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ADVANCES IN THE TREATMENT OF ISCHEMIC STROKE: A NARRATIVE REVIEW OF ACUTE THERAPIES, NEUROPROTECTION AND TECHNOLOGICAL INNOVATIONS

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Abstract: Ischemic stroke is one of the leading causes of morbidity and mortality worldwide, requiring constant advances in its clinical management. This article reviews recent advances in acute therapies, neuroprotective strategies and technological innovations applied to the treatment of ischemic stroke. Intravenous thrombolysis with alteplase and mechanical thrombectomy remain mainstays of treatment, with the emergence of alternatives such as tenecteplase and combined interventions, such as intra-arterial administration of alteplase after thrombectomy, broadening the therapeutic possibilities. Neuroprotective strategies, including antioxidants, ferroptosis modulators and inhibitors of inflammatory processes, show significant potential for mitigating the secondary damage caused by ischemia. Innovations such as nanotechnology, extracellular vesicles and artificial intelligence are redefining diagnosis and treatment, while cell therapies and remote ischemic conditioning are emerging as promising complementary approaches. Despite the advances, challenges remain in translating preclinical discoveries into the clinical context, accessibility to technologies and identification of subgroups benefiting from personalized treatments. The integration of vascular recanalization, neuroprotection and tissue regeneration represents a promising integrative approach with the potential to significantly improve the clinical outcomes of ischemic stroke patients. Future studies should validate these therapies in robust clinical trials, contributing to advances in the care of this devastating condition.

Keywords: ischemic stroke, thrombolysis, mechanical thrombectomy, neuroprotection.

INTRODUCTION

Ischemic stroke is one of the leading causes of global mortality and morbidity, contributing significantly to prolonged physical and cognitive disabilities. Representing around 87% of all stroke cases, the condition is characterized by the obstruction of blood flow in large or small cerebral vessels, leading to tissue ischemia and neuronal death (1, 3). The complexity of the pathogenesis of ischemic stroke, which involves processes such as excitotoxicity, inflammation, oxidative stress and programmed cell death, reflects the need for multifaceted and personalized therapeutic approaches (4, 6, 7). Advances in the treatment of ischemic stroke have transformed the clinical approach in recent decades. Acute therapies such as intravenous thrombolysis with alteplase (rt-PA) and mechanical thrombectomy are currently the standard of care for vascular recanalization (3, 12). However, these interventions have limitations, such as a narrow therapeutic window and the need for rapid diagnosis and adequate infrastructure (3, 10). In addition, many patients remain excluded from these interventions, highlighting the need for adjuvant strategies to mitigate secondary damage such as neuroinflammation and cell death (6, 13). Recent research has focused on emerging therapies, including the use of antioxidants, ferroptosis inhibitors, cell therapies and nanotechnology, with the aim of promoting tissue and functional recovery (1, 7, 8). In addition, technological innovations such as artificial intelligence applied to diagnosis and extracellular vesicles targeted at neuronal regeneration are redefining the future of ischemic stroke management (9, 15, 16).

OBJECTIVES

This article reviews therapeutic advances in the management of ischemic stroke, analyzing the main interventions, including acute therapies such as intravenous thrombolysis and mechanical thrombectomy, their limitations and alternatives such as tenecteplase and combined strategies. In addition, it explores emerging neuroprotective strategies, such as antioxidants, ferroptosis and oxytosis inhibitors, and inflammatory modulators, which act to mitigate the secondary damage of ischemia, as well as technological innovations, such as nanotechnology, extracellular vesicles and artificial intelligence, and their impact on diagnosis and treatment progress. It also addresses cell therapies, with emphasis on the use of mesenchymal stem cells and remote ischemic conditioning, integrating these emerging approaches with conventional therapies to promote tissue and functional regeneration, improving the clinical outcomes of patients with ischemic stroke.

RESULTS

ACUTE THERAPIES

Acute treatments for ischemic stroke, such as intravenous thrombolysis with alteplase (rt-PA), remain the standard of care for patients arriving within the therapeutic window of 4.5 hours. Although effective, alteplase has limitations such as a narrow therapeutic window and the risk of bleeding complications. Clinical trials, such as NOR-TEST, have highlighted tenecteplase as a viable alternative, with similar efficacy and greater practicality due to its single bolus administration (12).

Mechanical thrombectomy is one of the most significant advances in the management of ischemic stroke, especially in large vessel occlusions (LVO). Studies such as DAWN and DEFUSE 3 have shown that thrombectomy can be successfully performed up to 24 hours after symptom onset in patients selected for advanced imaging (3). Combined thrombectomy strategies, such as the simultaneous use of stent retriever and aspiration, were evaluated in the ASTER2 study, showing effective recanalization, although with no significant impact on functional outcomes (11). In addition, intra-arterial administration of alteplase after successful thrombectomy, as investigated in the CHOICE study, provided functional improvement without increasing bleeding complications (10).

NEUROPROTECTIVE STRATEGIES

In order to mitigate the secondary damage caused by ischemic stroke, various neuroprotective strategies have been investigated. Antioxidant compounds, such as edaravone and N-acetylcysteine, have shown efficacy in reducing oxidative stress in pre-clinical models (1, 4). In addition, ferroptosis, a type of iron-dependent cell death, and glutamate-mediated oxytosis have been identified as central mechanisms in the pathophysiology of stroke. Inhibitors such as liproxstatin-1 and ferrostatin-1 have reduced cell damage in experimental studies (6). Inflammatory modulation has also shown promise, with inhibitors of pro-inflammatory cytokines such as TNF-α and IL-1β reducing neuroinflammation and tissue damage (6, 14).

TECHNOLOGICAL INNOVATIONS

Technological advances have played a crucial role in the diagnosis and treatment of ischemic stroke. Nanotechnology has enabled targeted delivery of neuroprotective and thrombolytic agents, overcoming physiological barriers such as the blood-brain barrier (7). Extracellular vesicles, derived from the neurovascular unit, have emerged as mediators of tissue regeneration and inflammatory modulation, showing potential in preclinical models (9). On the other hand, artificial intelligence has been applied to advanced image analysis, speeding up the identification of areas of ischemic penumbra and optimizing clinical decisions (15, 16).

CELL THERAPIES

Cell therapies, especially with the use of mesenchymal stem cells (MSCs), have shown modest benefits in initial clinical trials. MSCs promote angiogenesis, neuronal regeneration and inflammatory modulation, although challenges related to cell viability and protocol standardization still limit their widespread application (8). Combined strategies, such as the use of nanotechnology to improve cell delivery, are being investigated as ways of maximizing the benefits of cell therapies.

REMOTE ISCHEMIC CONDITIONING

Remote ischemic conditioning (RIC), which consists of intermittent cycles of compression and reperfusion in peripheral limbs, has been evaluated as a non-invasive approach to improving functional outcomes. Studies such as RICAMIS have shown that RIC is effective in patients with moderate ischemia, highlighting its potential as an adjunct therapy to more conventional strategies (5).

DISCUSSION

Advances in the management of ischemic stroke have expanded therapeutic possibilities, combining acute interventions, neuroprotective strategies and technological innovations. However, the clinical challenges and limitations associated with existing approaches still require the development of new strategies to optimize functional outcomes. Intravenous thrombolysis with alteplase (rt-PA) remains the standard of care in eligible patients, but its narrow therapeutic window and the risk of hemorrhagic complications limit its broad applicability (3, 12). Tenecteplase, a genetically modified variant of rt-PA, has proved to be a promising alternative, offering advantages in practicality of administration and comparable efficacy, as assessed in clinical trials such as NOR-TEST (12). On the other hand, mechanical thrombectomy has established itself as the approach has the greatest impact on patients with large vessel occlusions (LVO) and is supported by studies such as DAWN and DEFUSE 3, which expanded the therapeutic window to up to 24 hours in selected cases (3). Combined strategies, such as the simultaneous use of stent retriever and aspiration (11), and the intra-arterial administration of alteplase after thrombectomy (10), offer adjuvant approaches that need to be further explored in larger populations. The introduction of emerging neuroprotective therapies marks a breakthrough in mitigating the secondary damage of ischemic stroke. Antioxidant compounds such as edaravone and N-acetylcysteine have shown efficacy in reducing oxidative stress in preclinical models (1, 4). In addition, ferroptosis, a type of iron-dependent cell death, and glutamate-mediated oxytosis have been identified as central mechanisms in the pathophysiology of stroke. Inhibitors such as liproxstatin-1 and ferrostatin-1 have reduced cell damage in experimental studies (6). Inflammatory modulation has also shown promise, with inhibitors of pro--inflammatory cytokines such as TNF-α and IL-1β reducing neuroinflammation and tissue damage (14). These processes, in addition to highlighting the complexity of stroke pathophysiology, reinforce the need for integrated approaches to mitigate excitotoxicity and oxidative stress, which remain crucial components in neuronal cell death (2). The use of regenerative therapies, such as extracranial--intracranial bypass (EC-IC), was explored in the CMOSS study. Although this technique did not show benefits in general patients, it was effective in subgroups with critical cerebral perfusion (17). Vascular regeneration and angiogenesis have also been addressed by the use of endothelial progenitor cells, modulated by pharmacological agents such as statins and VEGF, which promote the restoration of blood flow and endothelial integrity (18). Experimental models have played a crucial role in validating new therapies (19), reviewing preclinical strategies to assess pathophysiological mechanisms and identify new approaches. These models have been key to understanding the impact of emerging technologies, such as extracellular vesicles and nanodrugs, on the management of stroke (7, 9, 20). In addition, the integration of therapeutic advances has been reinforced by strategies that combine neuroprotection, tissue regeneration and vascular recanalization (21). Finally, the challenges in the management of ischemic stroke include translating preclinical findings into the clinical context, the accessibility of advanced technologies, and identifying subgroups of patients who can benefit from personalized therapies. The combination of vascular recanalization, neuroprotection and tissue regeneration represents a promising integrative approach to improving functional outcomes in ischemic stroke patients.

CONCLUSION

The management of ischemic stroke has evolved significantly in recent decades, integrating acute therapies, neuroprotective strategies and technological innovations. Intravenous thrombolysis with alteplase and mechanical thrombectomy remain mainstays of treatment, with advances expanding the therapeutic window and introducing alternatives, such as tenecteplase, and combined approaches, such as intra-arterial administration of alteplase after recanalization. However, the limitations of these interventions highlight the need for adjuvant strategies to address the secondary damage of ischemia. Neuroprotective therapies are emerging as a promising field, with antioxidants, ferroptosis modulators and inhibitors of inflammatory processes showing encouraging results in preclinical studies. At the same time, technologies such as nanotechnology, extracellular vesicles and artificial intelligence have shown the potential to transform diagnosis and treatment, facilitating more precise and personalized interventions. Therapies cellular and remote ischemic conditioning also represent important advances, with the potential to complement conventional interventions. Despite these advances, significant challenges remain, including the translation of preclinical findings into the clinical setting, the accessibility of advanced technologies and the need to identify subgroups of patients who would benefit from personalized approaches. The integration of vascular recanalization, neuroprotection and tissue regeneration offers a promising integrative perspective that could significantly improve functional outcomes in ischemic stroke patients. Future studies should focus on validating the efficacy of emerging therapies in robust clinical trials and exploring combinations of interventions to optimize patient care, helping to reduce the morbidity and mortality associated with ischemic stroke.

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