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The efficacy of glyceryl trinitrate for acute intracerebral hemorrhage: A systematic review and meta-analysis

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Abstract

Current research on the effects of glyceryl trinitrate (GTN) on the lowering of elevated blood pressure (BP) among patients with acute intracerebral hemorrhage (AIH) has not been highly emphasized. The aim of this meta-analysis is to examine the effects of GTN in patients with acute stroke. The lowering of BP was the primary outcome measure in patients treated with GTN compared to no-GTN treatment. A meta-analysis was performed to evaluate the efficacy of GTN in lowering BPs and analyze the outcomes of GTN treatment. Appropriate articles were searched using PubMed, Taylor & Francis Online, Cochrane, Scopus, ScienceDirect, Wiley Online Library, and Springer, with the use of appropriate keywords as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Out of 13 articles eligible for this study, 7 studies qualified for the meta-analysis by meeting the inclusion criteria. The PRISMA guidelines and the recommendations of Cochrane Collaboration were followed when conducting this meta-analysis. After subgroup analysis, differences between patients treated with GTN and without GTN were analyzed. The lowering of BP resulted in improved functional outcomes in patients treated with GTN. This meta-analysis showed differences between the 2 groups, with a risk ratio (RR) of 1.01 (95% confidence interval (95% CI): 0.92–10.07, $p = 0.30$, $I^2 = 18\%$). There was a significant improvement in outcome measures in patients treated with GTN by lowering elevated BP after acute stroke.

Key words: randomized controlled trials, acute stroke, elevated blood pressure, improved functional outcomes

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Introduction

Acute intracerebral hemorrhage (AIH) is a common subtype of hemorrhage. It is estimated to occur annually at a rate of 16 per 100,000 individuals worldwide.[1] However, research on whether the rapid lowering of blood pressure (BP) in patients with AIH improves the outcomes is still ongoing. Anderson et al. conducted a study on the rapid lowering of BP, which indicated no significant reductions in severe disabilities and mortality rate in patients.[2] However, intensive lowering of BP improved the functional outcomes. A clinical trial suggested that the risk of hematoma enlargement may be increased due to elevated BP. However, lowering BP below 150 mm Hg might help reduce the risk of hematoma.[3] The volume of the hematoma is the main predictor of 30-day mortality and poor functional outcomes.[4] The association between the baseline volume of the hematoma and oral anticoagulation has not been clarified. Some of the studies show an increased baseline volume,[5,6] while others[7,8] do not show any increase.

Transdermal glyceryl nitrate (TGN), one of the nitric oxide donors, is a candidate for the treatment of intracerebral hemorrhage (ICH). This agent can lower BP without causing any changes in cerebral blood flow. Moreover, no undesirable outcomes were reported regarding platelet function. In acute stroke patients, TGN did not cause reduction in mortality rate at 90 days. The treatment with TGN benefited patients who were randomized within 6 h of stroke onset.[9] Pre-hospital treatment with glyceryl trinitrate (GTN) resulted in worse outcomes in patients with AIH. In addition, time-by-treatment interaction was related to the negative effects of GTN if it was administered in patients randomized within 1 h of stroke onset. However, patients randomized within more than 2 h benefited from the treatment. Therefore, non-perfusion therapies should not be initiated at an earlier ultra-acute phase, because the brain is stunned, fragile and cannot respond well to the active modulation from external interventions.[10]

This systematic review and meta-analysis aimed to examine recent data in order to determine the efficacy of GTN for treating AIH patients. In the literature, the effects of time-by-treatment interaction from GTN have been studied in AIH patients in comparison to a placebo or control group. A recent review article found that GTN improved outcomes if it was administered within 2–6 h of stroke onset.[11] However, no meta-analyses regarding the safety of lowering elevated BP in ultra-acute stroke patients have been performed. Therefore, this meta-analysis investigates the efficacy of lowering the elevated systolic BP (SBP) using GTN and no GTN in patients with acute stroke.

Objectives

The objective of this study is to examine the effects of GTN in patients with acute stroke.

Materials and methods

Design

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[12] and the recommendations of Cochrane Collaboration[13] were followed when conducting this meta-analysis.

Inclusion and exclusion criteria

The inclusion criteria were as follows: 1) research articles focusing on GTN treatment in AIH; 2) studies including patients aged ≥18 years; and 3) studies published in English until February 10, 2023.

The exclusion criteria included 1) editorials, letters and commentaries; and 2) duplicate research articles with the same study population.

Search strategy

To perform an electronic search, PRISMA guidelines for a systematic review were followed, and PubMed, Taylor & Francis Online, Cochrane, Scopus, ScienceDirect, Wiley Online Library, and Springer databases were additionally

Table 1. Database search strategy

Database	Keywords
PubMed	(glyceryl trinitrate (title/abstract)) OR (trinitroglycerin (title/abstract)) OR ((nitroglycerine (title/abstract)) AND (intracerebral hemorrhage (title/abstract))) OR (stroke (title/abstract))
Taylor & Francis Online	"hemorrhage" OR "intracerebral hemorrhage" AND "glyceryl nitrate (GTN)" OR "transdermal glyceryl nitrate (TGN)"
Cochrane	"glyceryl trinitrate" (title, abstract, keyword) AND "acute intracerebral hemorrhage" (title, abstract, keyword) OR "acute ischemic stroke" (title, abstract, keyword) OR "blood pressure" (title, abstract, keyword)
Scopus	"glyceryl trinitrate, acute intracerebral hemorrhage, acute ischemic stroke" OR "blood pressure"
ScienceDirect	"glyceryl trinitrate for acute intracerebral hemorrhage"
Wiley Online Library	"glyceryl trinitrate" (anywhere) AND "acute intracerebral hemorrhage" (anywhere) AND "acute ischemic stroke" (anywhere)
Springer	"glyceryl" AND "trinitrate" AND "for" AND "acute" AND "intracerebral" AND "hemorrhage"

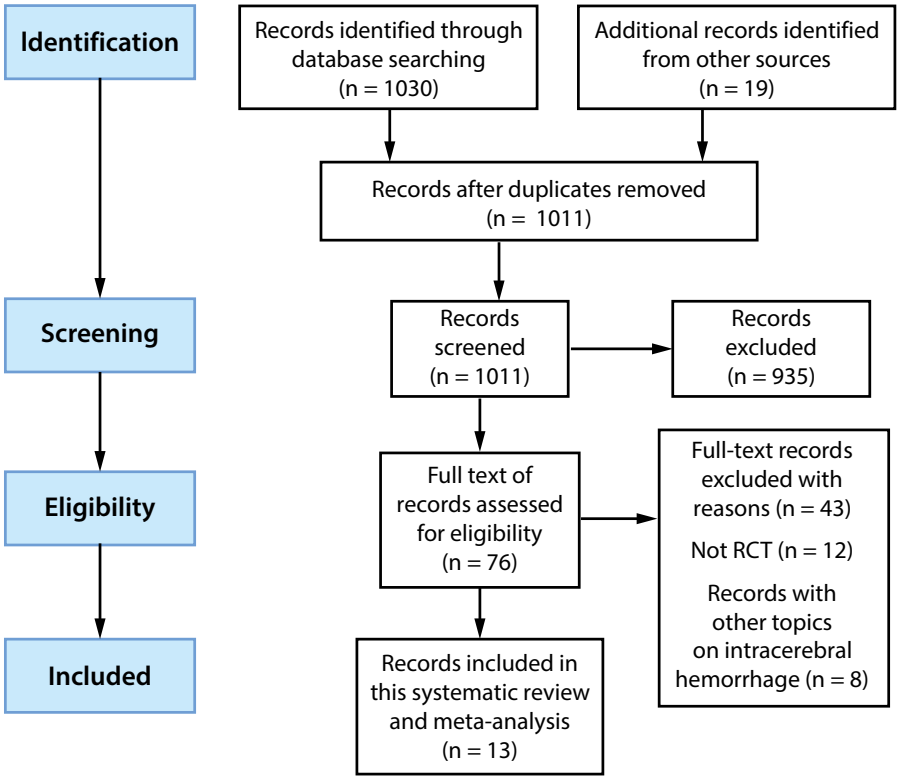

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart for the selection of research articles

RCT – randomized controlled trial.

searched to identify controlled trials that compared the effects of GTN with non-GTN medications (Table 1). Titles, abstracts and full-text articles were sequentially reviewed (Fig. 1). The quality of the included studies was assessed using the COCHRANE manual.[13]

Study selection

Endnote™ X9 (Clarivate, London, UK), a referencing package, was used to manage the references of research articles. After the removal of duplicates, 2 authors (QT and XS) independently performed the selection of research articles in 2 phases. Abstracts and titles of the articles were evaluated in order to exclude irrelevant studies. In the next phase, full-text research articles were assessed in detail.

Data extraction

Data from the eligible studies were independently extracted, including study ID or reference (first author and publication year), study design, and population, intervention, comparison, outcomes and study (PICOS) criteria-based information (Table 2).

Quality assessment

The Newcastle–Ottawa Scale (NOS)[14] has been jointly developed by the University of Newcastle (Australia) and the University of Ottawa (Canada). The scale is widely used to assess the quality of non-randomized trials in systematic reviews. The methodological quality of this meta-analysis was assessed using NOS. A study with a NOS score ≥7 points was considered of a high quality. Any disagreement between the 2 authors was settled through consensus.

Statistical analyses

Review Manager (RevMan) v. 5.4.1 (Cochrane, London, UK) was used to perform all statistical analyses in the present study. Data extracted from the included research articles were combined using a random effects model with Begg's and Egger's tests, which deflate the type I error rate and publication bias in a meta-analysis, respectively. Risk ratios (RRs) and 95% confidence intervals (95% CIs) were calculated for the dichotomous data. The χ^2 and I^2 tests were used to determine the heterogeneity between included research articles. Heterogeneity was assessed using Cochrane's Q, which is calculated as the weighted sum of squared differences between pooled effects and the individual study effects across the included studies, where Q has distribution as a χ^2 static with k (number of studies) minus 1 degree of freedom. Thus, heterogeneity (I^2) is measured as follows (Equation 1):

$$I^2 = \frac{Q - df}{Q} \times 100 \quad (1)$$

where Q expresses Cochrane's homogeneity test static, and df – degrees of freedom.

Table 2. Characteristics of the included studies

Author of the study, reference	Study design	Population	Intervention	Comparison	Outcomes
Anderson et al.[2]	RCT	n = 2839, mean age: 63.5 years	topical nitrate	intensive treatment compared to recommended guidelines	lowering BP improved functional outcomes
Krishnan et al.[9]	RCT	n = 629, mean age: 67 years, acute stroke	GTN	GTN compared to no GTN	improved functional ability outcomes, lowered BP
Bath et al.[10]	prospective randomized trial	n = 145, mean age: 73 years, presumed stroke	GTN and sham	GTN compared to sham	improved functional outcomes
Appleton et al.[15]	randomized trial	n = 4011, mean age: 70.3 years, acute stroke	GTN	transdermal GTN compared to no GTN	poor functional and cognitive outcomes
Ankolekar et al.[16]	RCT	n = 80, mean age: 79 years	GTN	placebo	improved functional outcomes
Woodhouse et al.[17]	RCT	n = 273, mean age: 69 years, acute stroke	GTN	GTN compared to no GTN	improved functional outcomes and lower mortality rate
ENOS Trial Investigators[18]	RCT	n = 4011, age ≥18 years, acute stroke	GTN	GTN compared to no GTN	GTN improved safety without improving functional outcomes
Qureshi et al.[19]	randomized trial	n = 1000, mean age: 61.9 years, acute cerebral hemorrhage	nicardipine	intensive compared to standard treatment	severe disability or death
Tunnage et al.[20]	RCT	n = 1149, mean age: 67 years, stroke mimic	GTN and sham	GTN compared to sham	functional disorder, migraine and seizure
Dixon et al.[21]	RCT	n = 1149, mean age: 73 years, hypertensive stroke	GTN and sham	GTN compared to no GTN	rapid delivery of GTN (within 2 h); both distance and time may impede patients to access stroke services
van den Berg et al.[22]	RCT	n = 1400, age ≥18 years, acute stroke	GTN	placebo (GTN)	prompt GTN prevents delay to revascularization; lowered BP
Bath et al.[23]	RCT	n = 1149, mean age: 73 years, ultra-acute presumed stroke	GTN and sham	GTN compared to sham	no improvement in functional outcomes, increased mortality rate
Beishon et al.[24]	RCT	n = 4011, mean age: 70.23 years, acute stroke	GTN	GTN compared to no GTN	poor clinical outcomes

GTN – glyceryl trinitrate; BP – blood pressure; RCT – randomized controlled trial.

A value of $p < 0.05$ and $I^2 > 0.50$ illustrated the substantial statistical heterogeneity. Therefore, we used a random-effects model. A subgroup analysis was performed in patients treated with GTN and without GTN. A funnel plot was employed to assess the publication bias.

Risk-of-bias assessment

The review process requires the validation of selected studies by evaluating the risk of bias in the results of the study. The risk of bias evaluates the robustness of the methodology used in the studies and assesses whether conclusions were based on objective and valid evidence. The risk of publication bias was assessed using Begg's rank test and Egger's linear test.

Results

The selection process of research articles was based on the inclusion and exclusion criteria, as shown in Fig. 1.

Search results

After performing a digital database search, a total of 1049 research articles were retrieved. Then, 38 duplicates were removed. The titles and abstracts of the remaining 1011 articles were screened. As a result, 935 research articles were excluded. The remaining 76 research articles were read and thoroughly assessed for their relevancy to the research topic. Based on the inclusion and exclusion criteria, 13 research articles were chosen for the final inclusion in this meta-analysis (Table 2).[2,9,10,15–24]

Characteristics of the included studies

Primary outcomes

The variability in the modified Rankin Scale (mRS) evaluated for several days was the primary outcome

measure. One study presented SBP variability over 1–7 days on the mRS and death at 90 days.[15] Seven studies were qualified for the meta-analysis based on SBP values.[9,15–18,23,24] Out of the 7 studies, 2 research articles[16,17] favored the use of GTN to improve functional outcomes, while 5 studies[9,15,18,23,24] did not show improvement in functional outcomes after GTN treatment.

We compared the primary outcomes of an acute stroke subgroup based on the variation in SBP between GTN and no-GTN treatments. There was no significant difference in the primary outcome from the subgroup analysis.

The remaining studies compared different treatment agents than the previously mentioned studies.[2,10,19,21–23] For example, Anderson et al. examined the intensive treatment and recommended guidelines in acute stroke.[2] Bath et al.[10] and Tunnage et al.[20] focused on the treatment groups (GTN compared to sham), while Qureshi et al.[19] evaluated intensive compared to standard treatment groups in a randomized controlled trial (RCT). Dixon et al.[21] and van den Berg et al.[22] examined studies on hypertensive stroke and acute stroke, respectively. A study by ENOS Trial Investigators revealed data on ischemic stroke (IS) and ICH.[18] Hence, the same study was represented twice in the forest plot.

The baseline of SBP, based on the SBP level, and subgroups (GTN compared to no GTN) were analyzed. Neutral results ($p < 0.05$) were obtained from 2 group analyses (Fig. 2).

We used a funnel plot and Begg's test to assess the publication bias (Fig. 3). Our study has a low risk of publication bias, as presented in a funnel plot, and the significant p-values of Begg's test[25] are greater than 0.05 (0.628). In addition to the funnel plot and Begg's test results, Egger's test showed significant results ($z = 2.04$, $p = 0.04$).

Discussion

Intracerebral hemorrhage is a type of stroke with a high mortality rate, accounting for 15–20% of acute strokes.[26–28] An increased risk of ICH is associated with ischemic and hemorrhagic strokes and evolves into chronic lesions causing local microstructural injuries. Data on the treatment with GTN and non-GTN medications come from a low number of studies.[29–32] Also, none of the previous meta-analyses compared GTN and its effects on patients with ICH to patients without GTN treatment.

High BP is common in patients with stroke, and is associated with poor outcomes, including acute stroke and death within a few weeks. Therefore, in most cases, BP control is an essential part of the ICH treatment. Nitrate agents help lower BP in acute stroke. Glyceryl trinitrate is one of the valuable agents, particularly in pre-hospital settings.[33–36] To investigate the effect of GTN administration in patients, a systematic review and meta-analysis of 13 studies recruiting a total of 16,686 participants was conducted. With the inclusion of 4011 patients from a RCT,[24] our systematic review had a greater number of recruited patients compared to other meta-analyses. Thus, our study filled the previously existing research gap. The results of our meta-analysis showed that differences in primary outcomes were significant in GTN compared to non-GTN groups. Our findings are consistent with those of a previous study.[37]

There were 5 previously published systematic reviews and meta-analyses on the topic.[11,38–41] Of these meta-analyses,

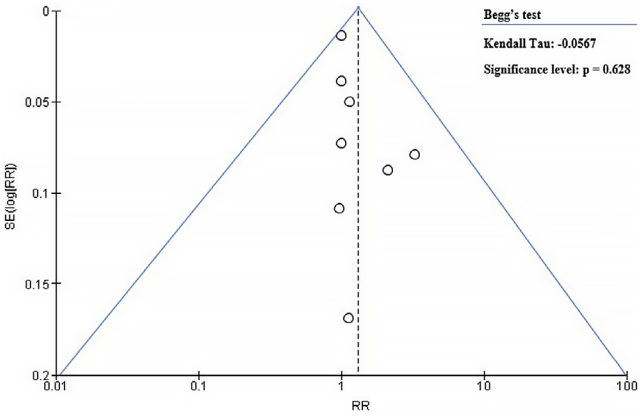

Fig. 3. Funnel plot of publication bias

SE – standard error; RR – risk ratio.

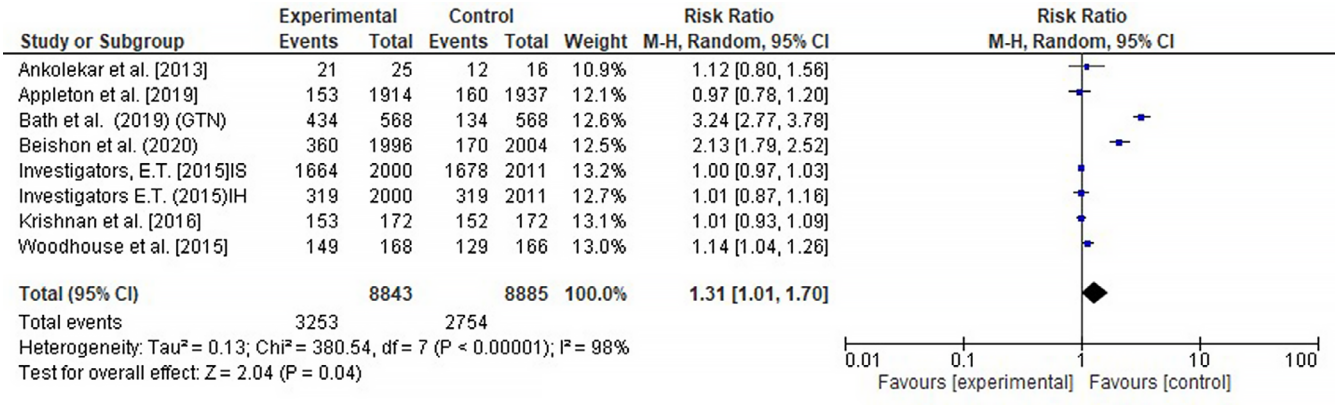

Fig. 2. Forest plot of random effects model

df – degrees of freedom; 95% CI – 95% confidence interval.

only 1 study showed a significant relationship between lowering the elevated BP in acute stroke and improved functional outcomes.[42] Overall, a positive link was observed between lowering BP and a reduction of the risk of acute stroke. The remaining 4 meta-analyses were consistent with the results stating that lowering BP did not show a strong association with the reduction of the risk of acute stroke.

This systematic review showed interesting results regarding the lowering of BP and safety in patients with an acute stroke. However, there were no functional improvements in patients participating in a RCT. This might have been due to the intake of a high concentration of nitric oxide (NO), which might damage brain tissues.[43–45]

The results of the subgroup analysis showed that patients with acute stroke treated with GTN had improved functional outcomes in a few cases with a longer pre-hospital duration or no history of hypertension. In patients with stroke, survival chances did not increase after GTN treatment.[46–48] However, the treatment was effective in pre-hospital conditions, which is consistent with the results of previous analyses.[23,49] These findings play a vital role in the selection of appropriate therapeutic strategies.

Limitations

This meta-analysis has several limitations. The main limitation is the low number of included research articles. Careful and extensive retrieval of information was performed to minimize the risk of publication bias. We included 7 RCTs that limited the statistical power to find differences. Although strict inclusion and exclusion criteria were followed, selection bias or observer bias may have influenced the research outcomes. To confirm the results of this meta-analysis, more RCTs should be performed with larger sample sizes.

Conclusions

This meta-analysis demonstrated the efficacy of GTN and its variants in patients with acute stroke. The lowering of SBP is associated with functional improvements in patients with AIH. Due to the small number of included studies, our meta-analysis shows high heterogeneity between the studies. Further research trials should be undertaken to provide stronger evidence and improve outcomes in acute stroke patients.

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