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Heparin therapy in sepsis and sepsis-associated disseminated intravascular coagulation: a systematic review and meta-analysis

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Abstract

Background Sepsis is a life-threatening condition that affects 49 million people annually. Managing sepsis-associated coagulopathy poses a significant challenge due to its high mortality rates in intensive care. Recent reports suggest that administering heparin may offer potential survival benefits in sepsis and coronavirus disease cases. However, there is currently no established evidence supporting the use of heparin for sepsis. Thus, in this study, we aimed to assess the efficacy of heparin administration in patients with sepsis.

Methods A systematic review was conducted following the PRISMA guidelines. The searches included MEDLINE, Cochrane, and Japanese databases up to January 2023. The inclusion criteria consisted of randomized control trials (RCTs) involving adult sepsis patients receiving heparin. The risk of bias was assessed using RoB2, and the data extraction included 28-day mortality and bleeding complications.

Results Out of 1733 initial articles, only three studies met the inclusion criteria. The analysis, which included 426 patients, showed no significant difference in 28-day and in-hospital mortality between the heparin and control groups (risk ratio [RR] = 0.86, 95% confidence interval [CI]: 0.60–1.24). Subgroup analysis of sepsis-associated disseminated intravascular coagulation (DIC) patients ($n = 109$) also did not show a significant reduction in mortality (RR = 0.84, 95% CI: 0.51–1.38). Heterogeneity was zero, and no publication bias was observed. Additionally, there was significant difference in bleeding complications (RR = 0.49, 95% CI: 0.24–0.99, $p = 0.047$).

Conclusions This meta-analysis did not demonstrate a survival benefit of heparin administration in patients with sepsis and sepsis-associated DIC. Further investigation into the potential benefits of heparin is warranted. Moreover, the analysis revealed no increase in bleeding risks with heparin administration; instead, a significant reduction in the risk of bleeding was noted.

Trial registration This review was preregistered with PROSPERO (registration: CRD42023385091).

Keywords Sepsis, Disseminated intravascular coagulation, Heparin, Low molecular weight heparin

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Background

Sepsis is a life-threatening disease affecting 49 million people annually and is a serious problem in intensive care medicine [1]. Furthermore, mortality rates increase when sepsis is complicated with coagulopathy. Recently, an anticoagulant therapy using heparins for coronavirus disease (COVID-19) has been reported to improve survival outcomes [2–4]. Heparin is popularly used globally and is recognized as a multifunctional agent, encompassing both anticoagulant and anti-inflammatory properties [5, 6]. However, the Japanese guidelines for sepsis do not recommend heparin for septic disseminated intravascular coagulation (DIC). Similarly, the Surviving Sepsis Campaign 2021 does not endorse the use of anticoagulants for patients with sepsis except for the prevention of deep vein thrombosis/venous thromboembolism [7]. Consequently, heparin has not been widely adopted as the treatment of sepsis in many countries. However, heparin may be effective in sepsis, as it was effective in COVID-19. Recent studies suggest that administering heparin for sepsis may contribute to improved prognosis [4, 8, 9]. Several meta-analyses examining the impact of heparin on sepsis have emerged [10–14]. Some of these analyses may be limited by heterogeneity in study design and patient populations. Thus, we aimed to re-evaluate the efficacy of heparin administration in patients with sepsis and sepsis-related DIC. We conducted a systematic review and meta-analysis, focusing mainly on English literature, to assess the efficacy of heparin administration in patients with sepsis and sepsis-associated DIC.

Materials and methods

Protocol and registration

This study was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42023385091). Ethical approval and consent to participate were not required for the systematic review.

Search strategy

We searched the MEDLINE (PubMed, 1966–January 2023), Cochrane Central Register of Controlled Trials (January 2023), SCOPUS (January 2023), Igaku-Chuo Zasshi (ICHU-SHI) Japanese Central Review of Medicine Web (1983–January 2023) databases. English articles were included in the analysis.

Each search query included the following terms: "heparin," "heparinoids," "heparin, low-molecular-weight, sepsis," "systemic inflammatory response syndrome," and "disseminated intravascular coagulation". The specific details of the search strategies and results are presented in Supplement Table 1, Additional file 1.

Additionally, we manually searched the references of the articles of interest to identify other potentially relevant studies.

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15].

Study selection and inclusion criteria

Two independent reviewers (T.T. and H.K.) screened the abstracts and titles of the studies and subsequently reviewed the full-text articles for inclusion. The inclusion criteria were as follows:

1. *Study types*: Randomized control trials (RCTs)
2. Population/Patients: Adult patients (age ≧18 years) with sepsis. The results of RCTs that included sepsis in general or mixed DIC due to other underlying diseases, such as trauma and leukemia, were considered only if the results of the subgroup analysis of "septic DIC" were presented in the main or separate papers.
3. *Intervention*: heparin administration at any dose
4. *Control*: Placebo or no intervention (without anti-DIC drugs)
5. *Outcomes*: 28-day mortality, in-hospital mortality

Risk of bias (RoB) in individual studies

Two independent reviewers (T.T. and H.K.) assessed the RoB in individual studies to determine the methodological quality of the articles. Disagreements were resolved through discussion and consensus. Uniform criteria were applied to evaluate the risk of bias associated with individual RCTs, based on the revised Cochrane risk of bias tool for randomized trials (RoB2) [16].

Data extraction

Two independent reviewers (T.T. and H.K.) extracted the data using a standardized data extraction sheet and disagreements were resolved via discussion and consensus. We identified the primary author's name, year of publication, inclusion and exclusion criteria, patient population, and heparin use.

The primary outcome measure was all-cause mortality 28 days after study entry (28-day mortality) and in-hospital mortality. The secondary outcome measures were serious bleeding complications, which are crucial patient outcomes. These were defined as fatal or life-threatening complications, as proposed by the authors of the individual studies.

Table 1 Main characteristics of all studies included in the meta-analysis

Author	Year	Number of sites	Country	Sample Size	Age[a]	Types of intervention	Types of control
Jaimes et al. [17]	2009	1	Columbia	319	I: 55(40–72), C: 57 (39–70)	heparin: 12,000 IU/day	Placebo
Liu et al. [8]	2014	1	China	37	I:48.86(± 14.3), C:47.47(± 14.68)	heparin: 70 U/kg/day	Saline
Weng et al. [19]	2021	1	China	72	I:47.92(± 2.58), C: 49.73 (± 2.50)	heparin: 50 mg/day	Not specified

Abbreviations: *NI* No information, *I* Intervention group, *C* Control group

[a] Presented as mean ± standard deviation or median (interquartile range)

Statistical analysis and data synthesis

We present the results of all analyses according to a random-effects model because this model incorporates statistical heterogeneity. The random-effects model provided a more conservative estimate of the pooled effect size compared to a fixed-effects model. Dichotomous variables (e.g., mortality and serious bleeding complications) are expressed as point estimates with a 95% confidence interval (CI) and p-value. All risk ratios (RR) refer to the risk for the heparin group compared with the placebo or no intervention (without anti-DIC drugs) groups.

All statistical analyses, including RoB within and/or across studies, were performed using Review Manager Version 5.4. (RevMan; The Cochrane Collaboration 2012, The Nordic Cochrane Centre, Copenhagen, Denmark). Statistical significance was set at $p < 0.05$. Furthermore, we created and examined funnel plots to assess the potential presence of publication bias related to the primary outcome.

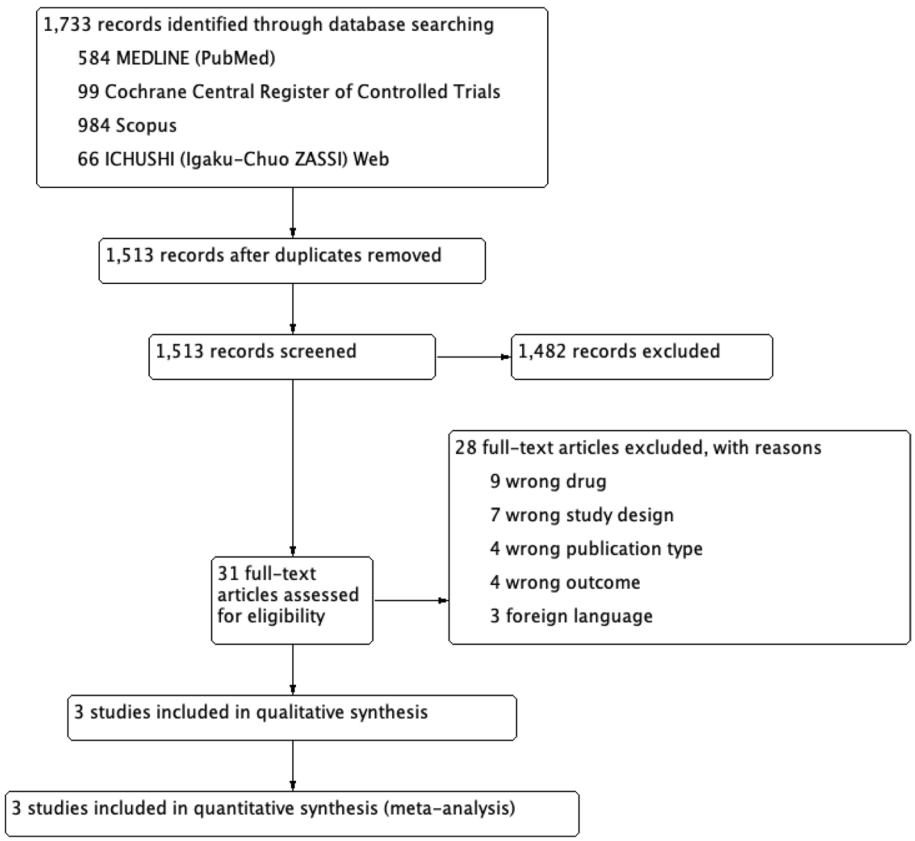

Fig. 1 Flowchart of preferred reporting items for systematic reviews and meta-analyses

Results

Literature search

The PRISMA flowchart selection is presented in Fig. 1. The initial search produced 1733 articles. After excluding duplicates, we identified 1513 studies from the electronic databases, among which 31 studies were retained based on the assessment of the study titles and abstracts. Following a comprehensive review of the full-text articles, 28 studies were excluded due to non-compliance with the inclusion criteria (i.e., the patients did not have sepsis, were not administered the target drug, the study employed a different study design, or the outcomes were incorrect). Ultimately, three studies met the criteria for qualitative synthesis [8, 17–20]. Among these, two studies specifically addressed patients with septic DIC [8, 19]. Geographically, two of the three studies originated from China, while the remaining studies were conducted in Colombia. Details of the characteristics of the included studies are listed in Table 1.

RoB within studies

The RoB assessment in RCTs using RoB2 is outlined in Table 2. Only one study exhibited a high RoB at D2 attributable to its unblinded intervention nature. While all domains raised some concerns, the remainder were deemed to be at low RoB, resulting in an overall judgment of low RoB.

Mortality

Mortality was assessed across three studies published between 2009 and 2021. These studies specifically investigated the 28-day mortality and in-hospital mortality [8, 17, 19] (Fig. 1). RRs were assessed through random-effects analysis ($n=426$) in articles focusing on 28-day mortality and in-hospital mortality based on RR; the RR was not significant at 0.86 and 95% CI of 0.60–1.24. The I^2 value was 0%, suggesting that the random effects resulted in a low degree of heterogeneity (Fig. 2a).

Two studies focusing on patients with septic DIC underwent a similar analysis [8, 19] (Fig. 2b). RR was evaluated using random-effects analysis ($n=109$) in articles where 28-day mortality was assessed based on RR; the RR was not significant at 0.84 and 95% CI of 0.51–1.38. The I^2 value was zero, suggesting that the random effects resulted in a very low degree of variability. No indication of publication bias was observed upon visual assessment of the funnel plot (Supplementary Fig. 1a, Additional File 2).

Bleeding complications

Bleeding complications were evaluated in two studies using RRs [17, 19] (Fig. 3). Random effects analysis of the RR for bleeding complications was significant at 0.49 and a 95% CI of 0.24–0.99, $p=0.047$. The I^2 value was 0. As only one study incorporated patients with septic DIC, the results were incorporated into Supplementary Fig. 2, Additional File 3. Visual examination of the funnel plot (Supplementary Fig. 1b, Additional File 2) revealed no discernible signs of publication.

Discussion

Principal findings

This study examined the effects and adverse events of heparin (Unfractionated heparin or heparins) in sepsis and sepsis-associated DIC. While previous reports have indicated the effectiveness of heparin in sepsis, no statistically significant difference was observed in the mortality rates and the risk of bleeding complications in sepsis. Furthermore, a subgroup analysis in patients with septic DIC also indicated no significant differences in mortality.

Comparison with previous systematic reviews

Five meta-analyses examining the impact of heparin on sepsis have been conducted [10–14]. Despite the widespread use of heparin globally, many prior systematic reviews and meta-analyses focused on studies

Table 2 Risk of bias assessment in three studies using RoB2

Author	D1	D2	D3	D4	D5	Overall
Jaimes et al. 2009 [17]	LOW	LOW	LOW	LOW	SOME	SOME
Liu et al. 2014 [8]	SOME	SOME	LOW	LOW	SOME	SOME
Weng et al. 2021 [19]	SOME	HIGH	LOW	LOW	SOME	SOME

Domains:

D1: Bias arising from the randomization process

D2: Bias due to deviation from intended intervention

D3: Bias due to missing outcome data

D4: Bias due to in measurement of the outcome

D5: Bias in selection of the reported result

RoB2, revised Cochrane risk of bias tool for randomized trials, SOME some concerns

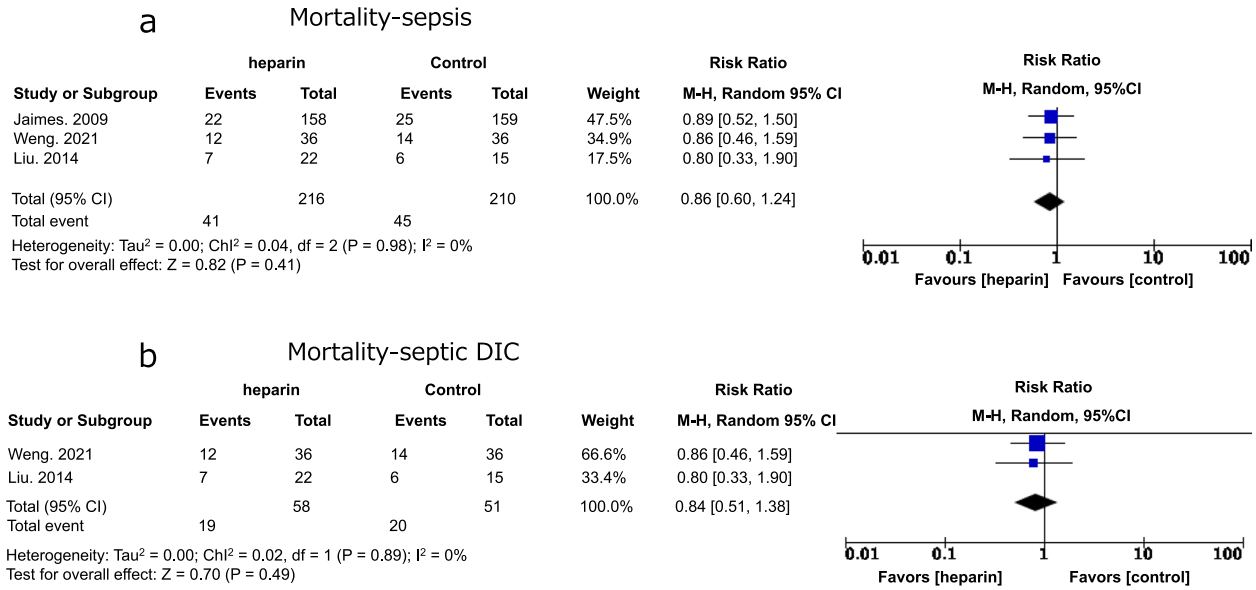

Fig. 2 Forest plot of random-effect analysis comparing mortality rates of heparin administration. **a** Analysis results for sepsis. **b** Analysis results for septic DIC. Disseminated intravascular coagulation: DIC

Fig. 3 Forest plot of random-effects analysis comparing bleeding complications associated with heparin administration for sepsis

conducted primarily in Asian countries. Many studies were inaccessible due to language barriers, primarily being non-English publications, and referencing errors. Concerns about bias arose from the repeated citation of multiple papers by the same author. To ensure rigor and transparency, and to eliminate language barriers allowing for international accessibility, only English articles were included in the analysis. Two of the three studies analyzed in this research originated from China, while the remaining were from South America. Consequently, our findings differed from those reported in a systematic review that included studies conducted in China [13, 14]. Since our study included only RCTs published in English, the power of detection was lower compared to previous research. However, this limitation reflects the current state of evidence. While the addition of recent RCTs did not show statistical significance, the observed trends were consistent with previous reports.

Mortality

This systematic review and meta-analysis examined the efficacy of heparin as an anticoagulant for sepsis and sepsis-associated DIC. Several studies have reported the possible benefits of heparin administration in patients with sepsis and COVID-19 [2–4], both of which are triggered by an infection and are similar in terms of coagulopathy [21]. Septic DIC results in a systemic thrombotic tendency [22], whereas thrombosis due to COVID-19 is more common in the lungs. This may be due to the high expression of angiotensin-converting enzyme 2 (ACE2), a receptor that serves as a gateway for severe acute respiratory syndrome coronavirus 2 to invade host cells, in the lungs [23, 24]. However, septic DIC and COVID-19 are regarded as essentially identical pathologies. COVID-19 was excluded from this study to determine the effect of heparin on sepsis.

After the review, three RCTs met the eligibility criteria. Of the three studies that examined mortality, two were conducted on patients with septic DIC. In each of these studies, the effect of heparin therapy was not statistically significant.

Weng et al. reported [19] a study that examined the efficacy of plasma exchange. In this study, there were three groups: the plasma exchange group, the heparin group, and the usual care group, and therefore they were included in the analysis of this study.

The articles reviewed in this study were published from 2009 to 2021, and the sepsis patient population in each study may have differed because of the influence of the 2016 Sepsis-3 (15), which changed the definition of sepsis. However, the heterogeneity was zero and the findings did not vary.

The meta-analysis was based on the results of only three RCTs. These studies did not demonstrate a survival benefit of heparin administration in patients with sepsis and sepsis-associated DIC. However, all three studies indicated a trend favoring heparin use. Consequently, heparin therapy for sepsis and septic DIC seemed to be effective, although the findings were not statistically significant. (Fig. 2a, b). The results should be interpreted with caution because the results are a synthesis of a limited number of studies, but the trends suggest that heparin could still be effective. It should be noted that anticoagulation therapy has been reported to be effective only for septic DIC, not for sepsis in general [25]; however, in this study, anticoagulation with heparin may be effective for both sepsis in general and septic DIC.

Additionally, recent studies based on the U.S. Mart for Intensive Care (MIMIC)-IV database on sepsis-induced coagulopathy have also reported that early heparin administration improves ICU mortality [9]. The timing of heparin administration was unclear in our study. Taken together, heparin may remain potentially beneficial when used in the right targets and at the right time, although anticoagulation therapy was thought to be effective only in patients with septic DIC.

It was not possible to draw conclusions from the present study due to the lack of studies. High-quality RCTs are required to provide further evidence.

Bleeding complications

In patients with sepsis-related coagulation disorders, the consumption of coagulation factors and platelets results in bleeding tendency [26, 27], and anticoagulant therapy can accelerate the bleeding. Previous studies have indicated an increased risk of bleeding with various anticoagulant therapies. Meanwhile, the present study did not observe such an increased risk; instead, we found a significant decrease in the risk of bleeding after the treatment with heparin (RR = 0.49, 95% CI: 0.24–0.99, $p = 0.047$). Moreover, there was no heterogeneity observed. Although heparin decrease the incidence of bleeding complications in this study, the results should be interpreted with caution due to the limited number of studies included in the analysis.

Although statistical heterogeneity was 0, differences were observed in the rates of bleeding complications between the studies by James et al. and Weng et al. This discrepancy may suggest the potential influence of racial differences. Previous research has indicated that Asians may have prolonged Activated Clotting Time (ACT) with heparin compared to other racial groups[28] and a lower incidence of venous embolism following pelvic fractures [29]. These findings highlight the possibility of racial differences in blood coagulation. Further detailed studies are needed to clarify the impact of these racial differences on hemorrhagic complications in the current context, and such investigations are anticipated in future research.

Limitations

This study has several limitations. Firstly, the restriction to English-language articles resulted in a reduced number of included studies and a concomitant decrease in the detection rate, which is considered a limitation of the current evidence. Secondly, because patients with sepsis in the studies included in the current meta-analysis were diagnosed according to previous sepsis diagnostic criteria (Sepsis-1 [30] or Sepsis-2 [31]), the results of this study may not be fully applicable to patients diagnosed according to the current sepsis diagnostic criteria, Sepsis-3 [32]. Thirdly, detailed treatment data (e.g., time from sepsis diagnosis to treatment initiation and timing of heparin administration) were not evaluated in this meta-analysis due to insufficient data from many individual studies. Future research should involve larger RCTs to explore heparin dosage and the timing of administration more comprehensively.

Conclusions

In all three studies analyzed, the point estimate was below 1.0, suggesting that heparin administration in patient with sepsis may provide a survival benefit; the meta-analysis did not reveal any statistically significant differences. This was probably caused by the small number of studies that could be combined. Therefore, further studies should be conducted on sepsis with coagulation disorders, in which anticoagulants are more likely to be effective.

In addition, regarding bleeding complications, the results of the analysis revealed no increase in bleeding risk, but the frequency of bleeding decreased. Bleeding risk is also influenced by the concentration of

antithrombin and other associated factors; therefore, the data should be interpreted with caution.

Abbreviations

CI	Confidence Interval
DIC	Disseminated Intravascular Coagulation
ICHU-SHI	Igaku-Chuo Zasshi (Japanese Medical Database)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RCTs	Randomized Control Trials
RevMan	Review Manager
RoB	Risk of Bias
RR	Risk Ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12959-024-00653-0.

Additional file 1: Supplementary Table 1: Specific details regarding the search strategies and results.

Additional file 2: Supplementary Figure 1: Funnel Plot for publication bias assessment.

Additional file 3: Supplementary Figure 2: Forest plot of random-effects analysis comparing bleeding complications associated with heparin administration for septic DIC.

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Authors' contributions
TT, HK, and YM identified the studies included in the meta-analysis and analyzed the data. TT drafted the manuscript. KY and TI wrote and revised the manuscript. KY designed the study. All authors interpreted the data and provided important input to the manuscript. All the authors have read and approved the final version of the manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Ethical approval was not required for this systematic review and meta-analysis, because the data were collected from scientific databases.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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