20.

BÖLÜM

SEREBROVASKÜLER HASTALIKLAR HAYVAN MODELLERİ

Metin ÇOKSEVİM [1]

Yıllık yaklaşık 142.000 ölümle sonuçlanan vaka sayısı ile inme; Amerika Birleşik Devletleri'ndeki ölüm nedenleri sıralamasında 5. sırada yer almaktadır. Yıllar içinde inme için yaşa göre belirlenmiş mortalite oranlarında bir düşme meydana gelse de her yıl inme geçiren birey sayısı dünya çapında artmaya devam etmektedir. Ayrıca inme edinilmiş sakatlığın en önce gelen nedenidiR (1).

İnmelerin yaklaşık %80›i iskemik orjinlidir ve büyük bir serebral arterin veya dallarının tromboembolikoklüzyonu sonucunda meydana gelir. Oklüzyon sonucunda beyin dokusunda oksijen ve enerji yoksunluğu başlar. Ardından reaktif oksijen türlerinin oluşumu, glutamat salınımı, hücre içi kalsiyum birikimi ve inflamatuar süreçlerin indüksiyonu gerçekleşerek "**iskemik kaskad"** olarak adlandırılan olaylar dizisi meydana gelir ve geri dönüşümsüz doku hasarı oluşur (enfarktüs)(2). İskemikpenumbra -enfarktüslü çekirdeği çevreleyen iskemik beyin dokusu alanı- belirli bir terapötik pencere içinde uygun bir tedavi uygulanırsa potansiyel olarak kurtarılabilir (3).

İskemik inmeyi tedavi etmek için iki ana yaklaşım geliştirilmiştir: '**nörolojik korunma (nöroproteksiyon)'** ve **'reperfüzyon'**. Reperfüzyon stratejisinde, oklüde olmuş damarı rekanalize etmek için trombolitik ilaçlar veya mekanik trombektomi kullanılır. Akut iskemik inme için onaylanmış tek medikal tedavi, rekombinant doku plazminojenaktivatörü (rtPA) ile intravenöztrombolizisdir (4). Ancak rtPA tüm hastaların sadece %5'ine uygulanabilmektedir (5). Bu nedenle, daha geniş çapta uygulanabilir alternatif tedavi seçeneklerine acilen ihtiyaç duyulmaktadır.

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KAYNAKLAR

1. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation. 2019;139:e56-e528.
2. Lipton P. Ischemic cell death in brain neurons. Physiol Rev. 1999;79:1431-1568.
3. Fisher M. The ischemic penumbra: identification, evolution and treatment concepts. Cerebrovasc Dis. 2004;17 Suppl 1:1-6.
4. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019;50:e344-e418.
5. Fonarow GC, Smith EE, Saver JL, et al. Timeliness of tissue-type plasminogen activator therapy in acute ischemic stroke: patient characteristics, hospital factors, and outcomes associated with door-to-needle times within 60 minutes. Circulation. 2011;123:750-758.
6. Fluri F, Schuhmann MK, Kleinschnitz C. Animal models of ischemic stroke and their application in clinical research. Drug Des Devel Ther. 2015;9:3445-3454.
7. O'Collins VE, Macleod MR, Donnan GA, et al. 1,026 experimental treatments in acute stroke. Ann Neurol. 2006;59:467-477.
8. Fisher M, Feuerstein G, Howells DW, et al. Update of the stroke therapy academic industry roundtable preclinical recommendations. Stroke. 2009;40:2244-2250.
9. Ström JO, Ingberg E, Theodorsson A, et al. Method parameters' impact on mortality and variability in rat stroke experiments: a meta-analysis. BMC Neurosci. 2013;14:41.
10. Kraft P, Göb E, Schuhmann MK, et al. FTY720 ameliorates acute ischemic stroke in mice by reducing thrombo-inflammation but not by direct neuroprotection. Stroke. 2013;44:3202-3210.
11. Bogousslavsky J, Van Melle G, Regli F. The Lausanne Stroke Registry: analysis of 1,000 consecutive patients with first stroke. Stroke. 1988;19:1083-1092.
12. Longa EZ, Weinstein PR, Carlson S, et al. Reversible middle cerebral artery occlusion without craniectomy in rats. stroke. 1989;20:84-91.
13. Howells DW, Porritt MJ, Rewell SS, et al. Different strokes for different folks: the rich diversity of animal models of focal cerebral ischemia. Journal of Cerebral Blood Flow & Metabolism. 2010;30:1412-1431.
14. Liu S, Zhen G, Meloni BP, et al. Rodent stroke model guidelines for preclinical stroke trials. Journal of experimental stroke & translational medicine. 2009;2:2.
15. Carmichael ST. Rodent models of focal stroke: size, mechanism, and purpose. NeuroRx. 2005;2:396-409.
16. McColl BW, Carswell HV, McCulloch J, et al. Extension of cerebral hypoperfusion and ischaemic pathology beyond MCA territory after intraluminal filament occlusion in C57Bl/6J mice. Brain research. 2004;997:15-23.
17. Pedrono E, Durukan A, Strbian D, et al. An optimized mouse model for transient ischemic attack. Journal of Neuropathology & Experimental Neurology. 2010;69:188-195.
18. Türeyen K, Vemuganti R, Sailor KA, et al. Ideal suture diameter is critical for consistent middle cerebral artery occlusion in mice. Operative Neurosurgery. 2005;56:ONS-196-ONS-200.
19. Bouley J, Fisher M, Henninger N. Comparison between coated vs. uncoated suture middle cerebral artery occlusion in the rat as assessed by perfusion/diffusion weighted imaging. Neuroscience letters. 2007;412:185-190.
20. Walberer M, Stolz E, Müller C, et al. Experimental stroke: ischaemic lesion volume and oedema formation differ among rat strains (a comparison between Wistar and Sprague–Dawley rats using MRI). Laboratory animals. 2006;40:1-8.
21. Schmid-Elsaesser R, Zausinger S, Hungerhuber E, et al. A critical reevaluation of the intraluminal thread model of focal cerebral ischemia. Stroke. 1998;29:2162-2170.

22. Li F, Omae T, Fisher M. Spontaneous hyperthermia and its mechanism in the intraluminal suture middle cerebral artery occlusion model of rats. Stroke. 1999;30:2464-2469.
23. Hossmann K-A. The two pathophysiologies of focal brain ischemia: implications for translational stroke research. Journal of Cerebral Blood Flow & Metabolism. 2012;32:1310-1316.
24. Sugimori H, Yao H, Ooboshi H, et al. Krypton laser-induced photothrombotic distal middle cerebral artery occlusion without craniectomy in mice. Brain Research Protocols. 2004;13:189-196.
25. Watson BD, Dietrich WD, Busto R, et al. Induction of reproducible brain infarction by photochemically initiated thrombosis. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 1985;17:497-504.
26. Kim H-S, Kim D, Kim RG, et al. A rat model of photothrombotic capsular infarct with a marked motor deficit: a behavioral, histologic, and microPET study. Journal of Cerebral Blood Flow & Metabolism. 2014;34:683-689.
27. Harrison TC, Silasi G, Boyd JD, et al. Displacement of sensory maps and disorganization of motor cortex after targeted stroke in mice. Stroke. 2013;44:2300-2306.
28. Yanagisawa M, Kurihara H, Kimura S, et al. A novel peptide vasoconstrictor, endothelin, is produced by vascular endothelium and modulates smooth muscle Ca2+ channels. Journal of hypertension. 1988;6:S188-191.
29. Hughes P, Anthony D, Ruddin M, et al. Focal lesions in the rat central nervous system induced by endothelin-1. Journal of Neuropathology & Experimental Neurology. 2003;62:1276-1286.
30. Biernaskie J, Corbett D, Peeling J, et al. A serial MR study of cerebral blood flow changes and lesion development following endothelin-1-induced ischemia in rats. Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine. 2001;46:827-830.
31. Mayzel-Oreg O, Omae T, Kazemi M, et al. Microsphere-induced embolic stroke: An MRI study. Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine. 2004;51:1232-1238.
32. Gerriets T, Li F, Silva MD, et al. The macrosphere model: evaluation of a new stroke model for permanent middle cerebral artery occlusion in rats. Journal of neuroscience methods. 2003;122:201-211.
33. Zhang L, Zhang ZG, Zhang C, et al. Intravenous Administration of a GPIIb/IIIa Receptor Antagonist Extends the Therapeutic Window of Intra-Arterial Tenecteplase–Tissue Plasminogen Activator in a Rat Stroke Model. Stroke. 2004;35:2890-2895.
34. Wang CX, Todd KG, Yang Y, et al. Patency of cerebral microvessels after focal embolic stroke in the rat. Journal of Cerebral Blood Flow & Metabolism. 2001;21:413-421.
35. Haelewyn B, Risso J-J, Abraini JH. Human recombinant tissue-plasminogen activator (alteplase): why not use the 'human'dose for stroke studies in rats? Journal of Cerebral Blood Flow & Metabolism. 2010;30:900-903.