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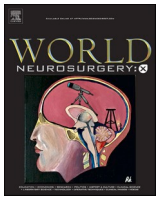

A systematic review on the use of Colchicine in Hemorrhagic Stroke

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1. Introduction

Hemorrhagic stroke occurs when a blood vessel ruptures and causes bleeding into the brain.[1] Hemorrhagic stroke is further subdivided into intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH).[1] SAH is bleeding into the subarachnoid space, whereas ICH is bleeding into the brain parenchyma. Hemorrhagic stroke has a high morbidity and mortality rate.[2] Despite improvements in management and treatment, there is still a need for efficient therapies that can help hemorrhagic stroke patients have better outcomes.

The potential therapeutic effects of colchicine, which has historically been used to treat gout, have been researched concerning cardiovascular diseases.[3] It has shown a promising role in the management of vascular diseases like coronary artery disease, heart failure, arrhythmias, etc. It expresses NLRP3 (nucleotide-binding oligomerization domain-, leucine-rich repeat-, and pyrin domain-containing protein 3)[4] which inhibits phagocytosis and suppression of Interleukin-6 (IL-6), IL-1beta and IL-18.[5] Colchicine has a high volume of distribution and is spread rapidly all over the body including the brain. Cytochrome P450 of hepatocytes metabolise colchicine into 2- and 3-dimethyl colchicine and is excreted by the liver and kidney.[6]

Colchicine has been used to treat hemorrhagic strokes, but the evidence is sparse and ambiguous. Because of this, a systematic review is required to assess the effectiveness and safety of colchicine in hemorrhagic stroke. Such a review could offer insightful information about this treatment's potential advantages and disadvantages and serve as a valuable tool for clinical practice and future research.

2. Materials and methods

2.1. Research question

The present systematic review was conducted based on the research question "**Is colchicine effective in the management of hemorrhagic stroke?**". The systematic search and identification of eligible studies were centred on the PICO criteria elaborated in Table 1. The present systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO), with **reference ID: CRD42023400819**.

2.2. Databases included and search strategy

The search was conducted in three databases: PubMed, Scopus and Web of Science on February 17, 2023. We also undertook a search in the pre-print servers such as medRxiv, arXiv, bioRxiv, BioRN, ChiRxiv, ChiRN, and SSRN. In addition, studies obtained by hand search in the references of the eligible primary research papers and reviews, which satisfied our eligibility criteria, were also included in the data extraction. The search keywords included "colchicine, hemorrhagic, cerebral, cranial, stroke". The database-wise search strategy applied and the results obtained have been enumerated in Table 2. Mendeley Desktop V1.19.5 software was utilized for importing the articles, managing the citations, removing duplicates, and coordinating the overall review process between the authors.[7]

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Table 1
PICO of the study.

	Inclusion	Exclusion
Population	People diagnosed with hemorrhagic stroke	A.Studies not published in English B. Not relevant to study C.Full text not available D.Low screening score
Intervention	Colchicine	
Comparators	Other treatment modalities	
Study designs	Original Studies, Observational Studies, Case report, Case series	Narrative Reviews, Editorials, Short communications, Case studies, Systematic review and meta-analysis

Table 2
Detailed search strategy for PubMed, SCOPUS, WoS.

Database	Keyword	Records identified(n)
Pubmed/ Medline	Colchicine[tiab] AND (hemorrhagic[tiab] OR cerebral[tiab] OR cranial[tiab]) AND stroke [tiab]	9
Scopus	TITLE-ABS-KEY(Colchicine) AND TITLE-ABS-KEY(hemorrhagic) OR TITLE-ABS-KEY(cerebral) OR TITLE-ABS-KEY(intracranial) AND TITLE-ABS-KEY(stroke)	50
Web of Science	TI=(Colchicine) AND (TI=(Hemorrhagic) OR TI=(Cerebral) OR TI=(Cranial)) AND TI=(Stroke)	1

2.3. Screening of studies

Title Abstract screening.

Two authors independently reviewed the title abstracts of the studies obtained from the above systematic search by applying the eligibility criteria and identified articles for full-text screening. If there was a disagreement regarding the inclusion of a study for full-text review, the co-authors conversed among themselves to build consensus and decided on the eligibility.

2.4. Full-text screening & data extraction

Eligible full-text articles were reviewed for suitability of data extraction by two authors, and data extraction was done by them, independently. Contradictions in data extraction between the authors were removed in a consensus meeting conducted at the end of the independent extraction. Irresolvable contradictions were adjudicated by the third author. A final table was formulated that included information such as the name of the first author, publication year, the geography of the study where it was conducted, the design of the study, the total number of patients, and the Preferred Reporting Standard of Systematic Reviews and Meta-Analysis (PRISMA) flowchart and checklist were utilised to report the overall process of search, screening, data extraction, systematic review, and the meta-analysis conducted. to ensure scientific precision (Fig. 1).

2.5. Quality assessment

The quality assessment of the included study was independently done by two authors using two tools: Newcastle–Ottawa Scale (NOS) for cohort studies and the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) to assess the quality of evidence for the outcomes of interest. The Author solved any disagreement in their assessment. The overall risk of bias in individual studies was categorized as "low" (if all domains were at low risk of bias), "high" (if at least one domain was at high risk of bias, or if the majority of domains presented with unclear concerns that significantly lowered the confidence in the results), or "presenting with some concerns" (if one or more domains were at unclear risk of bias). The author's contributions in the methodology section have been summarised in Table 3.

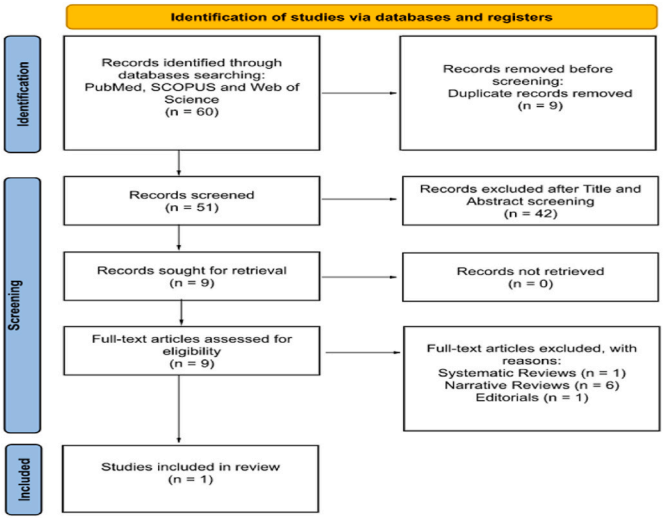

Fig. 1. PRISMA flow chart used for the selection of studies.

2.6. Summary measures and synthesis of results

It was predetermined to use Review Manager (RevMan, version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014)[8] to pool the data of an outcome with a high degree of similarity for quantitative analysis. The mean difference and 95% confidence interval (CI) were used for the continuous data. The statistical heterogeneity was intended to be tested using Tau^2 and I^2 statistics.[8] It was predetermined that the random-effect model would be used if the I^2 was more than 50%. It was planned to use a detailed narrative summary of the findings if there was considerable clinical and methodological heterogeneity across the included studies.

3. Results

3.1. Eligible studies/Study selection

Fig. 1 depicts the PRISMA flow chart used for the selection of studies. The systematic search yielded 51 articles after removing 9 duplicates. After the title abstract screening, 9 articles were eligible for full-text screening. In the full-text screening, 8 articles were excluded due to wrong outcomes, wrong study design, and an incorrect patient population. Finally, 1 study was found eligible for data extraction.

3.2. Study characteristics

The included study by Jun-Jun Yeh et al[9] is a retrospective cohort study that aimed to investigate the effect of colchicine use on the risk of stroke among patients with diabetes mellitus. The study was conducted between 2000 and 2013 and enrolled a total of 17,522 patients with

Table 3
Author's contribution summary.

Authors' Contributions	Authors
Title Abstract Screening	US & TB
Full-text Screening & Data Extraction	US & TB
Resolution of Contradictions in Data Extraction	US, TB, and SG
Quality Assessment of Included Studies	US & TB with SG resolving discrepancies

diabetes mellitus from the Longitudinal Health Insurance Database. The patients were divided into a colchicine cohort (n = 8761) and a non-colchicine cohort (n = 8761) using propensity score matching (PSM).

3.3. Results of individual studies

Table 4 summarises the results and parameters of the individual study.

3.4. Risk of bias

The quality assessment of the findings of the included study is summarised in Tables 5 and 6.

Based on the NOS assessment, the study appears to have a "low" risk of bias, with most of the domains receiving the maximum number of stars. However, as with any assessment tool, this is a rough adaptation of the Newcastle–Ottawa Scale (NOS) for cohort studies, and a more detailed assessment may uncover additional sources of bias.[10]

Using the GRADE tool, the quality of the retrospective cohort study was considered to be "moderate".[11]

The use of both the NOS and GRADE allowed for a comprehensive assessment of the risk of bias in the included primary study and the quality of evidence across studies.

4. Discussion

Hemorrhagic stroke is a medical emergency, which makes up approximately 10%–20% of all instances of strokes and has a mortality rate of 35%–52% within 30 days.[12] It results in increased mortality and morbidity as compared to ischemic stroke, whose prevalence is higher. It includes two subtypes: intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH). Following a hemorrhagic stroke, brain injury can lead to neural function impairments. The mechanisms that contribute to brain injury are related to several factors, including inflammation, apoptosis, oxidative stress, mitochondrial dysfunction, and blood–brain barrier disruption. Research has suggested that neuroinflammation plays a key role in causing brain injury.[13]

The most important etiological agent that accounts for 60% of the cases is Chronic hypertension.[14] Other causes include Cerebral amyloid angiopathy, Inherited bleeding diathesis, use of Antithrombotic agents, Vascular malformations, Aneurysms, Primary brain tumors and Metastatic tumors.[12] The current treatment options are, Managing hyperglycemia associated with stroke, using hypothermia to decrease cerebral edema and intracranial pressure (ICP), using mannitol to reduce ICP, controlling blood pressure, anti-inflammatory therapy.[2,12,15]

Although the effectiveness of these treatment methods in preventing hemorrhagic stroke has been demonstrated, patients who receive high doses of established secondary preventive medications still face a significant risk of stroke, intracranial haemorrhage, coronary events, and vascular death. There is increasing evidence indicating that inflammation plays a crucial role in the pathophysiology of atherosclerosis and thromboembolism. Inflammatory cells participate in all stages of the development of atherosclerotic plaque. Thus, therapies that target the inflammation of these plaques, such as anti-inflammatory treatments, could be significant contributors to plaque stabilization and the prevention of thromboembolic events.[16]

Colchicine is an anti-inflammatory medication that works primarily by blocking several processes, including neutrophil chemotaxis, adhesion, and mobilization, as well as the production of superoxide. It also inhibits NALP3 inflammasomes and interleukin (IL)1β.[17]

Its mode of action in hemorrhagic stroke is still a subject of active research because it is not well understood. Colchicine, however, is thought to have a number of potential mechanisms of action that could support its therapeutic effects in this condition. Its anti-inflammatory properties are one potential mode of action. Inflammasome activation and the release of pro-inflammatory cytokines like interleukin-1 beta and interleukin-18 have both been shown to be inhibited by colchicine.[18] It is well known that inflammatory processes contribute to the pathophysiology of hemorrhagic stroke and that reducing inflammation may lead to better outcomes.

Microtubule polymerization inhibition is one more potential mechanism of action. Cellular functions like cell division, intracellular transport, and cellular shape depend heavily on microtubules.[19] In the case of hemorrhagic stroke, inhibition of microtubule polymerization may be able to lessen oxidative stress and neuronal damage. Colchicine has also been demonstrated to have antiplatelet effects by preventing

Table 5
Summary of risk of bias assessment for randomized studies using the Newcastle–Ottawa Scale for cohort studies (**Total Stars: 9 out of a possible 9**).

	Component	Stars
Study Name: Jun–Jun Yeh et al 2022	Selection	
	Representativeness of the exposed cohort	1
	Selection of the non-exposed cohort	1
	Ascertainment of exposure	1
	Demonstration that outcome of interest was not present at the start of the study, OR baseline assessment	1
	Comparability	
	Adjustment for confounding	2
	Outcome	
	Assessment of outcome	1
	Was follow-up long enough for outcomes to occur?	1
	Adequacy of follow-up of cohorts	1
	Total	9

Table 6
Quality of evidence for non-randomized studies using GRADE tool.

Component	Assessment
Study design	Moderate (retrospective cohort study)
Risk of bias	Low
Inconsistency	Not significant
Indirectness	Direct
Imprecision	Not significant
Publication bias	Cannot assess

Table 4
Summary of the retrospective cohort.

Study	Intervention group	Control group	Overall duration of treatment	Primary outcomes	Other reported outcomes
Jun–Jun Yeh et al 2022[7]	The colchicine cohort consists of patients with diabetes mellitus who received colchicine treatment.	The non-colchicine cohort consisted of patients with diabetes mellitus who did not receive colchicine treatment.	The duration of treatment varied depending on the patient's use of colchicine. The study analysed the effects of colchicine use with a cumulative daily defined dose (cDDD) of >14 and duration of >28 days, as well as with a cDDD of >150 and a duration of >360 days.	The primary outcome was the incidence of stroke, including ischemic stroke and hemorrhagic stroke, between the colchicine cohort and the non-colchicine cohort.	The study also analysed the incidence of stroke, ischemic stroke, and hemorrhagic stroke in patients who received different durations and doses of colchicine treatment. The subdistribution hazard model was used to examine the competing risk.

platelet activation and aggregation, which may help patients with hemorrhagic stroke avoid rebleeding.[20]

These potential effects imply that colchicine may be therapeutically useful in hemorrhagic stroke, despite the fact that the precise mechanisms of action of this drug in this condition are not fully understood [Fig. 2]. To fully understand the mechanisms of action and to determine the safety and effectiveness of colchicine in hemorrhagic stroke, more research is required.

5. Result interpretation

Only one study by Jun–Jun Yeh et al met the inclusion criteria for the systematic review, which looked into the use of colchicine in hemorrhagic stroke. The study's findings suggested that taking colchicine may reduce the risk of hemorrhagic stroke in people with diabetes. The colchicine cohort, in particular, had a significantly lower incidence of hemorrhagic stroke than the non-colchicine cohort, as evidenced by an adjusted hazard ratio of 0.66 with a 95% confidence interval of 0.53–0.82. However, the subdistribution hazard model analysis revealed that the effect of colchicine on hemorrhagic stroke may be dependent on the patient's underlying condition. Colchicine, in particular, was not linked to hemorrhagic stroke in diabetics without gout.

The study found that the colchicine cohort had a significantly lower incidence of stroke, ischemic stroke, and hemorrhagic stroke compared with the non-colchicine cohort. It also found that colchicine uses with cumulative daily defined dose (cDDD) $>$ 14 and duration $>$28 days was associated with a lower risk of stroke and ischemic stroke, and colchicine use with cDDD $>$150 and duration $>$360 days played an auxiliary role in the prevention of stroke, ischemic stroke, and hemorrhagic stroke in patients with DM. However, the study found that colchicine was not associated with hemorrhagic stroke in DM patients without gout.[9]

Colchicine is commonly used for the secondary prevention and therapy of acute gout and Familial Mediterranean fever, and it is well-tolerated and efficacious. It has recently been shown to be effective in the treatment of various cardiovascular diseases like atrial fibrillation, Acute coronary syndrome, pericarditis and Coronary artery disease.[3]

Nevertheless, the quantity and quality of data supporting the efficacy of colchicine for stroke prophylaxis are debatable.

The (COLCOT) Colchicine Cardiovascular Outcome Trial was conducted where patients who had experienced a heart attack within the last 30 days were recruited for a randomized, placebo-controlled, investigator-initiated, double-blind trial. 4745 patients were randomly assigned to receive either a low dose of colchicine or a placebo. In these patients, the use of a 0.5 mg daily dose of colchicine resulted in a significantly reduced risk of ischemic cardiovascular events compared to those who received a placebo. The occurrence of a primary end-point event was observed in 5.5% of the patients who received colchicine, while it was found in 7.1% of those who received a placebo, hence it was considerably lower in patients who consumed low-dose Colchicine. Moreover, low-dose colchicine was found to decrease the occurrence of the primary outcome measure, which was a combination of cardiovascular death, stroke, resuscitated cardiac arrest, myocardial infarction, or urgent admission to the hospital for angina that required coronary revascularization.[21]

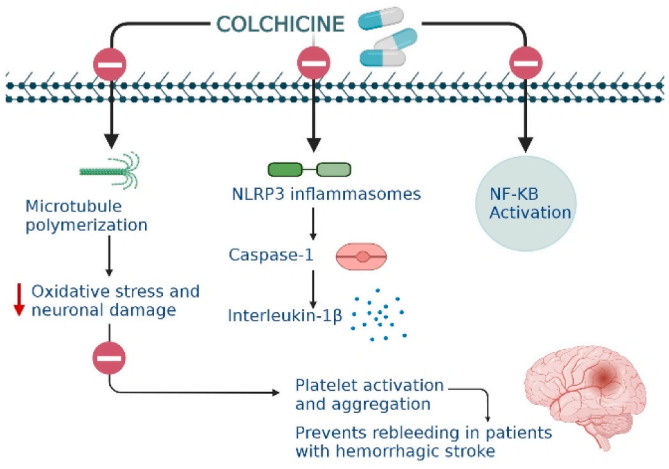

Fig. 2. Potential mechanism of action of colchine in treating hemorrhagic stroke.

In a similar study, the LoDoCo (Low Dose Colchicine) pilot trial was conducted on 532 patients. The aim of this study was to validate that the daily use of 0.5 mg colchicine is both safe and effective for the purpose of preventing the recurrence of cardiovascular events. It utilized a prospective randomized observer-blinded endpoint (PROBE) design, it was observed that the use of low-dose colchicine in combination with statins and anti-platelet therapy was both safe and effective in reducing the risk of cardiovascular events in patients with stable coronary disease. The results revealed that the group that received colchicine had a significant decrease in the occurrence of the primary endpoint.[22]

In the CANTOS trial, which is considered the standard model, the use of the anti-IL-1β monoclonal antibody canakinumab to inhibit the NOD-like receptor protein 3 inflammasome resulted in a reduction in the occurrence of cardiovascular events in patients with high levels of high-sensitivity C-reactive protein. Additionally, there was evidence suggesting that the risk of stroke may have been reduced by 30%.[23] A meta-analysis that combined data from four randomized controlled trials (RCTs), with a total of 11,594 patients, was conducted. These RCTs focused on populations with either stable coronary artery disease or acute coronary syndrome and compared the use of colchicine to a placebo. The results showed that colchicine was significantly associated with a reduction in the incidence of the primary composite endpoint and a considerably reduced risk of stroke.[24]

Currently, there are multiple clinical trials underway to evaluate the efficacy of colchicine in preventing vascular events following a stroke or transient ischemic attack (TIA). The goal of the CONVINCE trial is to offer high-quality randomized data that can demonstrate the effectiveness and safety of using colchicine as an anti-inflammatory therapy for secondary prevention after a stroke.[25]

5.1. Similar studies

To date, no review has been performed which has looked into the use of colchicine in hemorrhagic stroke. However, there have been several systematic reviews on the use of colchicine in ischemic stroke.[16,26,27] These reviews have examined the effectiveness of colchicine in reducing the risk of recurrent ischemic stroke and improving outcomes in patients with acute ischemic stroke. Despite the positive findings from these reviews, there remains a gap in the literature regarding the use of colchicine in hemorrhagic stroke, which is a different type of stroke with distinct pathophysiological mechanisms. Therefore, there is a need for a systematic review that specifically examines the use of colchicine in hemorrhagic stroke.

5.2. Strengths and limitations

This systematic review's strength is that it includes only one primary study which studied the effects of colchicine use on hemorrhagic stroke patients based on their propensity scores for a long time: 5.24 ± 3.42 years in the colchicine use cohort and 4.39 ± 3.34 years in the non-colchicine use cohort. As a result, even if the evidence is limited, it can help to synthesise the available evidence on the use of colchicine in hemorrhagic stroke. This can help to inform clinical practice and identify areas for further research.

Nevertheless, this systematic review has a number of drawbacks:

Limited generalizability: Because the study sample was so small (n = 17,522) and the cohort treated with colchicine had diabetes Mellitus, it's

possible that the findings won't apply to other populations.

Potential bias: The methodology, design, or analysis of the study could be biased, which would have an impact on the reliability of the findings.

Lack of precision: The small sample size or the insufficient statistical power may limit the results' precision.

Publication bias: Given that this was the only primary study that was available and that its findings were favourable, there may be a risk of publication bias.

Potential for errors: Because this systematic review is based solely on one primary study, it is more prone to errors and has fewer data sources and perspectives to draw upon.

Overall, when making clinical judgments or recommendations, this study should be interpreted cautiously and taken into account alongside other evidence.

6. Conclusion and future prospects

Although colchicine has been used as a therapeutic substance for a long time, its potential benefits have only been actively studied recently. This is because of its various effects on inflammatory cells, its systemic impact, and its mild side–effect profile at recommended dosages, making it useful for certain types of cardiovascular disease and other common ailments. The findings of the research suggest that colchicine can be beneficial for patients with hemorrhagic stroke by reducing inflammation and improving neurological outcomes.

This implies that colchicine could be a potential treatment option for hemorrhagic stroke with long-lasting benefits. Additionally, there is a requirement to develop a safe, effective, well-tolerated, and affordable treatment for preventing hemorrhagic stroke.

More ongoing research and clinical trials are expected to provide insight into how colchicine works, how it can be used in hemorrhagic stroke as well as a treatment for other neuroinflammatory disorders and to confirm its tolerability and benefits, thereby enhancing its historical significance.

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Ethical statement

Ethical review is not applicable to this study since it used data available in published literature.

CRediT authorship contribution statement

Mrinmoy Kundu: Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Shankhaneel Ghosh:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Anagha Shree:** Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Project administration, Methodology. **Tanvi Banjan:** Writing – original draft, Visualization, Project administration, Methodology, Data curation. **Biki Kumar Sah:** Writing – review & editing, Writing – original draft, Visualization, Methodology. **Usama Sakrani:** Writing – review & editing, Writing – original draft, Visualization. **Tariq Janjua:** Writing – review & editing, Conceptualization. **Luis Rafael Moscote Salazar:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

ICH: Intracerebral Haemorrhage
SAH: Subarachnoid Haemorrhage
IL-6: Interleukin-6
IL-1beta: Interleukin-1beta
IL-18: Interleukin-18
NLRP3: Nucleotide-binding Oligomerization Domain-, Leucine-rich Repeat-, and Pyrin Domain-containing Protein 3
PICO: Population, Intervention, Comparison, Outcome
PROSPERO: International Prospective Register of Systematic Reviews
cDDD: Cumulative Daily Defined Dose
NOS: Newcastle–Ottawa Scale
GRADE: Grading of Recommendations, Assessment, Development, and Evaluations
PRISMA: Preferred Reporting Standard of Systematic Reviews and Meta-Analysis
RCT: Randomized Controlled Trial
TIA: Transient Ischemic Attack