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Effectiveness of N-Acetylcysteine in Acute Ischemic Stroke: A Systematic Review

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Abstract

Background: N-Acetylcysteine (NAC) is a multi-target agent for Acute Ischemic Stroke (AIS), but its clinical efficacy and safety are unclear. This systematic review synthesized clinical trial evidence on NAC in AIS.

Methods: A systematic search of five databases was conducted from inception to December 2025. Randomized and non-randomized trials in adult AIS patients were included. Two reviewers performed data extraction and risk-of-bias assessment. A narrative synthesis was conducted.

Results: Five studies (256 patients) were included. In patient's ineligible for reperfusion, NAC improved neurological function and 90-day outcomes, with biomarker support. As an adjunct to intravenous alteplase, NAC showed early improvement but was associated with significant safety signals, including fatal hemorrhage, leading to one trial's early termination.

Conclusion: NAC shows neuroprotective potential with an acceptable safety profile in patients not receiving reperfusion. However, its adjunctive use with alteplase carries a substantial hemorrhage risk, requiring caution. Future trials must clarify its role with rigorous safety monitoring.

Keywords: Acute ischemic stroke, Biomarkers, Hemorrhage, Ischemic stroke, N-Acetylcysteine, Reperfusion, Tissue plasminogen activator, Treatment outcome

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Introduction

Acute Ischemic Stroke (AIS) is one of the most common causes of mortality and long-term disability in most societies across the world, and this presents a considerable burden to healthcare systems and society as a whole (1,2). Rapid revascularization is the basis of acute management, which is mainly achieved by intravenous thrombolysis with recombinant tissue plasminogen activator (alteplase) and mechanical thrombectomy (3). However, there are major limitations to the therapeutic efficacy of these strategies. Alteplase shows a modest recanalization rate especially on platelet-rich thrombi that are not susceptible to fibrinolytic therapy and its administration is accompanied by a threat of symptomatic Intracranial Hemorrhage (sICH) (4,5). Moreover, it is limited to a small range of eligible patients by a small treatment window and a large number of contraindications (6). It, therefore, presents a significant and unmet clinical requirement in adjunctive or alternative treatments that have the capacity to increase the effect of reperfusion, lengthening neuroprotective effects to the ischemic penumbra, and promoting better functional outcome but not increasing hemorrhagic risk.

A historical trend in this area is a translational roadblock, in which many neuroprotective agents that are promising based on their preclinical performance have repeatedly failed to be effective in large-scale, human, Randomized Controlled Trials (RCTs) (7,8). The synthesis of these efforts on agents such as citicoline, nerinetide and magnesium among others, has been generally found to lack substantial optimal clinical benefit due to a combination of timing, dosing, patient selection and trial methodology issues (9-11). Even in the wake of these disappointments, the neuroprotective strategy is still considered theoretically essential, since it treats the ubiquitous secondary injury cascades of oxidative stress, excitotoxicity, and inflammation that transform into hours to days following the stroke (12).

N-Acetylcysteine (NAC), a precursor to the endogenous antioxidant glutathione, has become an attractive multi-target stroke therapy. It is based on two possible complementary but different mechanism pathways that support its therapeutic potential. To begin with, NAC has the ability to reduce secondary neuronal damage as a powerful antioxidant and anti-inflammatory compound by inhibiting the sequence of oxidative stress and neuroinflammation occurring after cerebral ischemia (13,14). These neuroprotective mechanisms are repeatedly observed in preclinical studies to indicate that NAC lowers infarct volume and elevates neurological scores in animal stroke models by these neuroprotective mechanisms (15,16). Second, less explicable because more recently discovered, is the strong thrombolytic effect of NAC. It works by disulfide bonding the ultra-large von Willebrand factor (VWF) multimers which is a prime platelet cross-linking mediator in an arterial, high-shear thrombus (17). This move has the potential to dissolve thrombi that cannot be broken by the conventional fibrinolytic action, implying a special purpose of NAC as a supplement to alteplase to enhance recanalization rates (18).

Even with strong preclinical rationale NAC translation to clinical stroke care is in its early phases and characterized by ambiguity. Human studies in early phase have given mixed results. There is some limited evidence in the literature of clinical trials in patients who did not receive reperfusion therapy which indicates NAC oral/intravenous could be of benefit by improving the neurological scales and functional outcome, possibly through antioxidant effects (19,20). On the other hand, pilot trials of NAC as a supplement to intravenous alteplase include a complicated safety-efficacy profile, with both indications of the initial neurological relief and alarming degrees of hemorrhagic change (21). This contrast of potentially attractive mechanical activity with uncertain clinical outcome and harm highlights an important knowledge deficit.

So far, there are a number of systematic reviews assessing NAC use in neurological conditions, yet none synthesized evidence on NAC use in AIS systematically and in a comprehensive manner. Available reviews have been either psychiatric based, TBI based, or have incorporated AIS as a subgroup of more general neurological reviews without conducting a systematic, specific synthesis of stroke-specific studies (22-24). This is a considerable gap in knowledge. In addition, preclinical trials have already appeared, with apparently contradictory findings. The discipline does not have any authoritative overview

that would bring these results into agreement, estimate the risk-benefit balance in clinical settings, and determine the overall quality of evidence. Thus, the proposed systematic review will help address this gap, as the primary objective is to present the first multifaceted evaluation of the effectiveness and safety of NAC in patients with AIS.

Materials and Methods

Study protocol

This systematic review was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (25). The PICOS framework was used to select the studies that would help to make the review focused and reproducible. The authors considered articles in which adult patients (18 years and older) had a proven diagnosis of AIS without any limitations in stroke severity, post stroke interval, or concomitant administration of reperfusion treatments including intravenous thrombolysis or mechanical thrombectomy. The intervention of interest was the administration of NAC through any route (oral or intravenous) and any dose schedule as a part of AIS management. Comparators were placebo, standard medical care alone, or a control group not receiving NAC. Pre-specified outcomes included a primary efficacy endpoint of functional independence. Secondary efficacy outcomes included a change in neurological deficit, all-cause 90-day mortality and recanalization rates. For safety assessment, the primary outcome was sICH, using definitions provided by the original authors, while secondary safety outcomes included any intracranial hemorrhage, major extracranial bleeding, and other adverse events. In terms of the study design, all forms of clinical trials that mentioned one or more of the above outcomes have been incorporated. Case reports, narrative reviews, meta-analyses, and preclinical studies were not incorporated.

Search strategy

The search was done systematically through five large electronic databases of English papers published since the beginning until December 9, 2025: PubMed, Web of Science (ISI), Scopus, Google Scholar, and Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy was developed with the help of a medical librarian and incorporated a mix of Medical Subject Headings (MeSH) and free-text terms based on stroke, ischemic stroke, brain ischemia, N-Acetylcysteine (NAC), and clinical trial. Moreover, all included studies and other useful systematic reviews were manually scanned in terms of the identification of any other eligible publications that might be included. The search results of all databases were loaded into EndNote software where the duplicates were automatically and manually deleted. Two independent reviewers did the study selection in two stages. All the records retrieved were screened based on the eligibility criteria by their titles and abstracts. At that point, the contents of every or all possibly useful records were accessed and reviewed thoroughly to be included ultimately. Any conflict of reviewers in either of the stages was by discussion or where there was need, consultation with a third reviewer was done. A PRISMA flow diagram was used to document the process of the study selection.

Data extraction

A standardized, pilot-tested data extraction form was developed in Microsoft Excel. Two reviewers independently extracted data from every included study. Extracted data included study characteristics (first author, publication year, country, study design, sample size, inclusion/exclusion criteria, and time to treatment), participant characteristics (age, sex, stroke subtype, and concurrent treatments), intervention details (NAC formulation, dose, route, timing, and duration of administration), comparator details, outcome measures, and main findings. Discrepancies in extracted data were cross-checked and resolved by consensus.

Risk of bias assessment

The methodological quality and risk of bias of the included studies were assessed independently by two reviewers using the revised Cochrane Risk of Bias tool (RoB 2) for RCTs and the Risk of Bias in Non-randomized Studies-of Interventions (ROBINS-I) tool for non-randomized trials. The RoB 2 was used to evaluate bias across five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result (26). Each domain

was judged as low, some concerns, or high risk of bias, leading to an overall judgment. On the other hand, the ROBINS-I was used to assess bias across seven domains related to confounding, participant selection, intervention classification, deviations, missing data, outcome measurement, and result selection (27). An overall judgment of low, moderate, serious or critical risk of bias was assigned. Disagreements in bias assessments were resolved through discussion.

Results

A total of 653 records were obtained after the systematic search in 5 electronic databases (PubMed, ISI Web of Science, Scopus, Cochrane CENTRAL, and Google Scholar). Moreover, five additional records were retrieved from the reference lists of the eligible articles. Once 108 duplicates had been removed 550 individuals with unique records were screened by title and abstract. After this first screening, 26 full-text articles have been evaluated in relation to eligibility. A total of five studies were finally chosen to satisfy all the stipulated inclusion criteria and become part of the qualitative synthesis of this systematic review (19,28-31). The reviewed articles included four randomized controlled trials and one single-arm phase IIa trial, published in 2020-2025, with sample sizes ranging from 12 to 74 participants. The detailed selection process, including reasons for exclusion at the full-text stage, is illustrated in the PRISMA flow diagram (Figure 1). Due to substantial clinical heterogeneity among the included studies, a quantitative meta-analysis to generate a single pooled estimate of effect was deemed inappropriate. These heterogeneities are primarily stemming from fundamental differences in patient population (thrombolysis versus non-thrombolysis), intervention (intravenous versus oral NAC), and context of use (adjunctive thrombolytic versus stand-alone neuroprotectant). Instead, a structured narrative synthesis was conducted.

In total, the five included studies enrolled 256 patients. Three studies were conducted in Iran, one in India, and one in France. The total number of patients receiving NAC across all studies was 132, while 112

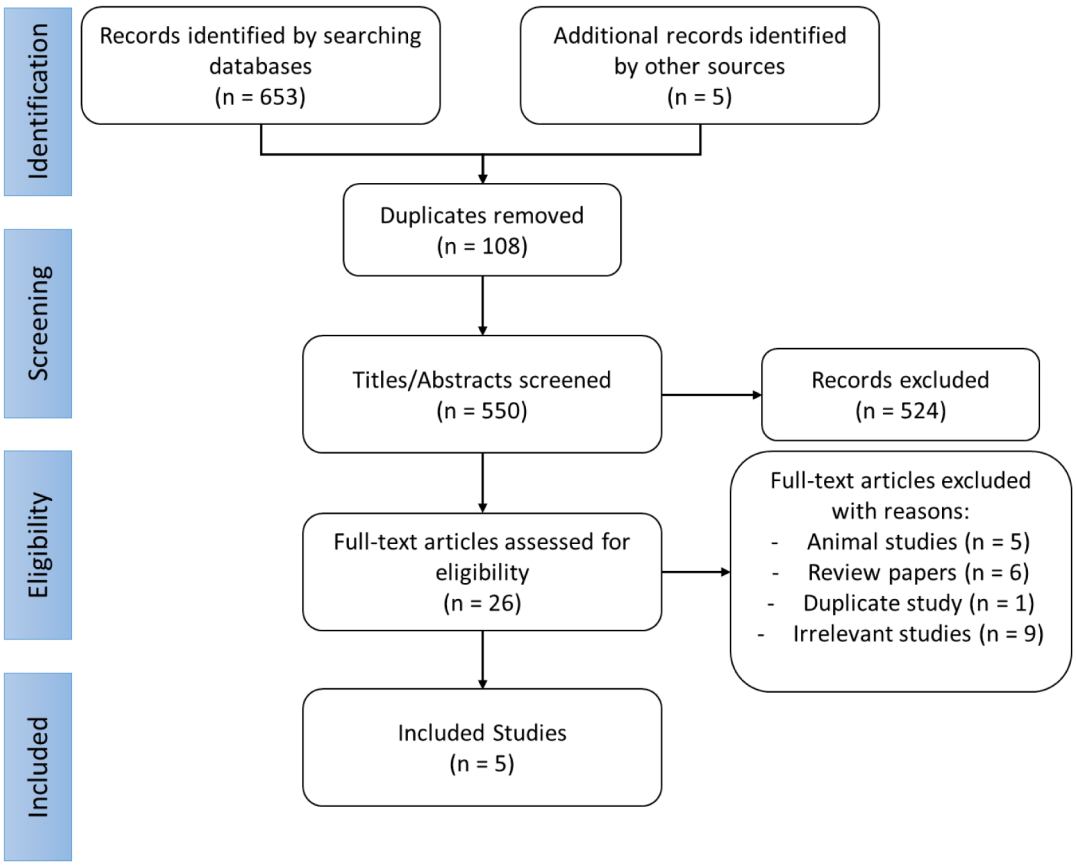


Figure 1. PRISMA flowchart to identify eligible trials for the review on N-Acetylcysteine in acute ischemic stroke.

served as controls (placebo or standard care), with 12 patients in the single-arm trial receiving NAC without a concurrent control. Treatment protocols varied substantially. In studies employing oral NAC (28), dosing consisted of a 4 *g* loading dose followed by 4 *g*/day in divided doses for two days (total 12 *g* over 72 *hr*). Intravenous NAC regimens involved weight-based dosing: two studies used a 100 *mg/kg* bolus followed by a 10 *mg/kg/hr* infusion for 10 *hr* (total ~200 *mg/kg*) (19,29), while two studies (30,31) administered a single IV dose of 150 *mg/kg*. The time from stroke onset to treatment initiation ranged from within 4.5 *hr* for thrombolysis-adjunct studies to within 24 *hr* for stand-alone neuroprotectant studies.

Methodological quality was assessed using RoB 2 for randomized trials (19,28-30) and ROBINS-I for the non-randomized study (31). Among the four RCTs, one was judged to have a low risk of bias (19), while two studies with blinded endpoint assessment was rated as having some concerns (29,30). Moreover, the study of Sabetghadam *et al* (28) had a high risk of bias due to concerns about the randomization process, missing outcome data, and selection of the reported results. The single-arm trial (31) was also assessed as having a high risk of bias due to the lack of a concurrent control group. Table 1 shows the details of the quality assessment of each study.

Table 2 shows the characteristics, features, and results of the included studies. In the five studies that were included, the baseline demographics and stroke severity were mostly balanced in trials. The average or median age of the participants was from about 58 to 72 years with slight male bias in line with the epidemiology of strokes. Initial NIHSS scores varied from mild to moderate severity (median range 4-15 in study populations), with no significant reported imbalances between intervention and control arms at baseline. The main efficacy outcome measures were neurological outcome, which was most frequently assessed using the NIHSS, and functional independence, assessed using a modified Rankin Scale (mRS) score of 0-1 or 0-2 at 90 days. The uniform safety assessment was on hemorrhagic transformation especially the sICH, with variable reporting of other adverse events. The attrition rate was also quite low in the randomized studies (smaller than 10%), and the attrition was similar to both arms of the study. The single-arm safety trial by (31) was an exception, and was prematurely terminated when 12 of the intended 19 patients had been enrolled because of emergent safety signals.

Three trials were done on patients who were not eligible to undergo reperfusion therapy (19,28,29). During such experiments, NAC (delivered orally or intravenously) proved to have steady indications of neurological improvement. A single trial had found a significant increase in NIHSS scores and the functional independence rates at 90 days in

Table 1. (A) Risk of bias assessment for non-randomized studies using ROBINS-I

Author (Year)	ROBINS-I							
	D1	D2	D3	D4	D5	D6	D7	Overall risk
Vivien *et al* (2025)								

Color code: Red (critical risk), Yellow (moderate risk), Green (low risk).

Table 1. (B) Risk of bias assessment for randomized studies using RoB2

Author (Year)	RoB2					
	D1	D2	D3	D4	D5	Overall risk
Sabetghadam *et al* (2020)						
Farzandway *et al* (2023)						
Komakula *et al* (2024)						
Mehrpooya *et al* (2025)						

Color code: Red (high risk), Yellow (some concerns), Green (low risk).

Table 2. Characteristics and efficacy/safety data from included studies

Author (Year)	Design & setting	Population & sample size (NAC/Control)	Intervention (NAC)	Control	Primary outcome(s)	Key efficacy results	Key safety results
Sabetghadam *et al* (2020)	Double-blind, placebo-controlled RCT; single-center, Iran.	AIS patients within 24 *hr* of onset, NIHSS 4-21, excluded if eligible for thrombolysis/ thrombectomy. N=68 (33/35)	Oral NAC: 4 *g* loading dose, then 4 *g*/day in 4 divided doses for 2 days (total 12 *g* over 72 *hr*)	Matched placebo oral solution	NIHSS at 90 days; mRS 0-1 at 90 days	- NIHSS at 90d: Lower in NAC (median 5 *vs.* 10, p=0.01) - mRS 0-1 at 90 d: Higher in NAC (57.6 *vs.* 28.6%, p=0.02) - Biomarkers: NAC improved antioxidant (SOD, GPx) and reduced inflammatory (IL-6, MDA) markers *vs.* placebo	- Adverse Events: More nausea, dyspepsia, headache in NAC group (mild-moderate) - Serious AEs: 3 deaths (1 NAC, 2 placebo) due to stroke severity; 3 withdrawals for AEs (2 NAC, 1 placebo)
Farzandway *et al* (2023)	Rando-mized, single-blind, controlled clinical trial, single-center, Iran	Adults with ischemic stroke (diagnosed by MRI/clinical exam). N=74 (37 / 37)	IV NAC: 100 *mg/kg* bolus dose, then 10 *mg/kg/hr* infusion for 10 *hr* (total ~200 *mg/kg*). Concomitant standard care.	Standard care only (Aspirin 300 *mg* + Clopidogrel 300 *mg* on day 1). No placebo.	Biomarkers: Change in serum TAC, TOS, MDA, catalase, para-oxonase, neopterin at 24 *hr*. Clinical: NIHSS at 24 *hr*, 2 w, 1 *m*, 3 *m*	- Biomarkers (Overall): No significant between-group differences except for TOS (p=0.02) - Subgroup (NAC Responders): Significant improvement in all biomarkers (p<0.001-0.002) - Clinical (NIHSS): Significantly lower in NAC group *vs.* own baseline at all time points (p<0.001-0.001). Trended lower *vs.* control (p=0.02 at 1 *m*; p=0.05-0.057 at other times)	- Safety Reported: None mentioned in the provided text. Adverse events or safety monitoring not described
Komakula *et al* (2024)	Open-label, blinded endpoint (PROBE) RCT; single-center, India	AIS patients within 4.5 *hr*, eligible for IV alteplase± thrombectomy. N=40 (19/21)	IV NAC: 150 *mg/kg*, single dose, co-administered with IV alteplase	IV alteplase alone	Safety: ICH, sICH, extracranial bleeding, adverse reactions	- NIHSS at 24 *hr*: Lower in NAC+alteplase (median 2 *vs.* 8, p=0.03) - mRS 0-2 at 90d: No difference (73.7 *vs.* 76.2%, p=0.85). • Mortality at 90d: No difference (10.5 *vs.* 9.5%, p=0.99)	- sICH: 1 case in NAC group *vs.* 0 in control (5.3 *vs.* 0%, p=0.47) - Any ICH: 2 cases in NAC group *vs.* 0 (10.5 *vs.* 0%, p=0.21) - Extracranial bleeding (mild): 2 cases in NAC *vs.* 0 - Adverse reactions: Comparable (1 pruritus in NAC *vs.* 1 vomiting in control) s

Contd. table 2.

Mehrpooya *et al* (2025)	Double-blind, placebo-controlled RCT; single-center, Iran	AIS patients (mild-moderate, NIHSS 1-15), within 24 *hr*, excluded if eligible for tPA. N=62 (31/31)	IV NAC: 100 *mg/kg* stat, then 10 *mg/kg/hr* infusion for 10 *hr* (total ~200 *mg/kg*)	Standard care+ placebo infusion	NIHSS at multiple time points (primary not explicitly stated). MMP-9	- NIHSS: Reported as significantly lower in NAC group at 24 *hr*, 2 w, 1 *m*, 3 *m* (all p=0.001). (Note: Abstract reported non-significant results) - mRS at 3 *m*: Lower (better) in NAC (mean 2.3 *vs.* 2.9, p=0.001) - MMP-9: Decreased in both groups; no between-group difference	- Adverse Events: Nausea (16.1%), vomiting (9.7%), headache (6.5%) in NAC group. All mild-moderate - Serious AEs: Not reported
Vivien *et al* (2025)	Single-arm, Phase IIa safety trial; single-center, France	AIS patients within 4.5 *hr*, eligible for IV alteplase ± thrombectomy. N=12 (all received intervention)	IV NAC (HIDONAC): 150 *mg/kg* over 15 *min*, started within 30 *min* of alteplase initiation	No concurrent control. External cohorts used for comparison	Rate of symptomatic intracranial hemorrhage (sICH)	- sICH: 2 fatal events (16.7%) - Both fatal sICH patients were on prior aspirin therapy - Tolerability: 10/12 (83%) tolerated combination without severe AEs. Other AEs: vomiting, hypotension, rash (mostly mild) - Trial terminated early after 12/19 planned patients due to safety signal	- Biomarker (VWF multimers): Rapid and significant reduction in ultra-large VWF multimers (-82%, p<0.001) within hours of NAC infusion - Biological Effect: Confirmed target engagement (VWF cleavage) in humans. Alteplase alone had no effect on VWF

comparison with placebo (28). The other two studies (19,29) reported substantial within-group changes in neurological scores over time, and the trend was in favor of NAC in between-group comparisons. Safety profiles in this subgroup were favorable, with adverse events generally mild to moderate and no increase in serious adverse events attributable to NAC.

Two studies investigated NAC in combination with intravenous alteplase (30,31). One RCT found significantly lower NIHSS scores at 24 *hr* in the NAC group, though this early benefit did not translate to improved functional outcomes at 90 days (30). The single-arm safety trial reported two cases of fatal sICH among 12 patients, prompting early trial termination (31). The RCT (30) also noted non-significant increases in intracranial hemorrhage events with adjunctive NAC. These findings highlight a potential safety concern when NAC is administered alongside thrombolysis.

Two studies provided mechanistic insights correlating clinical outcomes with biological effects. Sabetghadam *et al* (28) reported that oral NAC administration significantly improved serum antioxidant markers (SOD, GPx) and reduced inflammatory markers (IL-6, MDA) compared to placebo, supporting its presumed neuroprotective

pathway. In the thrombolysis context, Vivien *et al* (31) demonstrated that intravenous NAC induced a rapid and significant reduction (−82%, $p<0.001$) in ultra-large von Willebrand factor multimers, confirming its purported thrombolytic mechanism of action in humans. However, reporting consistency was limited; key outcomes such as recanalization rates were infrequently reported, and safety monitoring protocols were not described in one trial (29), constraining a comprehensive analysis of the dose-response and mechanism-outcome relationship.

Discussion

It is the first systematic review of clinical evidence on NAC effectiveness and safety in AIS. The analysis shows a twofold and context-dependent risk-benefit profile by differentiating between its application as a stand-alone neuroprotectant in patients not having access to reperfusion therapy and as an adjunct to intravenous alteplase. The findings highlight that NAC's therapeutic potential and safety are not uniform but are critically influenced by the clinical setting in which it is administered. NAC had a uniform and encouraging indication of neuroprotection in patients who did not undergo thrombolysis. Positive neurological and functional effects of NAC reported by Sabetghadam *et al* (28), Farzandway *et al* (29), and Mehrpooya *et al* (19) are biologically plausible and agree with the established role of NAC as a glutathione precursor and an oxidative stress and neuroinflammation modulator (32,33). The resulting enhancement in the antioxidant and anti-inflammatory biomarkers also promote this mechanistic pathway. For this large and therapeutically underserved population (*i.e.*, those presenting beyond the thrombolysis window or with contraindications), NAC emerges as a viable candidate for a neuroprotective strategy, meriting investigation in larger, definitive phase III trials.

The neurobiological explanation behind NAC in AIS is based on the fact that it operates on two mechanisms of pathology, namely secondary neuronal injury and vascular occlusion. First of all, NAC is the precursor of glutathione, which is the major endogenous antioxidant in the brain (34). By restoring glutathione reserves, NAC mitigates oxidative stress, which is a key driver of reperfusion injury and neuronal apoptosis following ischemia. At the same time, it has anti-inflammatory properties as it regulates the production of pro-inflammatory cytokines and prevents the activation of microglia, thus lowering the neuroinflammatory cascade that leads to worsening of tissue damage in the post-stroke period of hours to days (35). In addition to such neuroprotective effects, NAC also has a characteristic thrombolytic activity through the disulfide bond-cleaving activity against ultra-large von Willebrand factor multimers, which are essential in platelet-rich thrombi formation and resist standard fibrinolysis (36,37). This action may promote mechanical disruption of occlusive clots, particularly in arterial, high-shear environments. Collectively, these complementary effects (antioxidant, anti-inflammatory, and thrombolytic) make NAC a multi-target agent with the ability to deal with both the metabolic crisis in the ischemic penumbra and the vascular blockage at the core of AIS pathophysiology.

On the other hand, the application of NAC as a supplement to conventional intravenous alteplase is characterized by high safety issues that currently outweigh its potential benefits. Although the trial by Komakula *et al* (30) suggested an early neurological improvement, this did not translate to better long-term functional outcomes. More critically, the safety signal from the phase IIa trial by Vivien *et al* (31) cannot be overlooked, which reported fatal symptomatic intracranial hemorrhage in 2 of 12 patients, leading to early termination. This alarming rate indicates that there is a possible synergistic impairment of hemostasis in the event that the pleiotropic action of NAC, such as the direct thrombolytic effect of von Willebrand factor multimers, be coupled with fibrinolytic therapy. This risk can be enhanced in patients who receive antiplatelet therapy in the past, which creates a critical interaction and requires a close examination.

Limitations of the Evidence

A number of key limitations in the literature used moderate the conclusions of this review. First, the number of total studies and participants is limited, and the evidence itself is highly heterogeneous in terms of clinical variables of dosing schedule, routes of administration, and patient groups. Second, the

quality of methodology of the included studies was different, as one RCT was classified as having a high risk of bias, and the research of a single-arm safety trial does not include a concurrent control group, which restricts the power of making causal conclusions. Third, important outcomes like recanalization rates were rarely reported and the safety monitoring was irregularly described which would make it difficult to fully analyze the association of mechanism-outcome and also the safety profile.

Future directions

Future research must address these gaps with carefully designed studies that clearly define the role of NAC within the modern stroke treatment paradigm. In non-thrombolysis population, multicentric, large scale, placebo-controlled, RCTs are required to establish efficacy and determine the best dosing and timing. In the case of thrombolysis population, safety should be the main concern. Any additional research on NAC as an addition to alteplase must continue to be conducted in the context of strictly monitored trials with preset safety endpoints, express exclusion of patients on concomitant antiplatelet or anticoagulant therapy, and possibly reduced doses of NAC or alternative schedule. In addition, the future research must include standard imaging and biomarker measurements in order to clarify the mechanistic equivalents of benefit and harm.

Conclusion

To sum up, it is possible to state that N-acetylcysteine can be used as a neuroprotective agent in patients with acute ischemic stroke, who cannot receive reperfusion therapy, based on early evidence of effectiveness with a good safety profile in this case. Nonetheless, its adjunctive mode of application alongside intravenous alteplase is linked to a high and possibly dangerous potential of developing hemorrhagic complications, which is the primary reason it is not recommended in this application. NAC translation into clinical stroke practice is still conditioned by the context-specific high-quality evidence of larger and more rigorous clinical trials that put much emphasis both on efficacy evaluation and, most importantly, on safety evaluation.

Conflict of Interest

Authors declare no conflict of interest.

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