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Effect of heparin for the prevention of venous thromboembolism in patients with spontaneous intracranial cerebral hemorrhage: a meta-analysis

Yifu Zhou, Gang Wang, Chunxiao Xue, Guojun He, Yan Zhang, Feilong He, Chenjun He and Xiaosong Liang

Abstract

Background: Venous thromboembolism (VTE) has a serious impact on the prognosis of patients with spontaneous intracranial hemorrhage (sICH). However, the use of prophylactic heparin remains controversial.

Objectives: This study investigated the safety and timing of prophylactic heparin for VTE in patients with sICH.

Design: This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.

Methods: Two authors systematically searched Web of Science, Cochrane Library, Embase, and PubMed to find all published research before June 2023. The incidence of deep venous thrombosis (DVT) and mortality were set as primary endpoints.

Results: This meta-analysis included seven randomized controlled trials (RCTs) and five observational studies involving a total of 4419 sICH patients in the heparin ($n = 2808$) and control ($n = 1183$) groups. Among these patients, 205 received early heparin administration, while 223 received late heparin administration. The results suggested that, compared to the control group, patients in the heparin group had a lower incidence of VTE [odds ratio (OR), 0.47; 95% CI, 0.31–0.71; $p < 0.001$], DVT (OR, 0.53; 95% CI, 0.33–0.85; $p = 0.009$), pulmonary embolism (OR, 0.31 95% CI, 0.15–0.65; $p = 0.002$), and mortality (OR, 0.70; 95% CI, 0.54–0.90; $p = 0.006$), but there were no statistical differences in hematoma enlargement, extracranial hematoma, and major disability ($p > 0.05$). There was no statistically significant difference in DVT, mortality, hematoma enlargement, and extracranial hemorrhage between the early heparin group (<24–48 h) and the late heparin group ($p > 0.05$).

Conclusion: In patients with sICH, prophylactic use of heparin may be beneficial because it reduces the incidence of VTE and mortality without increasing the risk of additional bleeding. In addition, early prophylactic use of heparin appears to be safe. However, large-scale RCTs are lacking to support this evidence.

Plain language summary

Prophylactic use of heparin reduces the incidence of venous thromboembolism and reduces overall mortality in patients with spontaneous bleeding in the brain

Why was the study done? Venous thromboembolism has a serious impact on the prognosis of patients with spontaneous bleeding in the brain. However, the use of prophylactic heparin remains controversial. This study investigates the safety and timing

Correspondence to:
Xiaosong Liang
Department of Neurosurgery, Affiliated Hospital of Shaoxing University, No. 999, South Zhongxing Road, Shaoxing, Zhejiang 312000, China
yveszhou15@163.com

Yifu Zhou
Gang Wang
Chunxiao Xue
Guojun He
Yan Zhang
Feilong He
Chenjun He
Department of Neurosurgery, Affiliated Hospital of Shaoxing University, Shaoxing, China

of prophylactic heparin for venous thromboembolism in patients with spontaneous bleeding in the brain. What did the researchers find? Our results showed that patients in the heparin group had lower rates of blood clot in a deep vein, death, and pulmonary embolism compared with the control group, and there were no significant differences in hematoma enlargement, extracranial hematoma, and severe disability. There were no significant differences in blood clot in a deep vein, mortality, hematoma enlargement, and extracranial hemorrhage between the early and late heparin groups. What do the findings mean? This study suggests that prophylactic use of heparin may be beneficial in patients with spontaneous bleeding in the brain, and that early prophylactic use of heparin appears to be safe.

Keywords: meta-analysis, mortality, safety, spontaneous intracranial hemorrhage, venous thromboembolism

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Introduction

Spontaneous intracranial hemorrhage (sICH), affecting approximately 2 million individuals annually, represents a highly frequent and complex subtype of stroke that poses significant challenges in management.[1] The occurrence of venous thromboembolism (VTE) is a frequent complication in patients diagnosed with sICH and poses a substantial risk to them.[2,3] Prevention of VTE is crucial in patients with sICH due to the significantly elevated incidence of VTE, ranging from 7 to 13% according to several studies, and the substantial risk of fatal pulmonary embolism (PE).[4–6]

However, the treatment options of the therapy of sICH and VTE are full of contradictions. The primary objective of VTE prophylaxis is to prevent coagulation and reduce the risk of thrombosis, whereas the treatment of sICH is centered on hemostasis and the prevention of hematoma expansion.[3,7] The 2022 American Heart Association/American Stroke Association (AHA/ASA) guidelines refer to preventive heparin therapy as second-line treatment (a class 2a level of evidence C-LD),[8] and European guidelines do not recommend.[9] The second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2) reported less favorable data, with increased residual disability in patients using pharmacological prophylaxis.[10] Multiple recent meta-analyses indicated that prophylactic heparin in patients with sICH was associated with a nonsignificant increase in any hematoma enlargement and mortality.[11,12]

A number of recent studies have re-examined the effect of prophylactic heparin in patients with cerebral hemorrhage and focused on the timing of administration. To investigate the safety and timing of prophylactic heparin for VTE in patients with sICH, we conducted an updated meta-analysis comprising randomized controlled trials (RCTs) or observational studies.

Methods

This study adhered to the reporting guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) as well as Meta-analysis of Observational Studies in Epidemiology (MOOSE)[13] (Supplemental Table 1). The current study utilized publicly accessible data, all sourced from pre-approved studies that had undergone ethical considerations.

Literature search strategy

The two investigators independently and systematically searched multiple databases, including PubMed, Embase (*via* OVID), Web of Science, and Cochrane Library, to identify all publicly available research studies. The following search terms were used: (cerebral hemorrhage[ti/ab] OR intracerebral hemorrhage[ti/ab] OR intracerebral[ti/ab] OR hemorrhagic stroke[ti/ab]) AND (heparin[ti/

ab] OR heparinoids[ti/ab] OR low-molecular-weight heparin[ti/ab] OR anticoagulants[ti/ab]) AND (prevention[ti/ab] OR deep venous thrombosis[ti/ab] OR pulmonary embolism[ti/ab] OR venous thrombosis[ti/ab] OR caprini[ti/ab]). The most recent search was conducted in June 2023, followed by a comprehensive manual examination of relevant literature references to ensure an exhaustive review of potentially pertinent studies.[12]

Inclusion and exclusion criteria

The selection of studies was based on the following criteria: (1) patients with spontaneous intracerebral hemorrhage; (2) prophylactic doses of heparin; (3) the study focused on the results of two or more groups and clearly distinguished between heparin and control groups or between early heparin and late heparin groups; the early heparin group was defined as initiation of heparin 24–48 h after the onset of intracerebral hemorrhage[8]; (4) the type of study falls into the category of RCTs or observational studies; (5) utilization of objective methodologies to evaluate one or more study outcomes.[14]

Exclusion criteria: (1) ICH resulting from surgical procedures or traumatic brain injury; (2) studies published solely as conference abstracts, case reports, or narrative reviews; (3) non-English language publications; (4) inaccessible data for extraction purposes; (5) duplicated research.

Outcome measures

In this meta-analysis, data outcomes included deep venous thrombosis (DVT), mortality, hematoma enlargement, extracranial hemorrhage, PE, major disability as defined by Glasgow Outcome Scale (GOS) scores of 2 to 3 or modified Rankin Scale (mRS) scores of 3 to 5. The determination of these outcomes was based on the definitions provided in each individual study.

Data extraction and quality assessment

Two authors independently performed data extraction for all eligible studies, and the final results were reviewed and confirmed by the third senior author. The following data was gathered: (1) research attributes (author, publication year, country, and study design); (2) patient characteristics (patient count, age, and gender); (3) treatment regimen details (intervention type, treatment initiation time, duration of treatment, dosage, and follow-up period length); (4) patient outcome information (heparin *versus* control group comparison, early heparin *versus* late heparin). The extraction of data was repeated in case of disagreement between two authors.

We employed two assessment tools to evaluate the potential bias in the included studies, which encompassed both RCTs and observational studies. The Cochrane Collaborative Risk of Bias Assessment Tool was utilized for assessing the risk of bias in RCTs, categorizing it into three levels: high risk, low risk, and unclear risk.[15] To assess the methodological quality of observational studies, we employed the Newcastle-Ottawa Scale (NOS). Studies with scores ranging from 0 to 3 were considered as low quality, while those scoring between 7 and 9 were deemed as high quality.[16]

Statistical analysis

The statistical analysis was performed using Revman version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). The odds ratio (OR), along with 95% confidence intervals (CIs) were computed for dichotomous variables. Heterogeneity across studies was assessed using Q and I^2 statistics. Studies with an I^2 value of 0%, 25%, 50%, and 75% represented no, low, moderate, and high heterogeneity, respectively. The fixed-effect model was employed when $I^2 \leqslant 50\%$, while the random-effect model was used when $I^2 > 50\%$. We predetermined variables for sensitivity analysis, sequentially excluding one study after another until there was a significant change in the final results or heterogeneity that made us notice this during the analysis.

Result

Study selection

A total of 955 records were initially retrieved from the four public databases. Following the removal of duplicate records and initial screening, a total of 35 full-text articles were evaluated for eligibility. Out of these, 23 studies were excluded due to various reasons such as being written in a language other than English, not being original research articles, lacking comparison between heparin and control groups, absence of efficacy or safety outcome data, and unavailability of extractable data. Following the inclusion and exclusion

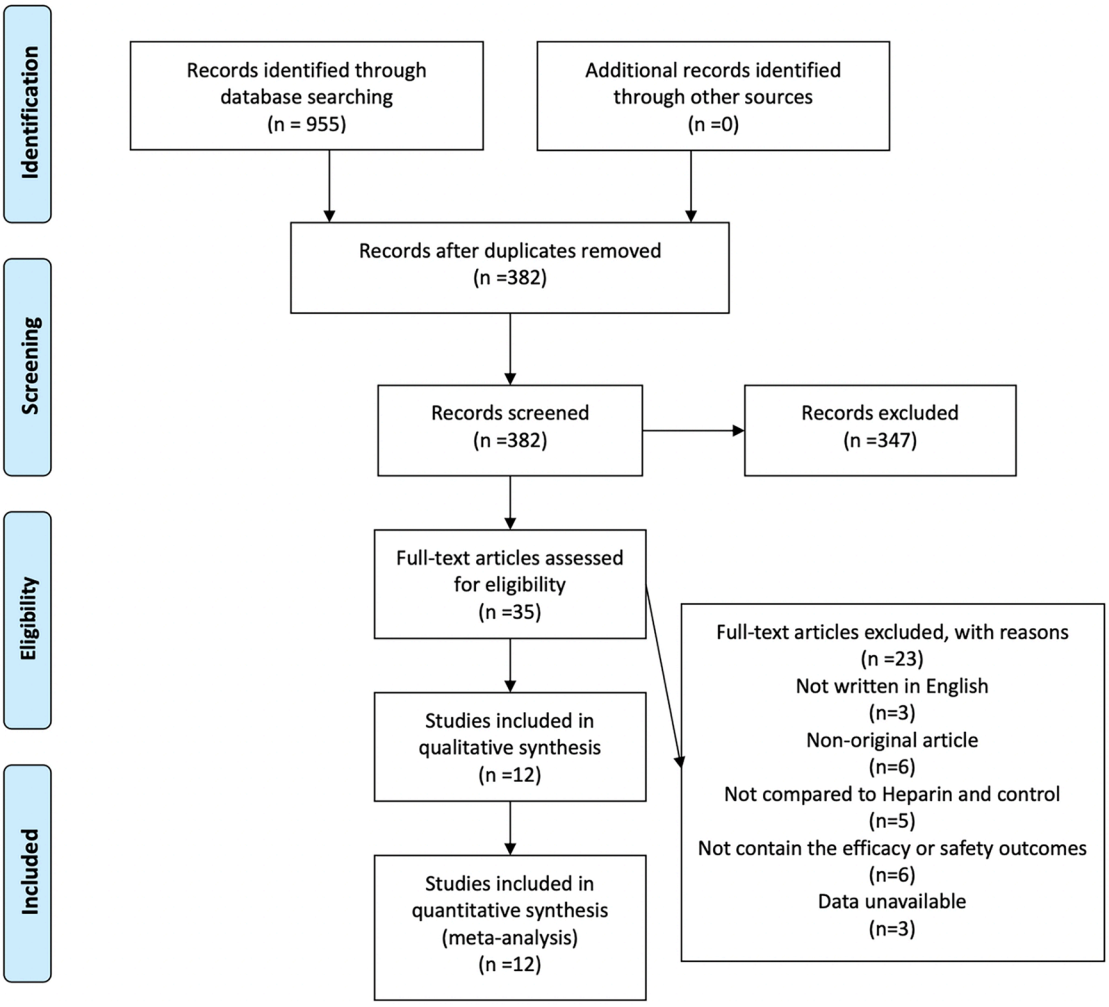

Figure 1. Flow diagram of selection.

criteria, 12 studies were eventually included to underpin this meta-analysis,[10,11,17–26] including 7 RCTs (6 for heparin *versus* control, 1 for early heparin *versus* late heparin) and 5 cohort studies (3 for heparin *versus* control, 2 for early heparin *versus* late heparin). The PRISMA flow chart of this meta-analysis is shown in Figure 1.

Study characteristics and quality assessment

Out of the total 4419 patients analyzed, prophylactic doses of heparin were administered to 2808 individuals (heparin group) while 1183 received placebo or physical therapy (control group). Additionally, early administration of heparin was given to 205 patients, and late administration was provided to 223 patients. In all studies (early *versus* late) with a group receiving early administration of heparin, this was after a repeat CT confirmed stable hematoma. The studies were conducted over a period spanning from 1991 to 2021 and included three Eastern countries and nine Western countries with one multicenter trial. Sample sizes ranged from as small as 68 participants up to the largest study, which had a sample size of 744 individuals. Table 1 provides an overview of the characteristics and protocols for administering heparin in each study that was included in this analysis.

The findings from the Cochrane Collaborative Risk of Bias Assessment Tool and NOS can be found in Supplemental Figures S1, S2, and Supplemental Table 2. All included studies demonstrate moderate to high levels of quality.

Table 1. Characteristics of all the studies included in the meta-analysis.

Author	Year	Country	Study design	Intervention	Treatment initiation	Duration of treatment	Dose	Length of follow-up	Quantity of patients		Sex (male, %)		Age (years)	
									Heparin	Control	Heparin	Control	Heparin	Control
Song	2021	China	ROBS	LMWH	NA	5 days	4000 IU/day	NA	52	46	48.1	50.0	NA	NA
Paciaroni	2020	Italy	RCT	LMWH	72 h	10 days	0.4 ml/day	90 days	38	35	57.9	51.4	70.4 ± 13.7	71.5 ± 11.6
Munoz-Venturelli	2016	Multicenter	RCT	UFH/LMWH	7 days	NA	NA	90 days	372	372	61.3	62.6	65.8 ± 13.3	65.3 ± 12.0
Orken	2009	Turkey	RCT	LMWH + CS	48 h	NA	40 mg/day	21 days	39	36	43.6	77.8	68.1 ± 12.0	66.1 ± 9.6
Tetri	2008	Finland	ROBS	LMWH	24 h	NA	20–40 mg/day	3 months	232	175	49.0	58.0	70.0 ± 11.7	66.2 ± 12.7
Wasay	2008	Pakistan	ROBS	UFH + CS	Day 1–6	7–14 days	2500–5000 IU/12 h	NA	200	258	54.0	58.0	59.0 ± 33	57.0 ± 29.0
Wurm	2004	Austria	RCT	LMWH	Day 3	21 days	20 mg/day	1 year	57	60	49.1	30.0	51.2 ± 12.7	53.8 ± 12.6
Siironen	2003	Finland	RCT	LMWH	24 h	10 days	40 mg/day	3 months	85	85	43.5	54.1	50.2 ± 1.4	49.5 ± 1.4
Boeer	1991	Germany	RCT	UFH+CS	96 h	10 days	5,000 IU/8 h	10 days	45	23	52.2	48.9	61 (45–83)	62 (46–83)
Kananeh	2021	USA	ROBS	UFH (<24 h) + CS	<24 h	NA	5000 IU/8 h	14 days	58	105	82.8	52.4	68.3 ± 13.7	68.2 ± 14.1
Qian	2021	Finland	RCT	LMWH(<24 h)	24 h	NA	40 mg/day	90 days	71	68	51.0	53.0	66.0 ± 19.0	68.0 ± 6.0
Lanosi	2019	Austria	ROBS	LMWH(<48 h)	<48 h	NA	2000 IU or 4000 IU/day	3 months	76	50	47.0	54.0	68 (60–75)	73 (63–78)

CS, compression stockings; LMWH, low-molecular-weight heparin; NA, not available; RCT, randomized clinical trial; ROBS, retrospective observational study; UFH, unfractionated heparin.

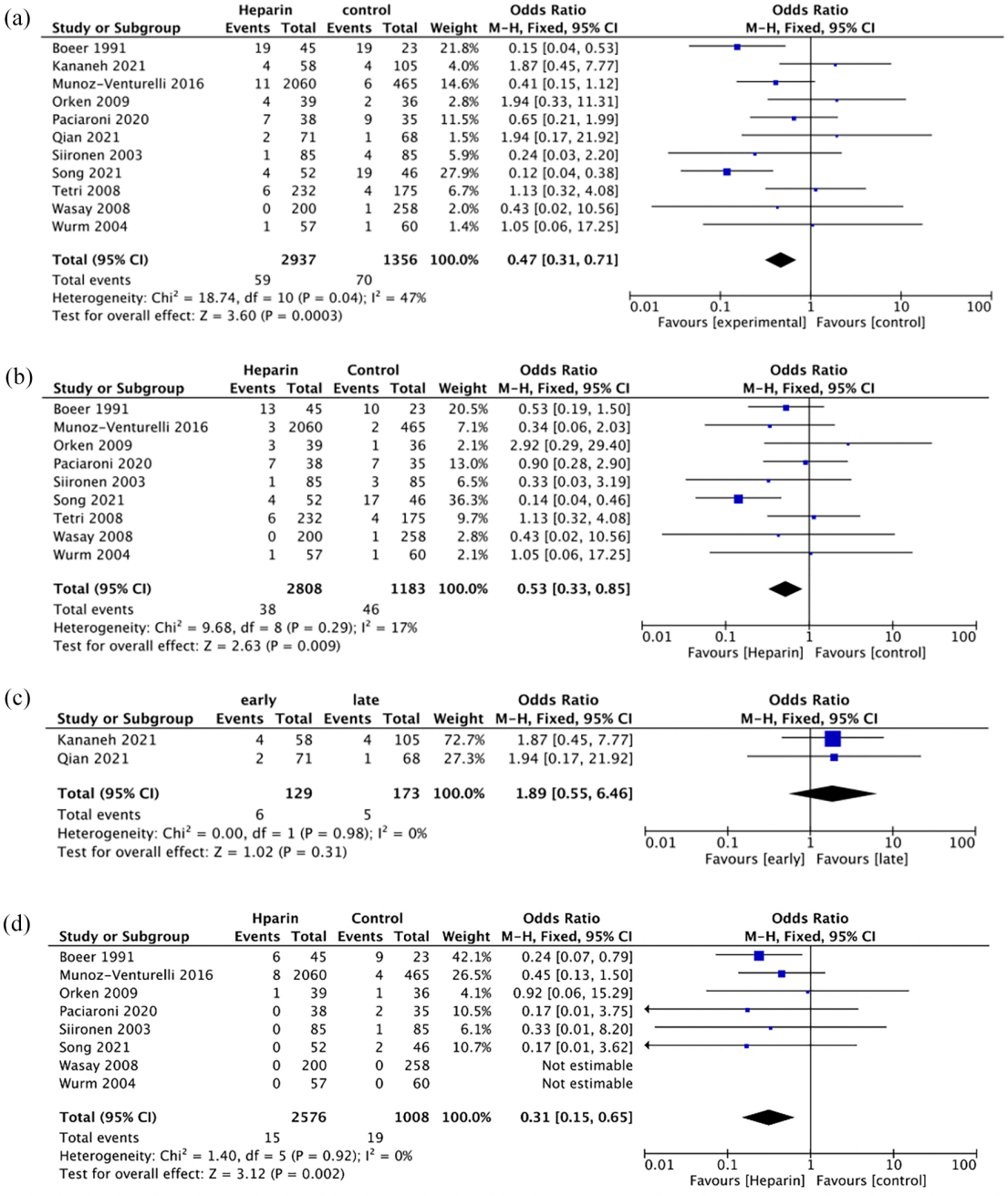

Figure 2. Forest plot of meta-analysis of venous thromboembolism: (a) the incidence of venous thromboembolism (heparin *versus* control group), (b) the incidence of deep venous thrombosis (heparin *versus* control group), (c) the incidence of deep venous thrombosis (early heparin *versus* late heparin group), and (d) the incidence of pulmonary embolism (heparin *versus* control group).

Venous thromboembolism

Eleven studies reported the incidence of VTE, with a significantly lower incidence of VTE in patients in the heparin group compared with controls (2.01% *versus* 5.16%; OR, 0.47; 95% CI, 0.31–0.71; $I^2 = 47\%$; $p < 0.001$) [Figure 2(a)].

Nine of these reported DVT outcomes, patients in the heparin group had a significantly lower rate of DVT compared to the control group (1.35% *versus* 3.89%; OR, 0.53; 95% CI, 0.33–0.85; $I^2 = 17\%$; $p = 0.009$) [Figure 2(b)]. However, there was no statistically significant difference

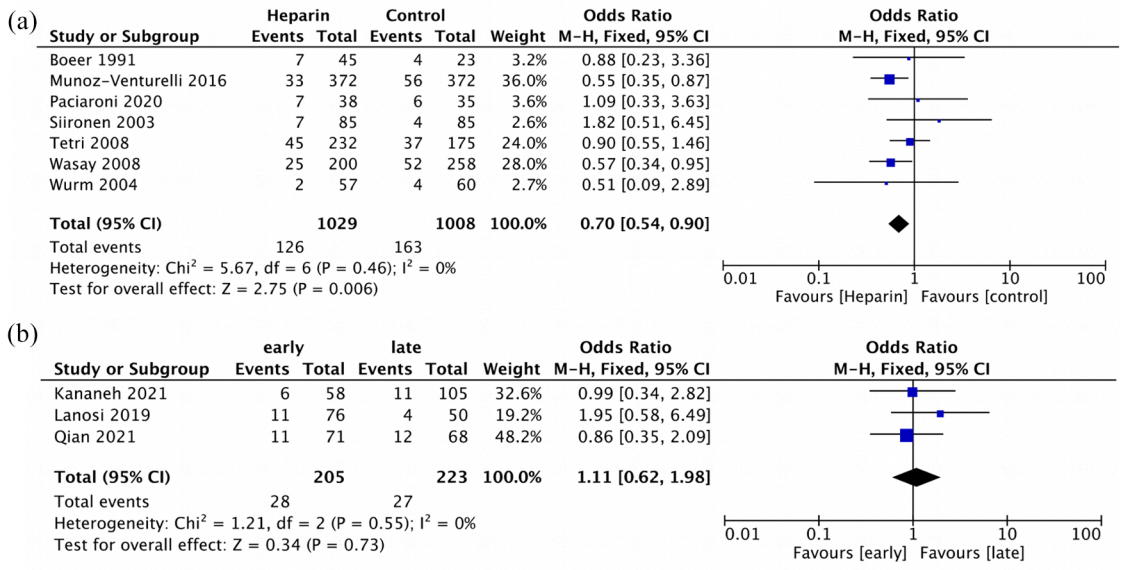

Figure 3. Forest plot of meta-analysis of mortality: (a) heparin *versus* control group and (b) early heparin *versus* late heparin group.

between early heparin and late heparin group (4.65% *versus* 2.89%; OR, 1.89; 95% CI, 0.55–6.46; $I^2 = 0\%$; $p = 0.31$) [Figure 2(c)]. Results for PE were reported in eight studies; the pooled result showed that the incidence of PE was significantly lower in the heparin group compared to the control group (0.58% *versus* 1.88%; OR, 0.31; 95% CI, 0.15–0.65; $I^2 = 0$; $p = 0.002$) [Figure 2(d)].

Mortality

The overall mortality rate was determined by evaluating seven studies, and the pooled result showed significantly lower mortality in the heparin group compared to the control group (12.24% *versus* 16.17%; OR, 0.70; 95% CI, 0.54–0.90; $I^2 = 17\%$; $p = 0.006$). There were no statistically significant differences in mortality between the early heparin group and the late heparin group (13.66% *versus* 12.11%; OR, 1.11; 95% CI, 0.62–1.98; $I^2 = 0\%$; $p = 0.73$) (Figure 3).

Hematoma enlargement

Six studies reported hematoma enlargement outcomes; the rate of hematoma enlargement was found to be comparable between the heparin and control groups, with no statistically significant difference observed in the result (6.61% *versus* 4.16%; OR, 0.88; 95% CI, 0.29–2.69; $I^2 = 50\%$; $p = 0.82$). Similarly, the pooled result showed no significant difference between the early heparin group and the late heparin group (12.68% *versus* 13.90%; OR, 0.80; 95% CI, 0.45–1.41; $I^2 = 9\%$; $p = 0.44$) (Figure 4).

Extracranial hemorrhage

Five studies reported this outcome, indicating no statistically significant difference between the heparin and control group (3.23% *versus* 3.49%; OR, 1.00; 95% CI, 0.48–2.07; $I^2 = 25\%$; $p = 1.00$). Additionally, one study revealed a statistically significant difference in extracranial hemorrhage rate between the early heparin group and the late heparin group (0% *versus* 15.49%; OR, 0.04; 95% CI, 0.00–0.67; $I^2 =$ not applicable; $p = 0.03$) (Figure 5).

Major disability

Three studies reported major disability at 90 days, according to scores 3 to 5 on the mRS, indicating no significant difference between the heparin and control group (48.48% *versus* 41.46%; OR, 1.00; 95% CI, 0.52–1.92; $I^2 = 69\%$; $p = 0.99$). In addition, two studies reported major disability at 90 days, according to scores 2 to 3 on the GOS, have had similar results, indicating no statistically significant difference between the heparin and control group (31.86% *versus* 16.92%; OR, 1.95;

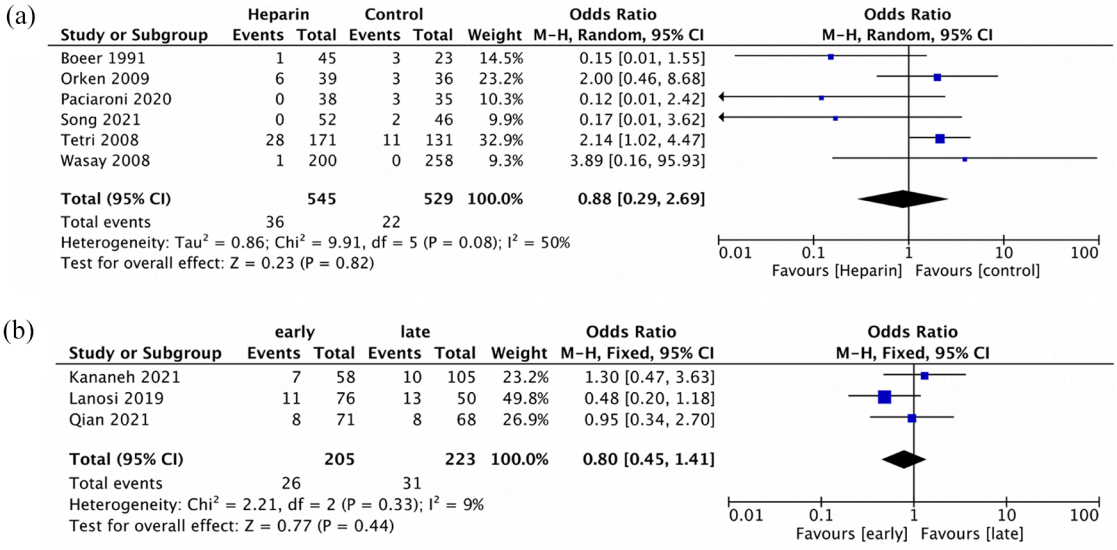

Figure 4. Forest plot of meta-analysis of hematoma enlargement: (a) heparin *versus* control group and (b) early heparin *versus* late heparin group.

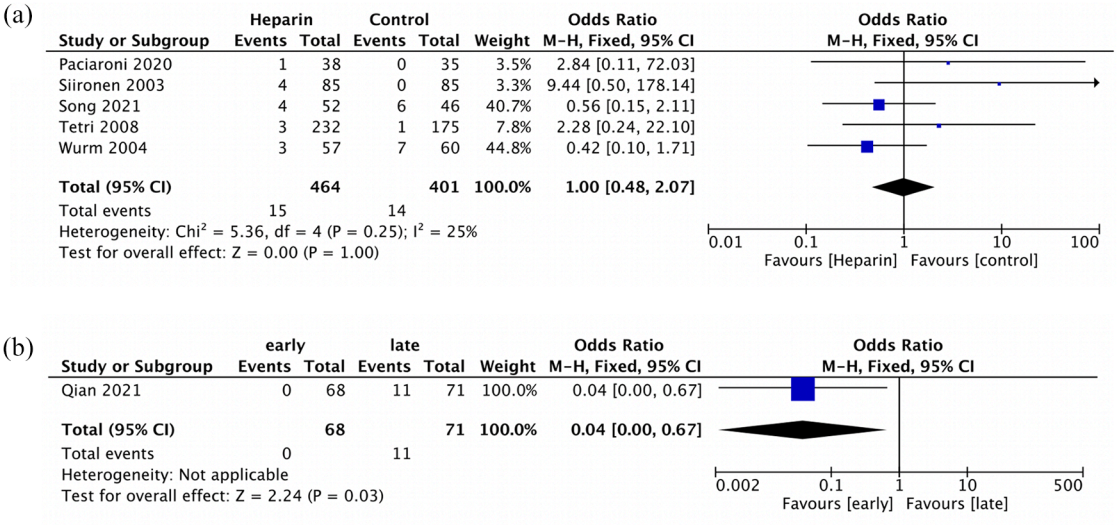

Figure 5. Forest plot of meta-analysis of extracranial hemorrhage: (a) heparin *versus* control group and (b) early heparin *versus* late heparin group.

95% CI, 0.74–5.11; $I^2 = 80\%$; $p = 0.18$) (Supplemental Figure S3).

Subgroup analysis

Further, we performed subgroup analyses (RCTs and observational studies) for each outcome. Most outcomes were less affected by the type of study overall. However, the results showed a significant reduction in the incidence of DVT in the heparin group in observational studies but did not appear to be observed in RCTs. In RCTs, mortality was reduced in the heparin group, with no significant difference in observational studies.

In RCTs, the incidence of PE was significantly reduced in the heparin group, and there was no significant difference in observational studies (Table 2).

Table 2. Subgroup analysis of outcomes (RCTs and observational studies).

Outcomes	No. studies	No. patients	OR	95% CI	*p*	Heterogeneity (I^2) (%)
DVT*	9	3991	0.53	0.33–0.85	**0.009**	17
RCTs	6	3028	0.69	0.37–1.29	0.24	0
Observational studies	3	963	0.36	0.17–0.77	**0.008**	63
Pulmonary embolism*	8	3584	0.31	0.15–0.65	**0.002**	0
RCTs	6	3028	0.33	0.16–0.70	**0.004**	0
Observational studies	2	556	0.17	0.01–3.62	0.26	NA
Death*	7	2037	0.70	0.54–0.90	**0.006**	0
RCTs	5	1172	0.68	0.47–0.98	**0.04**	0
Observational studies	2	865	0.72	0.51–1.02	0.07	38
Hematoma enlargement#	6	1074	0.88	0.29–2.69	0.82	50
RCTs	3	216	0.44	0.06–3.25	0.42	60
Observational studies	3	858	1.58	0.43–5.85	0.49	26
Extracranial hemorrhage*	5	865	1.00	0.48–2.07	1.00	25
RCTs	3	360	1.16	0.43–3.09	0.77	53
Observational studies	2	505	0.83	0.28–2.48	0.74	10

*Fixed-effect model was used.
#Random-effect model was used.
The bold entries represent $p<0.05$.
DVT, deep venous thrombosis; NA, not available; RCT, randomized clinical trial.

Publication bias and sensitivity analysis

The funnel chart depicting mortality studies exhibited a symmetrical and evenly distributed vertical distribution, with 95% CI encompassing all included trials, indicating the absence of publication bias among the trials (Supplemental Figure S4). Sensitivity analyses were conducted to evaluate the impact of individual studies on overall results. We excluded three studies that used heparin in combination with a compression device when performing sensitivity analyses, and we found the results to be consistent with the above results (Supplemental Figure S5). Upon the exclusion of each study individually, the analysis remained relatively stable.

Discussion

The safety of heparin utilization for prophylaxis against VTE in patients with sICH remains a subject of controversy due to concerns regarding bleeding hazards, particularly the potential expansion of intracranial hematoma and recurrent intracranial hemorrhage.[12,27] Our study showed that prophylactic use of heparin in patients with sICH significantly reduces the incidence of VTE and mortality from any cause and does not significantly increase the risk of hematoma enlargement and extracranial hemorrhage. In addition, we found no significant difference in efficacy and safety outcomes between early use of heparin for preventing VTE compared with late use.

More recently, a 2022 guideline from the AHA/ASA recommended (a class 1 level of evidence B-R) intermittent pneumatic compression (IPC) for inactive stroke patients has been shown to reduce VTE and improve survival.[8] However, there are several contraindications to the use of IPC in clinical practice, such as the presence of severe congestive heart failure, severe skin problems on the legs, or severe peripheral vascular

disease. Adherence issues were observed in both the Clots in Legs Or sTockings after Stroke (CLOTS) 3 study and PREvention of VENous Thromboembolism in Hemorrhagic Stroke Patients (PREVENTIHS) study, with less than a third of patients achieving perfect adherence (using IPC for the entire intended duration).[11,28] Sprügel *et al.*[29] reported that the frequency of prophylaxis against VTE with heparin in patients with sICH was less than 2% in all study subgroups, suggesting that clinicians are very cautious about the use of heparin. However, our results suggest that heparin reduces the incidence of VTE in patients with sICH without increasing the rate of hematoma enlargement and disability, consistent with previous meta-analyses,[12,14,30] which provides a positive basis for the safety and effectiveness of heparin in the prevention of VTE in patients with cerebral hemorrhage.

However, it's worth pointing out that several studies have suggested that heparin use may result in a worse prognosis. Hill *et al.* performed a comprehensive analysis of the INTERACT2 trial database and found that subcutaneous heparin administration was associated with adverse outcomes in acute sICH, primarily due to increased residual disability.[10,31] However, it should be noted that this study had limited statistical power, possible chance associations and selection bias, and lack of information on the timing and specific type of heparin used. A meta-analysis of nine controlled studies suggested that prophylactic heparin results in a no significant reduction in any VTE; also, no effect on bleeding was observed.[11]

Additionally, it is worth noting that our study has revealed in a meta-analysis that the prophylactic use of heparin in sICH patients can significantly reduce mortality rates and lead to favorable outcomes, which differs from previous research findings.[11,12,14] In a study targeting sICH patients with atrial fibrillation, anticoagulant therapy is associated with a reduced risk of thromboembolic events and all-cause mortality.[30] It is hypothesized that the reduction in mortality is attributable to the prophylactic use of heparin, which decreases the incidence of fatal PE in patients with sICH and ameliorates the prognosis of those with underlying conditions such as atrial fibrillation and cerebral infarction. This is achieved with the trade-off of a nonsignificant increase in hematoma enlargement, indicating the potential clinical benefits of antithrombotic prophylaxis in patients with cerebral bleeding.

In addition, there are also controversies about the timing of heparin to prevent VTE in patients with cerebral hemorrhage. It is important to confirm that the hematoma is stable before early heparin prophylaxis can be given. A 2022 guideline from the AHA/ASA recommending heparin prophylaxis at 24–48 h from ICH onset may be reasonable.[8] While the European Stroke Organization has no recommendations on when to begin heparin.[9] The lack of clear guidelines has resulted in varying initiation times for VTE prophylaxis across different institutions. In a Boeer *et al.*[23] small study involving 68 patients with sICH, the PE was significantly higher at 4.5%, 21%, and 39% when heparin administration was initiated at 2, 4, and 10 days post-onset, respectively. Several analyses have demonstrated the efficacy of risk of VTE and its safety in terms of hematoma enlargement when administered within a range of 1–4 days.[11,19,23] Qian *et al.*[25] showed that heparin for prevention of VTE in a sICH patient is safe regardless of whether it is started 24 h (early) or 72 h (late) after the hemorrhage, risk of hemorrhage enlargement is not associated with early treatment, administering late did not increase VTEs. Furthermore, the study conducted by Kananeh *et al.*[24] demonstrated that initiating prophylaxis with heparin within 24 h did not result in a significant increase in hematoma, although there was no change in length of stay and mortality compared to patients who started heparin after 24 h, the patients in the ultra-early group (⩽24 h) were likely highly selected individuals. Therefore, this study pooled data from these studies and showed no significant difference in efficacy or safety outcomes between early and late prophylactic heparin use in patients with sICH. It seems safe to start anticoagulant therapy within 24–48 h. However, this pooled result needs to be interpreted with caution due to differences in the definitions of the timing of early and late heparin use in the included studies and the small number of included studies. More RCTs are needed to determine a more appropriate duration of treatment.

We found three previously published meta-analyses on this topic up to the date of our search.[11,12,14] The study of Paciaroni *et al.*[14] was published earlier and included only four studies. However, the reported studies were limited in number, and their

sample sizes were insufficient. The quality of evidence is compromised by small sample sizes as outcomes frequently deviate from the desired informative magnitude. This makes it possible for small source trials with very positive results to unduly influence meta-analysis. The meta-analysis of Paciaroni *et al.*[11] included nine studies (including their original PREVENTIHS study), but only the outcomes of VTE and mortality were reported in his study, and safety outcomes such as extracranial hemorrhage and disability rates were not discussed. Some of the studies included in this analysis exhibited suboptimal quality, including those published in languages other than English. This could potentially introduce various biases and result in a reduced level of evidential support. Pan *et al.*[12] included nine studies with some language bias and did not perform subgroup analyses of the results did not further explore the sources of heterogeneity in the studies. This study builds on previously published publications, adds to recently published studies, and shows the latest pooled results with appropriate statistical methods.

On the contrary, our study possesses certain advantages: (1) it is a meta-analysis that includes the latest studies and boasts the largest sample size. Additionally, we performed subgroup analyses for various outcomes, encompassing both RCTs and observational studies. (2) This study is the first meta-analysis to explore the timing of prophylactic heparin treatment. (3) Prior research has provided limited coverage of diverse results. This study has garnered the highest number of reports and undergone the most extensive analysis, including not only DVT and mortality, but also hematoma enlargement, extracranial hemorrhage, PE, and major disability.

Limitations

Admittedly, it should be noted that this study has certain limitations: (1) not all of the studies included were RCTs; five of them were observational studies, which may introduce some bias and reduce the reliability of the sample. (2) Individual data was not available, and we could not stratify outcomes based on factors such as etiology of sICH or location and size of hematoma due to limited information. (3) There was no standardized anticoagulation regimen across studies in terms of treatment initiation, duration, dosage, etc., although Table 1 provides detailed protocols for each study. (4) There was a lack of uniformity in defining the outcome events (symptomatic and/or asymptomatic DVT), and certain studies experienced reduced sample sizes, particularly those that were randomized.

Conclusion

In conclusion, our findings suggest that administering heparin as a preventive measure for patients with spontaneous hemorrhagic stroke is associated with a significant reduction in the incidence of VTE and mortality. Furthermore, there is no significant increase observed in hematoma enlargement or extracranial bleeding and no significant rise in the incidence of severe disability among patients with sICH. In addition, no significant differences were found between early and late prophylactic use of heparin, but there is currently only limited evidence. Based on these findings, it appears safe to use prophylactic heparin in clinical practice for preventing VTE in patients with sICH. This meta-analysis provides valuable insights into how large RCTs should be designed and offers useful information regarding the safety of administering prophylactic heparin to individuals with sICH.

Declarations

Ethics approval and consent to participate

Not applicable (this paper was provided based on researching in global databases).

Consent for publication

Not applicable.

Author contributions

Yifu Zhou: Conceptualization; Investigation; Methodology; Validation; Writing – original draft; Writing – review & editing.

Gang Wang: Data curation; Investigation; Methodology; Software; Writing – review & editing.

Chunxiao Xue: Data curation; Investigation; Methodology; Resources; Software; Writing – review & editing.

Guojun He: Data curation; Investigation; Methodology; Software; Supervision; Writing – review & editing.

Yan Zhang: Investigation; Methodology; Resources; Writing – review & editing.

Feilong He: Investigation; Methodology; Software; Writing – review & editing.

Chenjun He: Investigation; Methodology; Resources; Validation; Writing – review & editing.

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ORCID iD
Xiaosong Liang https://orcid.org/0009-0006-8789-0609

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Appendix

List of abbreviations

AHA/ASA	American Heart Association/ American Stroke Association
CI	Confidence intervals
DVT	Deep venous thrombosis
GOS	Glasgow Outcome Scale
INTERACT2	The second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial
IPC	Intermittent pneumatic compression
mRS	modified Rankin Scale
NOS	Newcastle-Ottawa Scale
OR	Odds ratio
PE	Pulmonary embolism
RCTs	Randomized controlled trials
sICH	Spontaneous intracranial hemorrhage
VT	Venous thromboembolism