Systematic Review & Meta-Analysis

EFFECTS OF MINOCYCLINE AS A NEUROPROTECTIVE AGENT FOR STROKE ON MMP-9 LEVELS, FUNCTIONAL OUTCOME, AND MORTALITY

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ABSTRACT

Stroke is the most common and devastating cerebrovascular disease. Numerous neuroprotective medications, such as scale and minocycline, have been developed to help the recovery and regeneration of the nervous system post-stroke. However, the efficacy of minocycline remains unclear. The systematic review and meta-analysis were conducted to summarize the effects of minocycline in stroke treatment. This systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO), with registration number CRD42023485168. The quality of the eligible studies was assessed using the Jadad scale. This systematic review included three ischemic stroke trials, seven intracerebral hemorrhage trials, and one study on acute stroke. There was a significant correlation between minocycline intervention and stroke severity according to the National Institute of Health Stroke Scale (NIHSS), with a pooled mean difference (MD) of -1.92, a 95% confidence interval (CI) of -3.39 to -0.45, and a p-value of 0.01. In the ischemic stroke subgroup, the modified Rankin scale (mRS) was significantly lower in the minocycline treatment group compared to that of the control group (MD=-0.89, 95% CI: [-1.54, -0.25], p=0.007). Additionally, matrix metalloproteinase-9 (MMP-9) levels for the intracerebral hemorrhage subgroup were significantly lower in the minocycline treatment group compared to those of the control group (MD = -19.93, 95% CI: [-36.9, -2.96], p=0.02). The analysis revealed that minocycline intervention was not significantly correlated with hematoma volume, mortality, or stroke recurrence. These findings indicate that minocycline supplementation is a potential intervention strategy for treating ischemic stroke and intracerebral hemorrhage.

Keywords: Minocycline; neuroprotective agent; stroke; good health and well-being

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Highlights:
1. As minocycline plays an important role in stroke microglia activation and iron chelation, it is important to further analyze its effects on stroke treatment.
2. This meta-analysis revealed a significant effect of minocycline therapy, as evidenced by improved functional outcomes and inhibited matrix metalloproteinase-9 (MMP-9) activity.
3. Minocycline does not significantly affect hematoma volume, mortality, or recurrence stroke rate.

INTRODUCTION

Stroke is the most common cerebrovascular disease, with a high rate of mortality and morbidity. By 2030, we expect the global incidence of ischemic stroke to rise to 89.32 per 100,000 people. On a worldwide scale, previous studies indicate that interventions should focus on Asian and African nations with low-income levels (Saini et al. 2021, Pu et al. 2023). Neuroprotective agents have the potential to slow down or even halt the progression of the damaging process after a stroke attack, significantly improving

the quality of life for affected individuals. Patients receive these substances to preserve, recover, and regenerate their nervous systems by disrupting the stroke cascade.

For a long time, tetracycline has offered promising effects for stroke patients. Two well-known derivates of tetracycline are doxycycline and minocycline. However, recent studies have revealed that minocycline has more efficacy as a neuroprotective chemical than doxycycline. Minocycline has been found to be able to inhibit the activation of microglia, which plays an active part in brain inflammation and degeneration (Yrjänheikki et al. 1998). In addition, prior research conducted by Modheji et al. (2016) has found that minocycline carries a higher capacity to inhibit MMP-9 activity compared to tetracycline and doxycycline. Minocycline has multiple mechanisms of action, including anti-inflammatory and anti-apoptotic, which contribute to its appeal as a neuroprotective agent. Aside from that, minocycline demonstrates activity in multiple acute and chronic animal models of neurological diseases. Its efficacy has been demonstrated in preclinical models for the treatment of hypoxic-ischemic encephalopathy, cognitive disorder, multiple sclerosis, neuropathic pain, stroke, and hypomyelination (Hurkacz et al. 2021). Despite multiple preclinical trials producing encouraging data for minocycline, successful bench-to-bedside translations remain lacking. A multitude of studies have been published within the past ten years. Thus, we conducted this systematic review and meta-analysis to synthesize the treatment effects of minocycline in cerebral ischemic and hemorrhagic strokes.

MATERIALS AND METHODS

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42023485168. The search strategy for this systematic review was arranged according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (Sohrabi et al. 2021). We searched for relevant studies on multiple databases, i.e., PubMed, ScienceDirect, Sage Journals, Taylor & Francis, Google Scholar, and ClinicalTrials.gov.

We used a set of inclusion criteria to determine the eligibility of the studies. The inclusion criteria were as follows: (i) the availability of full texts in English; (ii) randomized-controlled studies comparing oral or intravenous minocycline with either placebo or standard stroke treatment; (iii) the inclusion of patients diagnosed with acute ischemic or hemorrhagic stroke; and (iv) the presence of at least one of the following outcomes: functional outcome measured by the modified Rankin Scale (mRS), National Institutes of Health Stroke Scale (NIHSS), Glasgow Coma Scale (GCS), or Barthel index; mortality rate; recurrence rate; or serum matrix metalloproteinase-9 (MMP-9) level. The exclusion criteria were: (i) nonrandomized-controlled studies such as case reports, cohort studies, literature reviews, or meta-analyses; (ii) the unavailability of full texts in English; (iii) the unavailability of original data or abstracts; (iv) animal studies; and (v) duplicate records (Bramer et al. 2018).

The evaluators selected articles for this systematic review by removing duplicates, screening titles and abstracts, and assessing full texts according to the inclusion criteria. Disagreements were resolved through discussion. We extracted author name(s), publication date, study design, total number of patients, age, sex, patient diagnosis, dosage and duration of minocycline treatment, control intervention, outcome, and adverse event (Sohrabi et al. 2021). We used Review Manager for Mac, version 5.4.1 for conducting the statistical analysis. Continuous data were used to analyze MMP-9 levels and functional outcomes, whereas dichotomous data were examined to determine side effects and mortality rates. The heterogeneity of the literature data was tested using I^2. A result with a value of $p<0.05$ was considered statistically significant. The quality of the articles was assessed using the Jadad scale (Casy et al. 2022).

RESULTS

Table 1 provides the summarized baseline characteristics of the studies. On the initial search, we collected a total of 1,650 studies. After sorting, eleven studies were categorized as eligible and thus included in this systematic review. The eleven studies were as follows: three studies on hemorrhagic stroke conducted by Chang et al. (2017), Fouda et al. (2017), and Strickland et al. (2022); seven studies on ischemic stroke carried out by Lampl et al. (2007), Switzer et al. (2011), Srivastava et al. (2012), Amiri-Nikpour et al. (2015), Shamsaei & Mohammadi (2017), Mehta et al. (2019), and Singh et al. (2019) and one study on acute stroke reported by (Kohler et al. 2013).

The results of the analysis are gathered in Table 2. Furthermore, Figure 2 displays the forest plots for studies related to NIHSS, mRS, and the Barthel index. The forest plot for NIHSS included eight studies. The analysis showed the presence of heterogeneity among the studies, with an I^2 value of >50%. There was a significant association between minocycline intervention and NIHSS, with a pooled mean difference (MD) of -1.92, a 95% confidence

interval (CI) of -3.39 to -0.45, and a value of p=0.01.

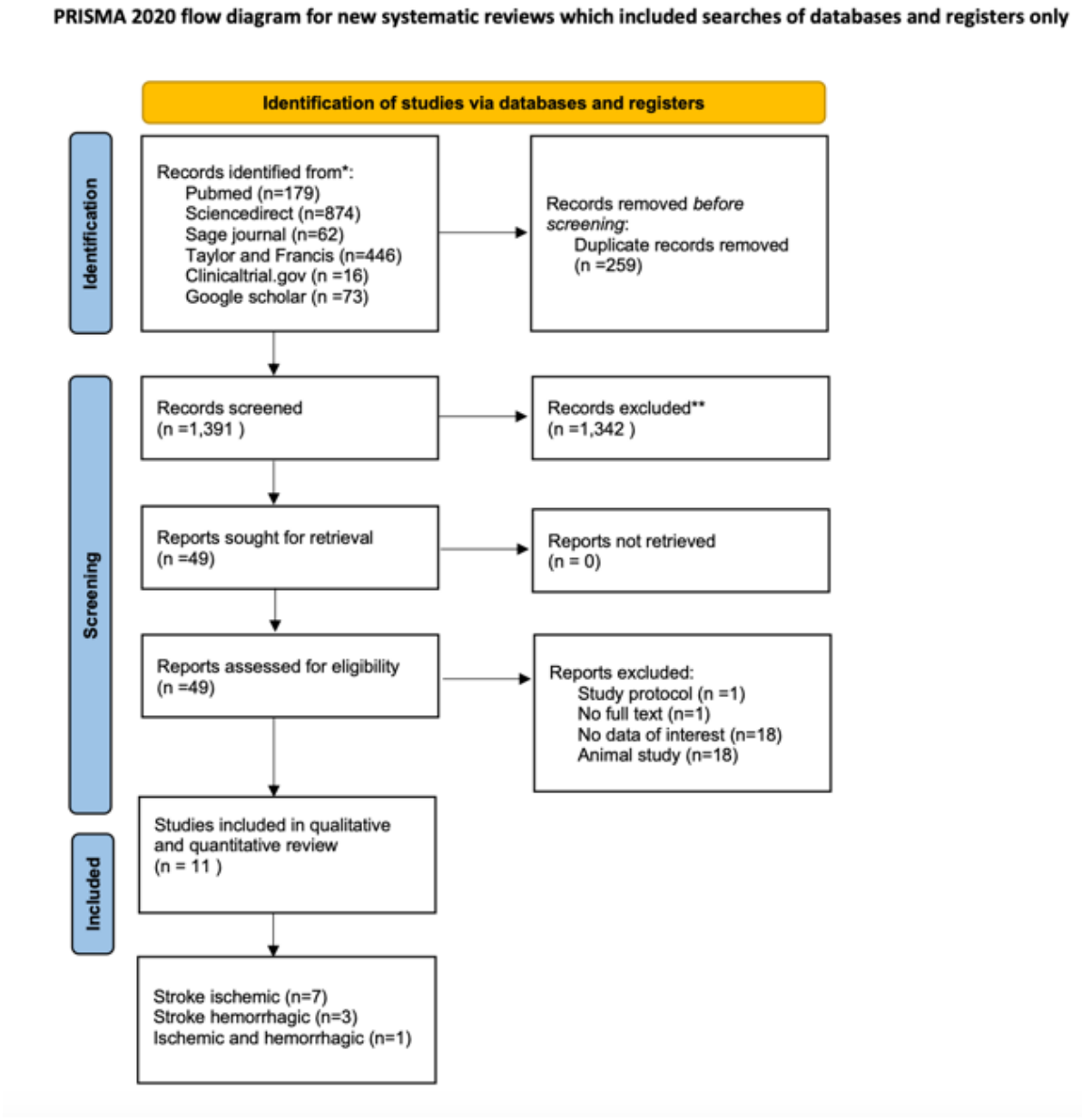


Figure 1. PRISMA flow diagram for the selected studies.

Table 1. Summary of the baseline characteristics of the selected studies.

No	Author, year	Country	Study design	Total patients	Age (y.o.)	Sex (M/F)	Diagnosis	Drug dosage	Comparison	Extracted outcome	Side effect	Jadad score
Hemorrhagic stroke												
1.	Chang et al. (2017)	USA	Multicenter, double-blind, and placebo-controlled.	M:10 P:10	57 (13)	55% M	Intracerebral hemorrhage with volume of <30 cc, <12 hours.	Intravenous administration of 10 mg/kg bw (maximum: 700 mg daily) of minocycline mixed in 500 mL of normal saline solution over 2 hours for 5 days.	Placebo	MMP-9 levels, mRS, NIHSS, Barthel index, depression and suicide questionnaire results, hematoma volume, edema volume, mortality.	N/A	8
2.	Fouda et al. (2017)	USA	Single-site, randomized controlled trial.	M:8 P:8	61.9 (12.7)	4/12	Acute cerebral hemorrhage within 24 hours.	Daily intravenous administration of 400 mg of open-label minocycline, followed by an oral dose of 400 mg for 4 days.	No minocycline	MMP-9, IL-6, and ferritin levels, mRS; NIHSS, GCS, hematoma volume, Hemphill scores.	Bihemispheric embolic strokes occurred after a week, leading to herniation and mortality that were not related to the medication studied.	8
3.	Strickland et al. (2022)	USA	Double-blind, randomized controlled trial.	M:6 P:5	M: 52.6 (44–66) P: 59.2 (54–68)	4/7	Imaging-confirmed aneurysmal subarachnoid hemorrhage.	Intravenous administration of 10 mg/kg bw (maximum: 700 mg daily) of minocycline mixed in 500	Normal saline (500 mL).	MMP-9 levels measured by OD .	N/A	8

								mL of normal saline solution over 2 hours for 4 days.				
Ischemic stroke												
1.	Lampl et al. (2007)	Israel	Open-label, evaluator-blinded study.	M: 74 P: 77	Minocycline: 67.2±11.1 Placebo: 66.2±11.1	35.1% F	Ischemic stroke with an onset of 0–6 hours.	Daily dose of oral minocycline at 200 mg for 5 days.	Placebo	NIHSS, mRS, Barthel index, death, recurrent stroke, hemorrhage transformation.	N/A	8
2.	Switzer et al. (2011)	USA	Nonrandomized, dose-escalation trial.	M: 60 P: 44	Minocycline: 65.0 (13.7), Controls: 61.8 (13.9)	Minocycline: 53% M Controls: 57% M	Ischemic stroke with an onset of 0–6 hours.	Intravenous minocycline at doses of 3, 4.5, 6, 10 mg/kg bw.	No minocycline	NIHSS, hemorrhage transformation.	N/A	8
3.	Srivastava et al. (2012)	India	Single blind, placebo-controlled trial.	M: 23 P: 27	Minocycline 52.7 (15.3), Controls: 57 (14.2)	31/19	First ischemic stroke with an onset of 6–24 hours.	Minocycline capsule at 200 mg per day.	Standard care	NIHSS, Barthel index.	There were no mortality, myocardial infarctions, recurrent strokes, or hemorrhagic transformations in treatment and control groups.	8
4.	Singh et al. (2019)	Singapore	Multicenter, randomized, double-blind, placebo-controlled trial	M: 69 P: 70	62 [range 19–88]	73.4% M	Ischemic stroke, with 3–48 hours of symptom onset	Daily dose of oral minocycline at 200 mg for 5 days	Placebo	mRS, NIHSS, Barthel index, mortality, recurrent stroke, myocardial infarction	N/A	8
5.	Amiri-	Iran	Single-site,	Total:	65.89 (8.35)	25/28	Ischemic	Oral	Aspirin only	NIHSS at 30	N/A	8

	Nikpour et al. (2015)		randomized controlled trial	53			stroke, 6-24 hours	minocycline at 200 mg once daily as an adjunct to aspirin for 5 days		days, 60 days, and 90 days		
6.	Mehta et al. (2019)	India	Prospective, single center, single-blind, and hospital-based study	20 patients in each group	Minocycline: 58.8 Citicoline: 59.5 Edaravone: 57.3 Cerebrolysin: 61.9 Placebo: 64.9	59/41	Acute ischemic stroke affecting the middle cerebral artery (MCA) territory	200 mg/day administered per oral	Aspirin, supportive care, 500 mg of intravenous citicoline twice for 6 weeks, 30 mg of edaravone administered twice over 60 minutes for 14 days, and 30 mL of intravenous cerebrolysin infusion diluted in 100 mL of saline administered over 60 minutes for 10 days	NIHSS, Barthel index, and mortality data	N/A	8
7.	Shamsaei & Mohammadi (2017)	Iran	Double-blind, randomized controlled trial	18 patients in each group	Minocycline: 69±10.3 Placebo: 68±10.3	15/21	Ischemic stroke, 24 hours	Daily dose of oral minocycline at 200 mg for 5 days	Placebo	NIHSS	N/A	8

Mixed diagnosis

1.	Kohler et al. (2013)	Australia	Multicenter, prospective, randomized, open-label, blinded,	M: 47 P: 48	Minocycline: 67.7 (11.0) No minocycline: 67.9 (16.3	47/48	Acute ischemic and hemorrhagic stroke, 6–24 hours	Intravenous administration of 100 mg of minocycline within 24 hours of stroke onset and continued every 12 hours for 3 days	No minocycline ne	mRS, NIHSS, Barthel index, recurrent stroke, creatinine, ALT, mortality	N/A	8

Legends: M=minocycline; P=placebo; OD=optical density; MMP-9=matrix metalloproteinase-9; mRS=modified Rankin Scale; NIHSS=National Institute of Health Stroke Scale; IL-6=interleukin 6; GCS=Glasgow Coma Scale; ALT=alanine transaminase.

Table 2. Summary of the pooled analyses and heterogeneity tests.

Outcome	Pooled overall effect				Heterogeneity test		
	MD/OR/RR	Lower limit 95% CI	Upper limit 95% CI	Z-score (p)	df	I^2	p
NIHSS	MD: -1.92	-3.39	-0.45	2.57 (0.01)	7	84%	<0.00001
IS	MD: -2.25	-3.77	-0.74	2.91 (0.004)	5	85%	<0.00001
ICH	MD: 0.50	-1.71	2.7	0.44 (0.66)	1	0%	0.35
mRS	MD: -0.53	-1.26	0.19	1.45 (0.15)	3	89%	<0.00001
IS	MD: -0.89	-1.54	-0.25	2.72 (0.007)	1	76%	0.04
ICH	MD: -0.0	-0.26	0.26	0.03 (0.98)	1	0%	0.84
Good outcome	OR: 2.7	0.84	8.69	1.67 (0.10)	5	77%	0.0006
IS	OR: 3.13	0.75	13.11	1.56 (0.12)	3	86%	<0.0001
ICH	OR: 1.6	0.23	11.3	0.47 (0.64)	1	0%	0.67
Barthel index	MD: 2.07	-9.41	13.56	0.35 (0.72)	4	93%	<000001
IS	MD: 3.54	-12.26	19.34	0.44 (0.66)	3	92%	<0.00001
ICH	MD: -3.47	-6.25	-0.69	2.44 (0.01)	N/A	N/A	N/A
Hematoma volume	MD: -0.64	-10.13	8.84	0.13 (0.89)	1	17%	0.27
Mortality	OR: 1.28	0.34	4.88	0.36 (0.72)	2	0%	0.89
Recurrent stroke	OR: 0.6	0.23	1.53	1.08 (0.28)	2	0%	0.81
MMP-9 levels	MD: -8.83	-33.29	15.62	0.71 (0.48)	2	52%	0.12
IS	MD: 11.30	-14.15	36.75	0.87 (0.38)	N/A	N/A	N/A
ICH	MD: -19.93	-36.9	-2.96	2.3 (0.02)	1	0%	0.69

Legends: MD=mean difference; OR=odds ratio; RR=relative risk; CI=confidence interval; df= degrees of freedom; IS=ischemic stroke; ICH= intracerebral hemorrhage; MMP-9=matrix metalloproteinase-9.

The forest plot for mRS incorporated four studies, which exhibited heterogeneity with an I^2 value of >50%. There was a significant association between minocycline intervention and the degree of functional outcome according to the mRS (pooled MD=-0.53, 95% CI=-1.26 to 0.19, p=0.15).

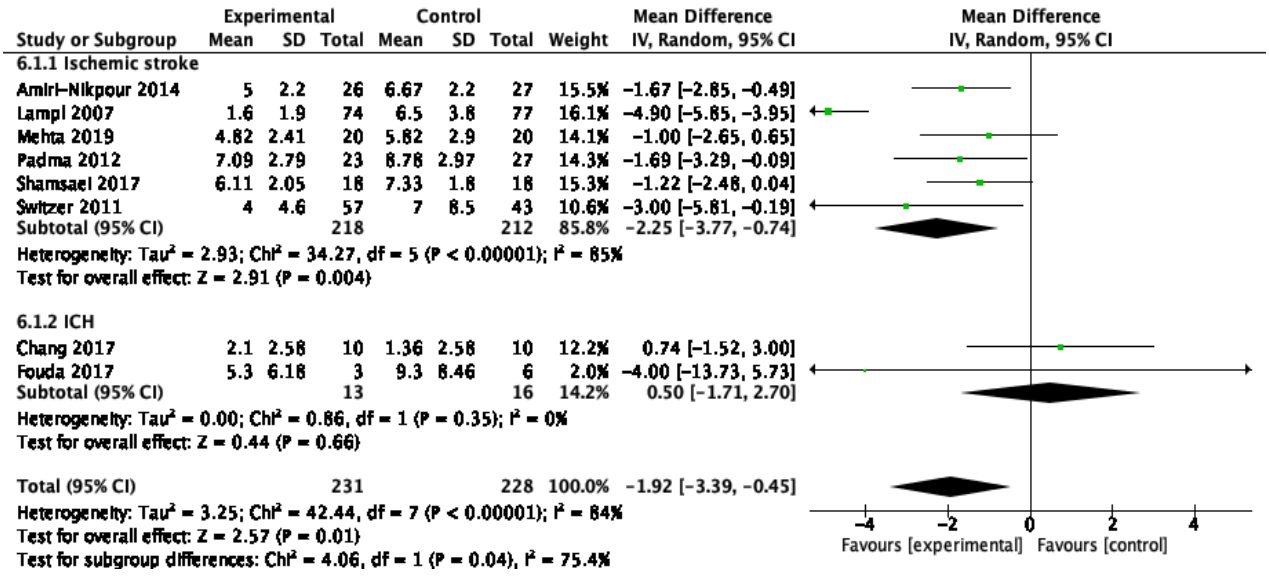
There were six studies in the forest plot for a favorable outcome, which was indicated by an mRS score of less than 2. The forest plot showed heterogeneity among the studies, with an I^2 value greater than 50%. No significant odds ratio was observed between minocycline intervention and favorable outcome according to the mRS (pooled OR=2.71, 95% CI=0.84 to 8.69, p=0.10).

In the forest plot for the Barthel index, five studies were featured. Heterogeneity was seen among the studies, with an I^2 value of >50%. However, the forest plot did not demonstrate any significant association between minocycline intervention and the scores of the Barthel index assessment (pooled MD=2.07, 95% CI=-9.41 to 13.56, p=0.72).

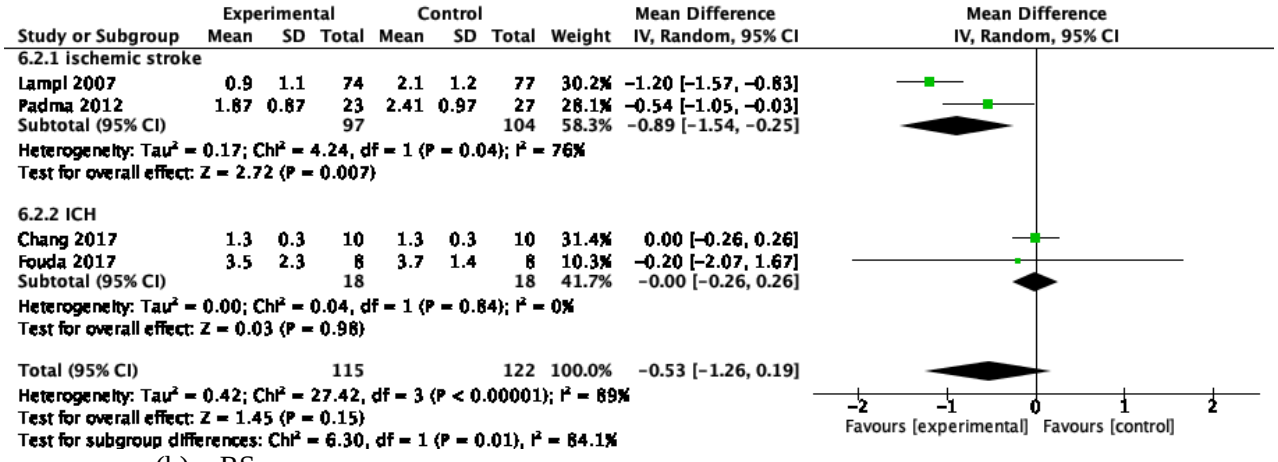
As displayed in Figure 3, the forest plot analysis for hematoma volume consisted of two studies. The two studies did not exhibit any heterogeneity, as indicated by an I^2 value of <50%. The analysis found no significant association between minocycline intervention and hematoma volume (pooled MD=-0.64, 95% CI=-10.13 to 8.84, p=0.89).

Figure 4 displays three studies in each forest plot for mortality and recurrent stroke. The studies did not show any heterogeneity, with an I^2 value of <50%. Additionally, no significant odds ratio was observed between minocycline intervention and mortality (pooled OR=1.28, 95% CI=0.34 to 4.88, p=0.72) as well as recurrent stroke (pooled OR=0.60, 95% CI=0.23 to 1.53, p=0.28).

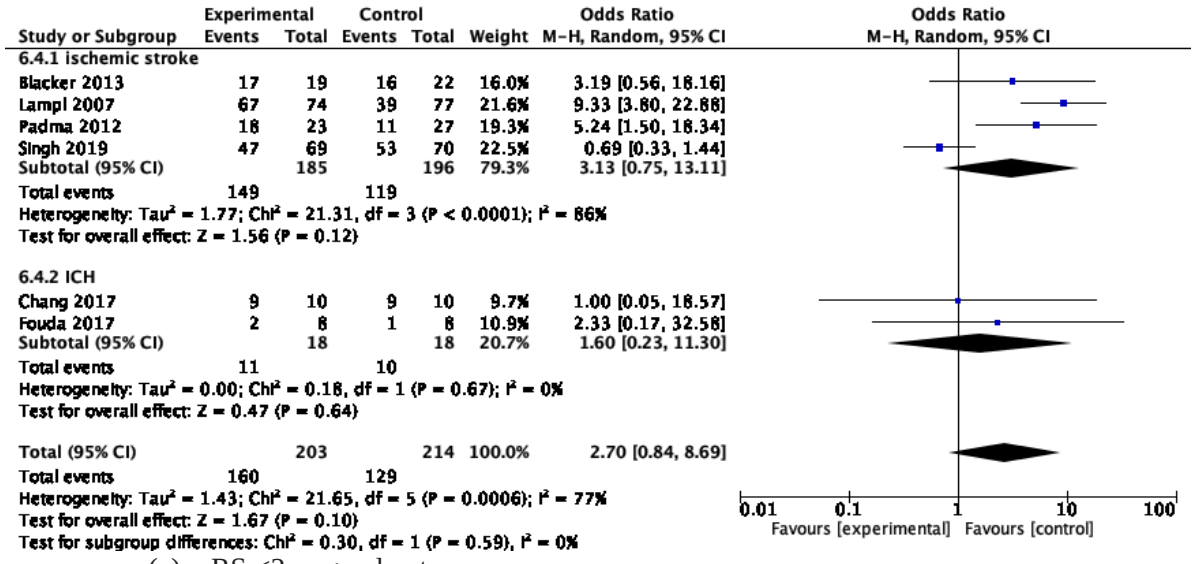
In Figure 5, the forest plot included three studies that examined MMP-9 levels. The three studies demonstrated heterogeneity, with an I^2 value of >50%. Nevertheless, there was no significant association between minocycline intervention and MMP-9 levels (pooled MD=-8.83, 95% CI=-33.29 to 15.62, p=0.48).



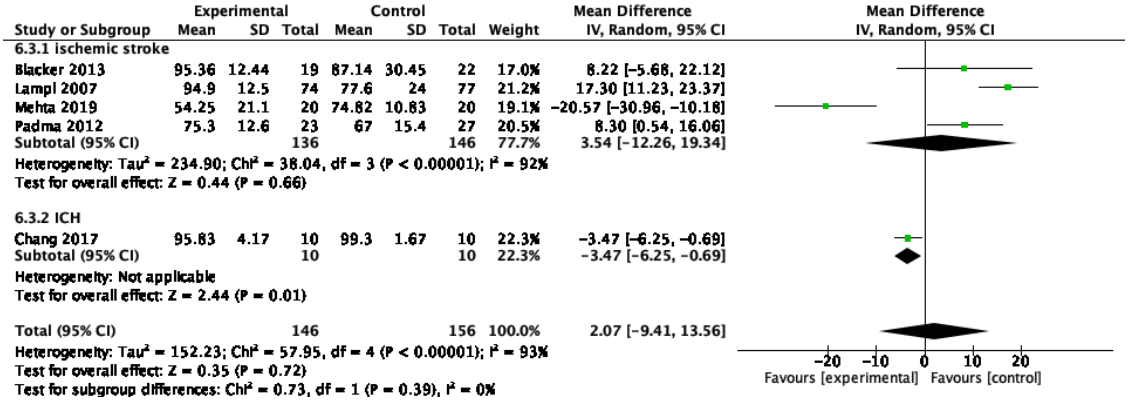
(a) NIHSS



(b) mRS



(c) mRS <2 or good outcome.



(d) Barthel index

Figure 2. Forest plots showing the analysis results for (a) NIHSS, (b) mRS, (c) good outcome indicated by mRS below 2, and (d) Barthel index.

Subgroup analyses of studies related to ischemic stroke

We divided several studies with a focus on ischemic stroke into different subgroups to better analyze the administration of minocycline among ischemic stroke patients. The subgroup analysis of six studies revealed a significant association between minocycline intervention and NIHSS (MD=-2.25, 95% CI=-3.77 to -0.74, p=0.004).

In addition, we analyzed another subgroup consisting of two studies that examined the mRS of ischemic stroke patients. The analysis revealed a significant association between minocycline intervention and mRS among ischemic stroke patients (MD=-0.89, 95% CI=-1.54 to -0.25, p=0.007).

The third subgroup analysis included four studies that examined favorable outcomes measured using mRS. The subgroup analysis revealed no significant association between minocycline intervention and favorable outcomes according to mRS among ischemic stroke patients (OR=3.13, 95% CI=0.75 to 13.11, p=0.12).

In the subgroup analysis of two studies, we also found no significant association between minocycline intervention and the Barthel Index among ischemic stroke patients (MD=3.54, 95% CI=-12.26 to 19.34, p=0.66). Furthermore, the analysis did not reveal any significant association between minocycline intervention and MMP-9 levels among the ischemic stroke patients (MD=11.30, 95% CI=-14.15 to 36.75, p=0.38).

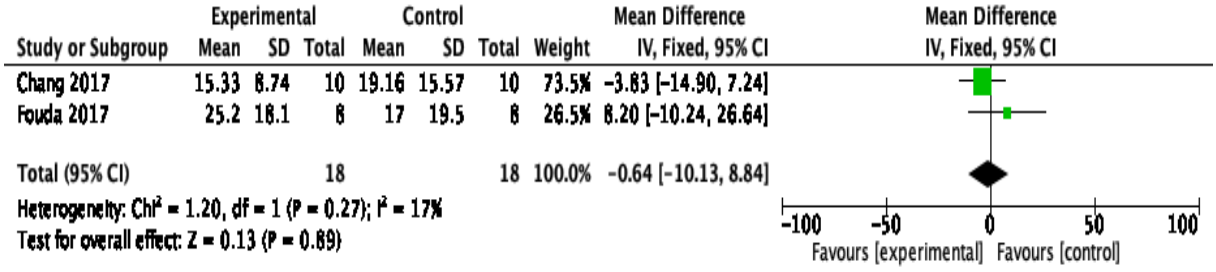
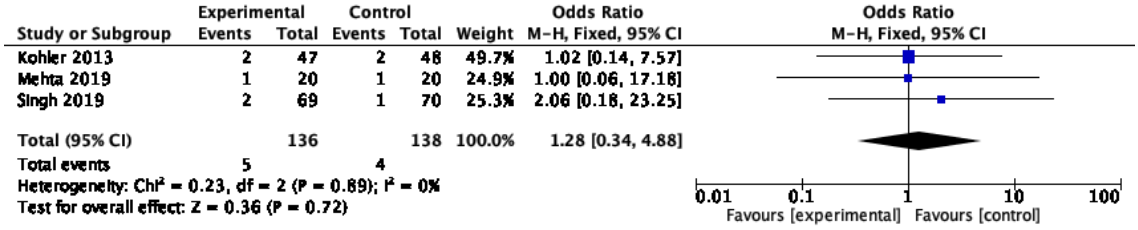
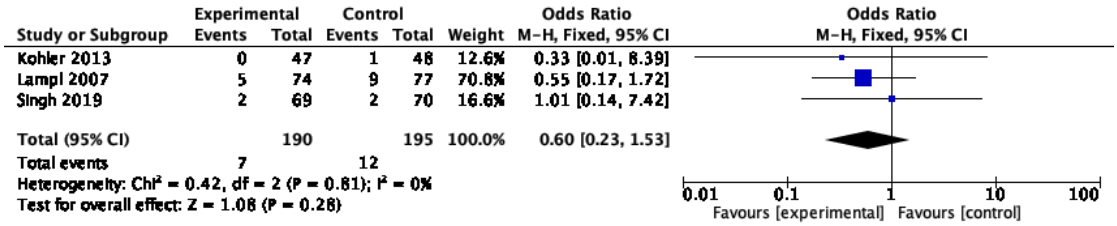


Figure 3. A forest plot for the analysis of hematoma volume.



(a) mortality



(b) reccurent stroke

Figure 4. Each forest plot showing the analysis results for (a) mortality and (b) recurrent stroke.

Subgroup analyses of intracerebral hemorrhage studies

In this systematic review, there were several subgroups of studies pertaining to intracerebral hemorrhage. Two studies revealed that minocycline intervention was not significantly associated with NIHSS among intracerebral hemorrhage patients (MD=0.5, 95% CI=-1.71 to 2.7, p=0.66). There was no heterogeneity between these studies, with an I^2 value of <50%.

We performed another subgroup analysis of two studies related to intracerebral hemorrhage. It was revealed that there was no significant association between minocycline intervention and mRS among patients with hemorrhagic stroke (MD=0, 95% CI=-0.26 to 0.26, p=0.98).

There were four studies in the subgroup analysis of minocycline intervention and there were favorable outcomes determined by mRS. We found no significant association between these two variables among hemorrhagic stroke patients (OR=1.6, 95% CI=0.23 to 11.3, p=0.64).

We analyzed a subgroup consisting of two studies on intracerebral hemorrhage. The analysis demonstrated a significant association between minocycline intervention and the Barthel index among intracerebral hemorrhage patients (MD=-3.47, 95% CI=-6.25 to -0.69, p=0.01).

Additionally, two studies examined MMP-9 levels among patients with intracerebral hemorrhage. The two studies exhibited that there was a significant mean difference of -19.93 in the MMP-9 levels of intracerebral hemorrhage patients (95% CI=-36.90 to 15.62, p=0.02).

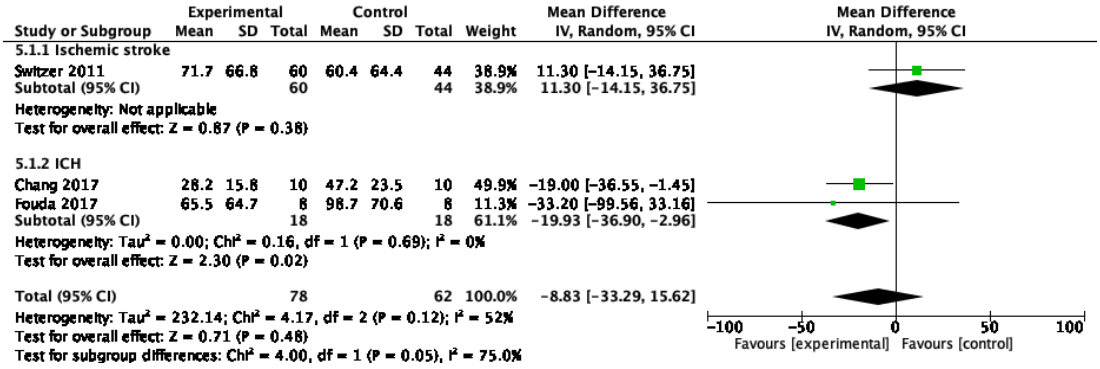


Figure 5. A forest plot showing the analysis results for MMP-9 levels.

DISCUSSION

Neuroprotective drugs exert their effects in a variety of ways, such as by lowering inflammation, increasing cell survival, improving neuronal function, and protecting against oxidative stress. By protecting neuronal integrity and function, these medicines have the potential to halt the course of neurodegenerative illnesses and enhance general brain health. Neuroprotective drugs are essential in stroke treatment because they reduce damage and improve outcomes. They protect brain cells against decreased blood flow and oxygen supply by targeting stroke-related processes such as excitotoxicity, oxidative stress, inflammation, and apoptosis. Neuroprotective medicines include N-methyl-D-aspartate (NMDA) receptor antagonists, anti-inflammatory medications, antioxidants,

neurotrophic factors, and other compounds. One of the emerging antibiotics to improve outcomes following stroke is minocycline, a second-generation tetracycline derivative that has been used as an antibiotic since 1971 (Rusu & Buta 2021).

Efficacy of minocycline for ischemic stroke

Minocycline has demonstrated anti-inflammatory, anti-apoptotic, and neuroprotective properties in several models of cerebral ischemia and neurodegenerative illnesses. Myeloid cells, including macrophages, dendritic cells, and neutrophils, migrate to ischemic sites after stroke. Neutrophils that migrate to lesions may cause secondary injuries. Minocycline can inhibit microglial activation and peripheral neutrophil invasion during stroke. The medication has anti-inflammatory effects that are associated with toll-like receptor (TLR)-mediated pathways (Otxoa-de-Amezaga et al. 2019, Chen et al. 2022, Cao et al. 2023). Minocycline may pass through the blood-brain barrier due to its high lipophilic properties. Furthermore, it has been demonstrated to decrease microglial activation. Minocycline enhances microglial M2 polarization while also inhibiting M1 polarization. This results in neuronal survival and neurological functional recovery.

Earlier research conducted by Lu et al. (2021) and Suárez-Rivero et al. (2023) has demonstrated that minocycline therapy improved survival rates and functional outcomes over a 14-day period. As a result, there was a decrease in brain infarct volume, recovery of neuronal damage, and suppression of reactive gliosis. It was found that minocycline therapy resulted in improved motor function recovery in peri-infarct tissue. Additionally, minocycline therapy reduced CD68 cell expression by 57% while simultaneously increasing glial fibrillary acidic protein and vimentin expression. These findings suggest an increase in reactive astrogliosis (Yew et al. 2019). In an experimental study carried out by Myers et al. (2023), the effects of post-stroke minocycline therapy on chronic microglia and astrocyte expression were investigated in a rat model. The study focused on the expression of ionized calcium-binding adaptor molecule 1 (Iba1), major histocompatibility complex-II (MHC-II), and glial fibrillary acidic protein (GFAP), as well as cognitive function performance in behavioral tasks. The findings of the study demonstrated that minocycline therapy was effective in improving outcomes. Minocycline may hinder microglial activation by inhibiting the nod-like receptor protein 3 (NLRP3) inflammasome signaling pathway. This leads to a decrease in pro-inflammatory factors and an increase in anti-inflammatory factors in microglia near infarction sites. Moreover, minocycline reduces the early phagocytic activity of microglia (Wang et al. 2022, Qiao et al. 2023, Zhao et al. 2023). This explanation supports our analysis results, indicating that minocycline has significant effects on mRS and NIHSS.

Efficacy of minocycline for hemorrhagic stroke

In relation to microglial activation, a single-dose administration of minocycline has been found to improve neuron survival and reduce ischemia-induced neurodegeneration, which results in decreased infarct volume. It has also been found that minocycline decreases tumor necrosis factor alpha (TNF-α) levels while increasing heat shock protein-70 (HSP-70) and human antigen R (HuR) levels in the penumbra. HuR specifically targets HSP-70 transcripts, hence promoting a protective response. In a study reported by Pawletko et al. (2023), lower inflammation in brain-damaged regions led to increased motor ability. This evidence suggests the regulating effect of minocycline on several inflammatory cytokines. In our study, we found significantly lower matrix metalloproteinase-9 (MMP-9) activity levels among stroke patients who were treated with minocycline. The quantitative analysis revealed that MMP-9 levels significantly differed in the intracerebral hemorrhage subgroup. In contrast, a study conducted by Strickland et al. (2022) did not find considerable variations between the minocycline group and the saline group. The differences were measured by observing the optical density of MMP-9.

A study reported by Fouda et al. (2017) exhibited no significant difference in the levels of IL-6, iron, and ferritin in the plasma of the subjects examined. Preclinical experiments have demonstrated that minocycline provides protection against intracerebral hemorrhage-induced secondary brain damage at several stages. Minocycline inhibits heme oxygenase-1 (HO-1) activity, chelates iron, reduces oxidative stress, prevents various forms of cell death, protects blood-brain barrier (BBB) integrity, modulates leukocyte function, and suppresses pro-inflammatory activities in microglia while increasing their regulatory phenotype. Minocycline, which acts as an iron chelator and neuroinflammation inhibitor, effectively reduces intracerebral hemorrhage-induced iron overload, brain edema, neuroinflammation, neuron death, delayed brain atrophy, and neurological impairments (Dai et al. 2019, Zhang et al. 2022). A study conducted by Cao et al. (2018) used magnetic resonance imaging (MRI) R2* mapping to investigate the effect of minocycline. The study

discovered that minocycline decreased intracerebral hemorrhage-induced perihematomal iron buildup and brain damage in elderly rats. In a separate study by Wang et al. (2022b), minocycline effectively prevented nerve cell death caused by intracerebral hemorrhage in a juvenile mouse model. This was achievable as minocycline suppressed the expression of the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) signaling pathway.

Treatment with a high minocycline dosage has been found to significantly improve neurological function while also reducing cerebral bleeding and edema. Minocycline therapy has the potential to prevent neuronal death in the prefrontal cortex, which is linked to lower levels of inflammatory cytokines. In addition, it has been demonstrated that the purinergic receptor P2X 4 (P2X4R) on microglia can be activated following subarachnoid hemorrhage. Minocycline therapy decreases P2X4R activation and further reduces the phosphorylation of downstream p38 mitogen-activated protein kinase (MAPK) (Li et al. 2019). In contrast, our analysis revealed that hematoma volume in intracerebral hemorrhage did not differ significantly when minocycline treatment was compared to the control group. The non-significant finding might be due to the limited number of studies evaluated. However, no clinical study has been conducted on subarachnoid hemorrhage. More research is required to draw a conclusion about the possible link between minocycline therapy and hematoma volume in hemorrhagic stroke, particularly in cases of subarachnoid hemorrhage and intracerebral hemorrhage.

Kohler et al. (2013) conducted a study to assess the safety of minocycline interventions on the liver and kidneys using measurements of alanine transferase (ALT) and creatinine. Between the minocycline group and the control group there was no significant difference in adverse events, including rash, gastrointestinal disorders, pneumonia, urinary tract infection, and increased ALT or creatinine levels. Minocycline has shown promise in preclinical investigations and clinical trials for its ability to protect neurons from damage and improve stroke outcomes.

Strength and limitations

There were a few limitations in this study, including the small number of clinical trials that might limit the generalizability of the findings and reduce the statistical power to detect true effects. Several confounding variables were not accounted for in this study, such as stroke onset and location, which might have influenced the non-significant findings for stroke outcomes, including mortality or recurrent stroke. Nevertheless, this meta-analysis employed rigorous methods, including randomization and blinded clinical trials, thus increasing the likelihood of producing reliable results. We also used validated instruments to enhance the credibility of this study.

CONCLUSION

Minocycline treatment has shown beneficial effects in improving clinical outcomes in stroke patients. The inhibitory effect of minocycline on microglial activation and peripheral neutrophils may confer restorative benefits in acute stroke. Future large-scale randomized controlled trials should evaluate the long-term safety and determine the ideal dosage and route of administration of minocycline in stroke patients. Minocycline should not be used as a stand-alone therapy for stroke, but considered in combination with other established treatments.

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Conflict of interest

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Author contribution

AIN, AAD, and JN contributed to the conception and design as well as the drafting of the article. AIN contributed to the analysis and interpretation of the data as well as statistical expertise. AM, MFQ, R, and BLH provided the study materials as well as analyzed and interpreted the data. All authors gave final approval to the article.

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