* CSF drainage day 21.

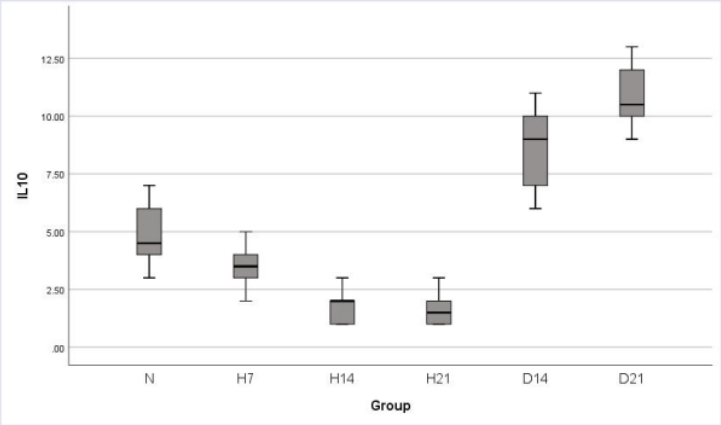

Figure 5. The expressions of IL-10 cytokine in the subventricular zone *IL-10* interleukin IL-10, *N* normal control, *H7* hydrocephalus day 7, *H14* hydrocephalus day 14, *H21* hydrocephalus day 21, *D14* CSF drainage day 14, *D21* CSF drainage day 21.

DISCUSSION

The animal model of hydrocephalus could be developed in a variety of ways. Injection of kaolin into the cisterna magna could obstruct the CSF pathway and mimic hydrocephalus after meningitis. This method has several advantages, including its simplicity, low cost, titratability, replicability in any animal and age, and high success rate with variable mortality rates (20 - 80%).[2,14] In our study, the mortality rate was 30%. Older age in rats is hypothesized to be associated with a decreased mortality rate.

The relationship between cytokines and hydrocephalus has been investigated, with most research focusing on idiopathic normal pressure hydrocephalus (iNPH) and post-hemorrhagic hydrocephalus using CSF or blood plasma samples. According to the researchers' knowledge, no studies have examined the expression and ratio of cytokines in cells in the subventricular zone. The subventricular zone is our primary focus because this region is crucial to the neurogenesis process due to the presence of numerous neural stem cells, which are vital in cases of pediatric hydrocephalus. Damage to this region can result in cortical developmental disorders. A range of disorders encompassing lissencephaly, cortical ectopia with epilepsy, psychiatric and cognitive disorders, motor deficits, and cortical vision loss can be observed. Mild damage to the subventricular zone may not be clinically detectable, but a decrease in stem cell count may impede future cell repair.[4,15] Previous studies also stated that the proliferation activity in the subventricular zone, as shown by Ki-67 expression, was significantly reduced in hydrocephalus rats.[2]

This study examined the absolute expression and ratios of pro- to anti-inflammatory cytokines in the subventricular zone of hydrocephalic rats with or without CSF drainage. In our research, hydrocephalus was associated with increased pro-inflammatory cytokine expression and decreased anti-inflammatory cytokine expression. Hydrocephalus is also associated with an imbalance ratio of pro- to anti-inflammatory cytokines in favor of pro-inflammatory. Our study showed that CSF drainage could reduce the expression of pro-inflammatory cytokines and increase the expression of anti-inflammatory cytokines.

Our study revealed a significant increase in IL-β cytokine expression in the hydrocephalus group 7-, 14-, and 21 days following kaolin induction. In other studies, expression of IL-β cytokines is increased in preterm neonates with post-hemorrhagic hydrocephalus and ventriculitis cases.[16-17] According to our study, the expression of IL-β cytokines decreased significantly after CSF drainage. These results are comparable to those of a previous study demonstrating a decrease in IL-β cytokines following CSF drainage.[18]

The expression of IL-6 cytokine increases significantly on days 14 and 21 in the hydrocephalus group and decreases following CSF drainage. Previous research has demonstrated increased IL-6 cytokine expression in patients with normal-pressure hydrocephalus.[19] Sosvorova *et al.* (2015) reported decreased IL-6 cytokine expression in patients with normal-pressure hydrocephalus.[17]

The expression of TNF-α cytokine increases significantly on days 14 and 21 in the hydrocephalus group and decreases after CSF drainage. This result is comparable to a previous study that found elevated TNF-α cytokine expression in normal pressure hydrocephalus cases and congenital hydrocephalus in the hyh mouse.[21-22] Overall, there was an observed elevation in the expression of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) within the hydrocephalus group. The decrease in levels of pro-inflammatory cytokines suggests that CSF drainage may possess a neuroprotective impact by attenuating the neuroinflammatory reaction.

Our study showed that after 14 and 21 days of kaolin induction, IL-10 cytokine expression in the hydrocephalus group decreased significantly. In the CSF drainage-treated group, IL-10 cytokine expression increases significantly on 14- and 21 days following kaolin induction. The increase of IL-10 cytokine expression in the drainage group suggests a prompt amelioration in hydrocephalus rats following the drainage procedure. Previous research on IL-10 cytokine has yielded diverse results. Czubowicz *et al.* (2017) reported no disparities in IL-10 cytokine levels between normal pressure hydrocephalus and the control group.[16] In preterm infants with post-hemorrhagic hydrocephalus, Habiyaremye *et al.* (2017) reported that the level of IL-10 cytokine is elevated.[20]

The primary function of pro-inflammatory cytokines is to initiate an immune response to pathological conditions. Nevertheless, excessive production of pro-inflammatory cytokines can be neurotoxic. The function of anti-inflammatory cytokines downregulates an exaggerated inflammatory response and leads to the resolution phase, characterized by homeostasis and tissue repair. However, excessive expression of anti-inflammatory cytokines can suppress immune function.[23] Appropriate immune response requires a balanced ratio of pro- and

anti-inflammatory cytokines; excessive or insufficient inflammation can result in complications.[15]

To the best of the author's knowledge, there has never been a study that discusses the ratio of pro- and anti-inflammatory cytokines in cases of hydrocephalus, particularly in kaolin-induced hydrocephalus, which is similar to post-meningitis hydrocephalus.

In other diseases, the ratio between pro- and anti-inflammatory cytokines is estimated to be more significant than the absolute value of individual cytokines.[13,23-26] In the hydrocephalus group on days 7, 14, and 21, our study revealed a significant imbalance in the IL-1β/IL-10 ratio, favoring the pro-inflammatory cytokine. In the hydrocephalus groups, the ratios of IL-6/IL-10 and TNF-α/IL-10 also shifted in favor of a pro-inflammatory status. Following CSF drainage, the ratios of IL-1β/IL-10, IL-6/IL-10, and TNF-/IL-10 favored an anti-inflammatory status.

There are several limitations to this study. First, the mediators, cytokines, neurotrophic factors, and other immune pathways that may have been involved were not investigated. Second, a radiographic evaluation of the severity of hydrocephalus was not performed. Furthermore, an assessment of behavioral study or the Neurologic Deficit Score (NDS) was not conducted. Lastly, this study did not compare cytokine levels in serum and CSF. Further research can be conducted on other cytokines, neuroinflammatory processes, and anti-inflammatory drug usage in hydrocephalus cases.[27] Therefore, in cases of hydrocephalus where shunt surgery cannot be directly performed, anti-inflammatory medications may be administered to suppress the inflammatory response temporarily. It is important to acknowledge that the expression of inflammatory cytokines is not solely depend upon the CSF drainage procedure. Numerous additional factors exert influence and are not considered variables within this study's scope, including animal stress, post-operative care, the placement of the ventricular catheter, and various other aspects.

CONCLUSION

In cases of hydrocephalus, CSF drainage protects the brain from excessive neuroinflammatory processes. CSF drainage decreases pro-inflammatory cytokine expression and increases anti-inflammatory cytokine expression in the subventricular zone. In addition, CSF drainage can alter the pro- to anti-inflammatory cytokines ratio in favor of anti-inflammatory status. Additional research is required to make inflammatory cytokines expression a valuable biomarker for hydrocephalus, and this research can serve as a foundation for future research on the administration of anti-inflammatory medications in hydrocephalus cases.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest: There is no conflict of interest.

Ethical approval: All animal procedures in this study were performed according to the guidelines of The Institutional Animal Care and Use Committee of the Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, where the research was conducted (No. 2.KE.062.06.2020).

Acknowledgment: The authors would like to thank all the staff of the Department of Neurosurgery, Faculty of Medicine, Universitas Airlangga.

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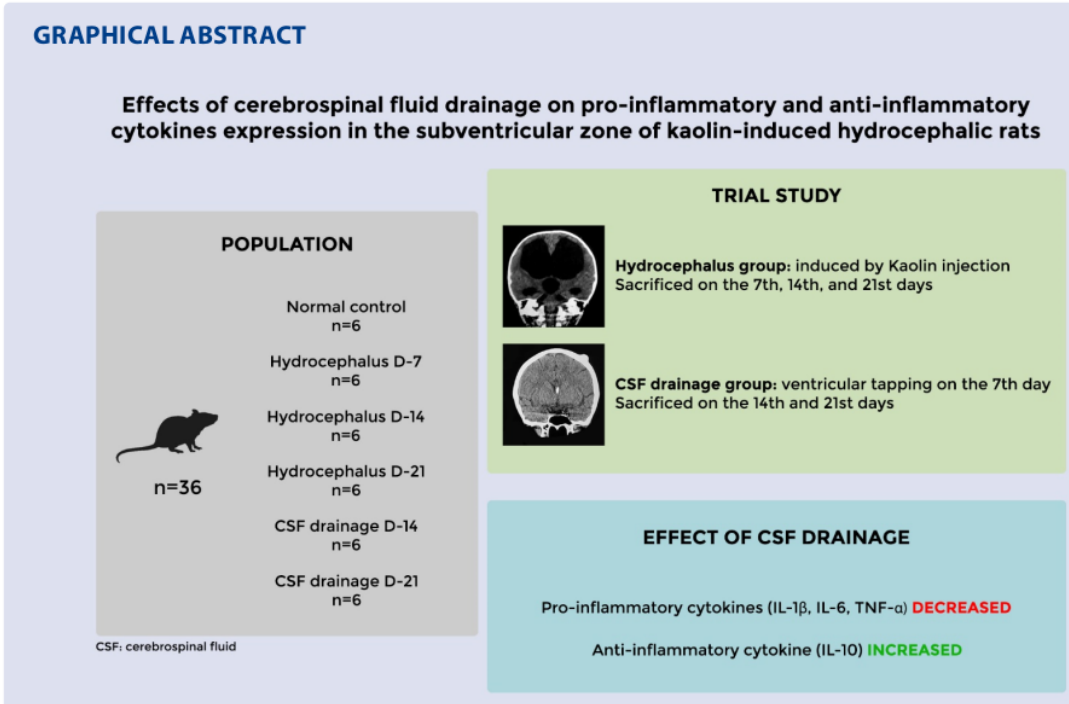

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Cite this article: Parenrengi MA, Dariansyah AD, Suryaningtyas W, Fauziah D, Sudiana IK, Utomo B, Gunawn PI. Effects of Cerebrospinal Fluid Drainage on Pro-Inflammatory and Anti-Inflammatory Cytokines Expression in the Subventricular Zone of Kaolin-Induced Hydrocephalic Rats. Pharmacogn J. 2024;16(1):.

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