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Risk and Benefit of Antiplatelet Therapy After Spontaneous Intracerebral Hemorrhage: A Systematic Review and Meta-analysis

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ADMINISTRATIVE INFORMATION

Support - No.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 09 January 2024 and was last updated on 09 January 2024.

INTRODUCTION

Review question / Objective This study aimed to assess the risk and benefit of antiplatelet therapy after spontaneous intracerebral hemorrhage (ICH) through a systematic review and meta-analysis. Antiplatelet therapy is commonly used to reduce major vascular events in patients with occlusive vascular diseases, but its use in ICH patients may increase the risk of bleeding.

Condition being studied Based on the findings, reinitiating antiplatelet therapy after spontaneous ICH appears to be generally safe. However, the benefits in terms of reducing the risk of all-cause mortality are not evident and require confirmation through large-scale, long-term prospective randomized controlled trials.

METHODS

Participant or population A comprehensive search was conducted on databases including MEDLINE, Embase, Cochrane Library, clinicaltrials.gov, and the International Standard Randomised Controlled Trial Number Register (ISRCTN).

Intervention Randomized controlled trials and cohort studies that investigated the use of antiplatelet therapy after hemorrhagic stroke were included. Data on ICH recurrence, major bleeding events, major occlusive cerebrovascular events, ischemic stroke, and all-cause mortality were extracted and analyzed using R software.

Comparator Study Types: Prospective or retrospective observational cohort studies, case-control studies, and randomized controlled trials.•

Participant Types: Surviving patients diagnosed with spontaneous intracerebral hemorrhage (ICH) through CT or MRI.• Intervention Measures: Application of at least one antiplatelet (APT) drug.• Outcome Measures: Severe vascular events, including ischemic stroke, myocardial infarction, other major ischemic events, ICH, cerebral hemorrhage, and vascular death during planned follow-up.

Study designs to be included To identify relevant studies, comprehensive computer searches were conducted on several databases up to December 1, 2023. The databases searched included MEDLINE, Embase, Cochrane Library, clinicaltrials.gov, and the International Standard Randomised Controlled Trial Number Register (ISRCTN). The search terms used were: ("intracranial hemorrhages" OR "ICH" OR "cerebral hemorrhages") AND ("stroke") AND ("antiplatelet"). This search strategy aimed to retrieve articles that assessed the efficacy of antiplatelet therapy (APT) post-ICH. To avoid duplication, in cases where a study had multiple publ.

Eligibility criteria Study Types: Prospective or retrospective observational cohort studies, case-control studies, and randomized controlled trials.• Participant Types: Surviving patients diagnosed with spontaneous intracerebral hemorrhage (ICH) through CT or MRI.• Intervention Measures: Application of at least one antiplatelet (APT) drug.• Outcome Measures: Severe vascular events, including ischemic stroke, myocardial infarction, other major ischemic events, ICH, cerebral hemorrhage, and vascular death during planned follow-up.

Information sources The databases searched included MEDLINE, Embase, Cochrane Library, clinicaltrials.gov, and the International Standard Randomised Controlled Trial Number Register (ISRCTN). The search terms used were: ("intracranial hemorrhages" OR "ICH" OR "cerebral hemorrhages") AND ("stroke") AND ("antiplatelet").

Main outcome(s) The study included a total of 10 studies with 6,340 participants. The control group consisted of 2,964 patients who did not receive antiplatelet therapy, while the study group included 1,285 patients who received antiplatelet therapy without restrictions on the specific drug type. The meta-analysis showed that antiplatelet therapy significantly reduced the risk of ICH recurrence (RR=0.72, 95% CI: 0.59, 0.87), had no significant impact on the risk of severe bleeding events (RR=0.93, 95% CI: 0.80, 1.08), significantly lowered the risk of major occlusive cerebrovascular events (RR=0.59, 95% CI: 0.46, 0.77), had no significant effect on the risk of ischemic stroke (RR=0.77, 95% CI: 0.53, 1.12), and did not significantly influence the risk of all-cause mortality (RR=0.75, 95% CI: 0.45, 1.15).

Additional outcome(s) The study included a total of 10 studies with 6,340 participants. The control group consisted of 2,964 patients who did not receive antiplatelet therapy, while the study group included 1,285 patients who received antiplatelet therapy without restrictions on the specific drug type. The meta-analysis showed that antiplatelet therapy significantly reduced the risk of ICH recurrence (RR=0.72, 95% CI: 0.59, 0.87), had no significant impact on the risk of severe bleeding events (RR=0.93, 95% CI: 0.80, 1.08), significantly lowered the risk of major occlusive cerebrovascular events (RR=0.59, 95% CI: 0.46, 0.77), had no significant effect on the risk of ischemic stroke (RR=0.77, 95% CI: 0.53, 1.12), and did not significantly influence the risk of all-cause mortality (RR=0.75, 95% CI: 0.45, 1.15).

Data management For the meta-analysis, the R language meta-package was employed. Risk ratios (RR) and 95% confidence intervals (CI) were used for analyzing binary variables, while standard mean differences (SMD) and 95% CIs were used for continuous variables. The heterogeneity between studies was analyzed using the I2 test. An I2 value of 0% indicated no observed heterogeneity, while increasing values indicated greater heterogeneity. If I2 > 50%, indicating significant heterogeneity, subgroup analysis or analysis using a random-effects model was performed. For I2 ≤ 50%, indicating no significant heterogeneity, a fixed-effects model was used for analysis. A significance level of $\alpha = 0.05$ was considered for statistical significance.

Quality assessment / Risk of bias analysis The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS). The NOS involves scoring for population selection, comparability, and exposure/outcome, with a maximum of 2 stars for comparability and 1 star for the remaining items. The total score ranged from 0 to 9 stars, with higher scores indicating higher study quality.

Strategy of data synthesis For the meta-analysis, the R language meta-package was employed. Risk ratios (RR) and 95% confidence intervals (CI) were used for analyzing binary variables, while standard mean differences (SMD) and 95% CIs were used for continuous variables. The heterogeneity between studies was analyzed using the I2 test. An

I2 value of 0% indicated no observed heterogeneity, while increasing values indicated greater heterogeneity. If I2 > 50%, indicating significant heterogeneity, subgroup analysis or analysis using a random-effects model was performed. For I2 ≤ 50%, indicating no significant heterogeneity, a fixed-effects model was used for analysis. A significance level of α = 0.05 was considered for statistical significance.

Subgroup analysis Among the 10 included studies, one was a prospective randomized controlled trial, four were prospective cohort studies, and five were retrospective cohort studies. The control group in these studies did not receive APT treatment and consisted of a total of 2,964 patients, while the treatment group received APT treatment without specifying the type of medication, totaling 1,285 patients. The quality of the literature was assessed using the NOS score, which ranged from 4 to 8, indicating generally high-quality literature.

Sensitivity analysis Out of the 10 included studies, four reported the incidence of major occlusive vascular events after treatment, as shown in Figure 5. Three studies reported the occurrence of ischemic stroke, as shown in Figure 6. Heterogeneity analysis of the four literature reports on major occlusive vascular events showed an I2 value of 36%, indicating mild heterogeneity among studies, and a fixed-effects model was used for analysis. The statistical analysis results indicated that APT treatment significantly reduced the risk of major occlusive vascular events (RR = 0.59, 95% CI: 0.46, 0.77). Heterogeneity analysis of the three literature reports on the occurrence of ischemic stroke showed an I2 value of 61%, indicating significant heterogeneity among studies, and a random-effects model was used for analysis. The statistical analysis results indicated that APT treatment had no significant impact on the risk of ischemic stroke (RR = 0.77, 95% CI: 0.53, 1.12).

Country(ies) involved China, Heibei.

Keywords Antiplatelet Therapy; Spontaneous Intracerebral Hemorrhage; Systematic Review; Meta-analysis.

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