

DAFTAR PUSTAKA

1. Winkler EA. et al. Cerebral Edema in Traumatic brain injury. *Neurosurgery Clinics of North America*. Elsevier Inc 2016; 27(4): pp. 473–88. doi: 10.1016/j.nec.2016.05.008
2. Vos PE. Arrastia RD. *Traumatic brain injury*. 1st ed. Oxford: Wiley Blackwell; 2015. pp. 3.
3. Khan A, Prince M, Brayne C, Prina AM. Lifetime prevalence and factors associated with head injury among older people in low and middle income countries: a 10/66 study. *PLoS One* 10 2015: e0132229.
4. Sekeon SAS, Maja PS, Kembuan M. Executive function disorder in acute traumatic brain injuryin Manado, Indonesia. *Global Journal of Medicine and Public Health* 2015; 4(2). ISSN 2277-9604
5. Zeng J. et al. Emodin attenuates brain edema after traumatic brain injuryin rats, 2017;10(11):15213–20.
6. Michinaga S. and Koyama Y. Pathogenesis of brain edema and investigation into anti- dema drugs, *International Journal of Molecular Sciences* 2015;16(5): 9949–75. doi: 10.3390/ijms16059949.
7. Donkin JJ. and Vink R. Mechanisms of cerebral edema in traumatic brain injury: Therapeutic developments, *Current Opinion in Neurology* 2010; 23(3): 293–9. doi: 10.1097/WCO.0b013e328337f451.
8. Alluri H, Wilson RL, Anasooya Shaji C, Wiggins-Dohlvik K, Patel S, Liu Y, Peng X, Beeram MR, Davis ML, Huang JH and Tharakan B. Melatonin preserves

blood-brain barrier integrity and permeability via matrix metalloproteinase-9 inhibition. PLoS One 2016; 11: e01544

9. Robinson BD, Lomas A, Shaji CA, Isbell CL, Tharakan B. Doxycycline blocks matrixmetalloproteinase-9 and attenuates blood-brain barrier dysfunction and hyperpermeability after traumatic brain injury. The FASEB Journal 2017; 31(1).
10. Weinstein E. Clinical review doxycycline hyclate tablets. Center for drug evaluation and research. 2013: pp. 6.
11. Caprio RD, Lembo S, Costanzo LD, Balato A, Monfrecola G. Anti-inflammatory properties of low and high doxycycline doses: An in vitro study. Hindawi Publishing Corporation 2015: 1-2.
12. Nascimento GC, Rizzi E, Gerlach RF, Leite-Panissi CR. Expression of MMP-2 and MMP-9 in the rat trigeminal ganglion during the development of temporomandibular joint inflammation. Braz J Med Biol Res 2013; 46: 956-67.
13. Shen LC, Chen YK, Lin LM, Shaw SY. Anti-invasion and antitumor growth effect of doxycycline treatment for human oral squamous-cell carcinoma-in vitro and in vivo studies. Oral Oncol 2010; 46: 178-84.
14. Saekhu M, et al. MMP-9, Brain edema, and length of hospital stay of patients with spontaneous supratentorial intracerebral hemorrhage after hematoma evacuation along with the administration of tigecycline. Med J Indones, December 2016; 25(4): 221-6. eISSN: 2252-8083
15. Jia F, Pan Y, Mao Q, Liang Y, Jiang J. Matrix metalloproteinase-9 expression and protein levels after fluid percussion injury in rats: the effect of injury severity

and brain temperature. *Journal of Neurotrauma*. June 2010. 27:1059–68. DOI: 10.1089=neu.2009.1067

16. Hayashia T. Quantitative analyses of matrix metalloproteinase activity after traumatic brain injury in adult rats. *Elsevier Brain research*. 2009:172-7. doi:10.1016/j.brainres.2009.05.040
17. Haddas O, et al. Selective inhibition of matrix metalloproteinase-9 attenuates secondary damage resulting from severe traumatic brain injury. *PLoS ONE* 8(10): e76904. doi:10.1371/journal.pone.0076904
18. Prasetyo E, Islam AA, Hatta M, Widodo D, Pattelongi I. The Profile of MMP-9, MMP-9 mRNA Expression, -1562 C/T polymorphism and outcome in high-risk traumatic brain injury: the effect of therapeutic mild hypothermia. *Neurologia medico-chirurgica Advance*. October 2017. doi: 10.2176/nmc.oa.2016-0322
19. Chanhung ZL, Xiu B, Hashimoto T, McCulloch CE, Yang GY, Young W. Doxycycline suppresses cerebral matrix metalloproteinase-9 and angiogenesis induced by focal hyperstimulation of vascular endothelial growth factor in a mouse model. *American Heart Association, Inc. Stroke* 2004; 35(7):1715-9.
20. Moore AJ. Management of severe head injury. In: Newell DW, editor. *Neurosurgery*. London: Springer-Verlag; 2005. pp. 369-71. ISBN 1-85233-522-X
21. Webster KM. et al. Inflammation in epileptogenesis after traumatic brain injury. *Journal of Neuroinflammation* 2017; 14(1): pp. 1–17. doi: 10.1186/s12974-016-0786-1.

22. Zollman, Felise S. Manual of traumatic brain injury: assessment and management. 2nd ed. New York, NY : Demos Medical Publishing; 2016. pp. 369-71. ISBN 9781620700938
23. McBride DW. et al. Reduction of cerebral edema after traumatic brain injury using an osmotic transport device. *Journal of Neurotrauma* 2014; 31(23): 1948–54. doi: 10.1089/neu.2014.3439.
24. Bosoi CR, Rose CF. Brain edema in acute liver failure and chronic liver disease: Similarities and differences. *Neurochem. Int* 2013; 62: 446–57.
25. Wright G, Sharifi Y, Jover-Cobos, M, Jalan, R. The brain in acute on chronic liver failure. *Metab. Brain Dis* 2014; 4: 965–73.
26. Kahle KT, Simard JM, Staley KJ, Nahed BV, Jones PS, Sun D. Molecular mechanisms of ischemic cerebral edema: Role of electroneutral ion transport. *Physiology (Bethesda)* 2009; 24: 257–65.
27. Rabinstein AA. Treatment of brain edema in acute liver failure. *Curr. Treat. Opt. Neurol* 2010; 2: 129–41.
28. Weiss N, Miller F, Cazaubon S, Couraud PO. The blood-brain barrier in brain homeostasis and neurological diseases. *Biochim. Biophys. Acta* 2009; 4: 842–57.
29. Argaw AT, Gurfein BT, Zhang Y, Zameer A, John GR. VEGF-mediated disruption of endothelial CLN-5 promotes blood-brain barrier breakdown. *Proc. Natl. Acad. Sci. USA* 2009; 6: 977–82.
30. Jha, RM., Kochanek, PM., Simard, JM,. Pathophysiology and treatment of cerebral edema in traumatic brain injury. *Neuropharmacology* 2019; 145: 230–46

31. Aliah A, Widjaja D. Edema Cerebri, pendekatan patogenetik dan terapeutik. Makassar: Laboratorium Saraf FK UH 2006:1-19
32. Grossetete M. et al. 'Elevation of matrix metalloproteinases 3 and 9 in cerebrospinal fluid and blood in patients with severe traumatic brain injury', *Neurosurgery* 2009; 65(4): 702-8. doi: 10.1227/01.neu.0000351768.11363.48.
33. Falo MC, Fillmore HL, Reeves TM, Phillips LL. Matrix metalloproteinase-3 expression profile differentiates adaptive and maladaptive synaptic plasticity induced by traumatic brain injury *J. Neurosci. Res* 2006; 84: 768–81.
34. Gidday JM. et al. Leukocyte-derived matrix metalloproteinase-9 mediates blood-brain barrier breakdown and is proinflammatory after transient focal cerebral ischemia. *American Journal of Physiology-Heart and Circulatory Physiology* 2005; 289(2): H558–68. doi: 10.1152/ajpheart.01275.2004.
35. Vajtr D. et al. Correlation of ultrastructural changes of endothelial cells and astrocytes occurring during blood brain barrier damage after TBI with biochemical markers of blood brain barrier leakage and inflammatory response. *Physiological Research* 2009; 58(2): pp. 263–8.
36. Yong VW. Metalloproteinases: mediators of pathology and regeneration in the CNS. *Nat Rev Neurosci* 2005; 6:931–44.
37. Wang L, Zhang ZG, Zhang RL, Gregg SR, Hozeska-Solgot A, LeTourneau Y, Wang Y, Chopp M. Matrix metalloproteinase 2 (MMP2) and MMP9 secreted by erythropoietin-activated endothelial cells promote neural progenitor cell migration. *J Neurosci* 2009; 26:5996–6003.

38. Cunningham LA, Wetzel M, Rosenberg GA. Multiple roles for MMPs and TIMPs in cerebral ischemia. *Glia* 2005; 50:329–39.
39. Liu KJ, Rosenberg GA. Matrix metalloproteinases and free radicals in cerebral ischemia. *Free Radic Biol Med* 2005; 39: 71–80.
40. Rosenberg GA. Matrix metalloproteinases in neuroinflammation. *Glia* 2002; 39: 279–91.
41. Yang Y, Estrada EY, Thompson JF, Liu W, Rosenberg GA. Matrix metalloproteinase-mediated disruption of tight junction proteins in cerebral vessels is reversed by synthetic matrix metalloproteinase inhibitor in focal ischemia in rat. *J Cereb Blood Flow Metab* 2007; 27:697–709.
42. Rosenberg GA, Taheri S, Jalil EC. Brain Edema in Neurological Diseases; Neurochemical Mechanisms in Disease, Neurobiology. London. Springer Science Business Media. 2011: pp.125-56. doi: 10.1007/978-1-4419-7104-3.
43. Yang Z, Fan R, Sun P, Cui H, Peng W. Rhubarb attenuates cerebral edema via inhibition of the extracellular signal-regulated kinase pathway following traumatic brain injury in rats. *Phcog Mag* 2018;14:134-9.
44. Ding JY, Kreipke CW, Schafer P, Schafer S, Speirs SL Synapse Loss Regulated by Matrix Metalloproteinases in Traumatic brain injury Is Associated with Hypoxia-Inducible Factor-1 α Expression. *Brain Res* 2009; May 1; 1268: 125–34.
45. Holmes NE, Charles PGP. Safety and efficacy review of doxycycline. *Clinical Medicine: Therapeutics* 2009; 1: pp. 472-74

46. Chopra I, Roberts M. Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. *Microbiol Mol Biol Rev* 2001; 65: 232–60.
47. Pasquale TR, Tan JS. Nonantimicrobial effects of antibacterial agents. *Clin Infect Dis* 2005; 40:127–35
48. Welling PG, Koch PA, Lau CC, Craig WA. Bioavailability of tetracycline and doxycycline in fasted and nonfasted subjects. *Antimicrob Agents Chemother* 1977; 11: 462–9.
49. Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylicyclines. *J Antimicrob Chemother* 2006; 58:256–65.
50. Alestig K. Studies on the intestinal excretion of doxycycline. *Scand J Infect Dis* 1974; 6:265–71.
51. Sloan B, Scheinfeld N. The use and safety of doxycycline hyclate and other second-generation tetracyclines. *Expert Opin Drug Saf* 2008; 7: 571–7.
52. Roeland RH, Lent NV, Sorsa T, Salo T, Yrjö Lindeman J. Inhibition of matrix metalloproteinases (MMPs) by tetracyclines. *Tetracyclines in Biology, Chemistry and Medicine*. 2001. London: Springer. pp 267-81
53. Michael W. Manning, Lisa A. Cassis, Alan Daugherty. Differential effects of doxycycline, a broad-spectrum matrix metalloproteinase inhibitor, on angiotensin ii-induced atherosclerosis and abdominal aortic aneurysms. *Arterioscler Thromb Vasc Biol* 2003: 483-8.

54. Danielle, et al. Doxycycline dose-dependently inhibits mmp-2-mediated vascular changes in 2k1c hypertension. *Basic & Clinical Pharmacology & Toxicology* 2010; 108: 318–25.
55. Damian N. et al. Doxycycline reduces mortality and injury to the brain and cochlea in experimental pneumococcal meningitis. *Infection and Immunity* 2006; 74(7): 3890–6
56. Pyo R, et al. Targeted gene disruption of matrix metalloproteinase-9 (gelatinase B) suppresses development of experimental abdominal aortic aneurysms. *J Clin Invest.* 2000;105: 1641–9.
57. Zhang C, Gong W, Ge S. Inhibition of matrix metalloproteinase-9 with low-dose doxycycline reduces acute lung injury induced by cardiopulmonary bypass *Int J Clin Exp Med.* 2014; 7(12): 4975–82.
58. Leung LY, et al. Blast related neurotrauma: a review of cellular injury. *Mol Cell Biomech.* 2008; 5:155–168. [PubMed: 18751525]
59. Dixon CE, Clifton GL, Lighthall JW, Yaghami AA, Hayes RL. A controlled cortical impact model of traumatic brain injury in the rat. *J Neurosci Methods.* 1991; 39:253–262. [PubMed: 1787745]

LAMPIRAN



KEMENTERIAN PENDIDIKAN DAN KEBUDAYAAN
UNIVERSITAS HASANUDDIN FAKULTAS KEDOKTERAN
KOMITE ETIK PENELITIAN KESEHATAN
RSPTN UNIVERSITAS HASANUDDIN
RSUP Dr. WAHIDIN SUDIROHUSODO MAKASSAR
Sekretariat : Lantai 2 Gedung Laboratorium Terpadu
JL.PERINTIS KEMERDEKAAN KAMPUS TAMALANREA KM.10 MAKASSAR 90245.





Contact Person: dr. Agussalim Bukhari, MMed, PhD, SpGK TELP. 081241850858, 0411 5780103. Fax : 0411-581431

REKOMENDASI PERSETUJUAN ETIK

Nomor : 1113/UN4.6.4.5.31/ PP36/ 2019

Tanggal: 21 Nopember 2019

Dengan ini Menyatakan bahwa Protokol dan Dokumen yang Berhubungan Dengan Protokol berikut ini telah mendapatkan Persetujuan Etik :

No Protokol	UH19090776	No Sponsor Protokol	
Peneliti Utama	dr. Komet Rama Daud	Sponsor	
Judul Peneliti	Pengaruh Pemberian Doksisisklin Terhadap Kadar Matriks Metalloproteinase Pada Edema Cerebri Dalam Cedera Otak Traumatika Tikus Albino Galur Wistar		
No Versi Protokol	2	Tanggal Versi	21 Nopember 2019
No Versi PSP		Tanggal Versi	
Tempat Penelitian	Laboratorium Hewan dan Laboratorium Penelitian Fakultas Kedokteran Universitas Hasanuddin Makassar		
Jenis Review	<input type="checkbox"/> Exempted <input checked="" type="checkbox"/> Expedited <input type="checkbox"/> Fullboard Tanggal	Masa Berlaku 21 Nopember 2019 sampai 21 Nopember 2020	Frekuensi review lanjutan
Ketua Komisi Etik Penelitian Kesehatan FKUH	Nama Prof.Dr.dr. Suryani As'ad, M.Sc.,Sp.GK (K)	Tanda tangan 	
Sekretaris Komisi Etik Penelitian Kesehatan FKUH	Nama dr. Agussalim Bukhari, M.Med.,Ph.D.,Sp.GK (K)	Tanda tangan 	

Kewajiban Peneliti Utama:

- Menyerahkan Amandemen Protokol untuk persetujuan sebelum di implementasikan
- Menyerahkan Laporan SAE ke Komisi Etik dalam 24 Jam dan dilengkapi dalam 7 hari dan Laporan SUSAR dalam 72 Jam setelah Peneliti Utama menerima laporan
- Menyerahkan Laporan Kemajuan (progress report) setiap 6 bulan untuk penelitian resiko tinggi dan setiap setahun untuk penelitian resiko rendah
- Menyerahkan laporan akhir setelah Penelitian berakhir
- Melaporkan penyimpangan dari prokol yang disetujui (protocol deviation / violation)
- Mematuhi semua peraturan yang ditentukan