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Comparison of Efficacy and Safety of Talc to Povidone-Iodine Pleurodesis in Malignant Pleural Effusion: A Systematic Review and Meta-Analysis

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Abstract

Malignant pleural effusion (MPE) poses a substantial clinical challenge, necessitating effective interventions. Pleurodesis, commonly employed in MPE management, involves inducing pleural symphysis to prevent fluid accumulation. Talc and povidone-iodine have emerged as prominent agents for pleurodesis, each with its unique characteristics and considerations. This systematic review and meta-analysis aimed to compare the efficacy and safety of talc powder pleurodesis (TPP) and povidone-iodine pleurodesis (PIP) in the management of MPE. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, we conducted a systematic review registered in PROSPERO (CRD42023470930). Randomized controlled trials (RCTs) with TPP and PIP arms for MPE were included. The information sources included electronic bibliographic databases such as PubMed, Scopus, Web of Science, Cochrane, and Embase from inception to November 2023. The Cochrane risk of bias tool was used for the critical appraisal. A meta-analysis using RevMan 5.3 compared outcomes. Out of 105 identified records, 3 RCTs were included in our review. Our review findings revealed a higher success rate for TPP. However, variability existed, with one study indicating better success rates in PIP groups. Adverse events were reported less frequently in the PIP group, suggesting a potentially superior safety profile. TPP showed higher overall success in comparison to PIP, emphasizing the need for cautious clinical decision-making given variability. The potential superior safety profile of povidone-iodine underscores the importance of context-specific choices, considering patient preferences and resource constraints in selecting pleurodesis interventions for MPE management.

Keywords

- malignant pleural effusion
- talc pleurodesis
- povidone-iodine pleurodesis
- efficacy
- safety

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Introduction

Malignant pleural effusion (MPE) poses a substantial challenge in clinical settings, requiring effective interventions to alleviate its symptoms and prevent its recurrence.[1] Pleurodesis, a common therapeutic approach, aims to induce pleural symphysis to prevent fluid accumulation due to MPE, recurrent pneumothorax, and some nonmalignant effusions. It involves chemical agents or physical abrasion during thoracotomy or thoracoscopy. The ideal agent for pleurodesis should be highly effective, having specific characteristics, yet none meet all the criteria, prompting ongoing research.[2]

Talc is widely used despite a lack of consensus on the best agent. Though effective for MPEs, concerns about talc-related acute respiratory distress syndrome arose but were later challenged.[2] Cost and availability limit medical-grade talc use, particularly in resource-poor countries. Povidone-iodine, an affordable antiseptic, proved safe and effective for pleurodesis in prior studies.[1,2]

Talc and povidone-iodine have emerged as prominent agents for pleurodesis in MPE management due to their efficacy and safety profiles.[1,3] Talc pleurodesis (TP), employing sterile talc powder, has long been considered a gold standard due to its high success rates in achieving symphysis and preventing effusion recurrence.[1] Povidone-iodine, an iodophor solution, has gained attention as a potential alternative to talc, this attention is attributed to povidone-iodine having higher efficacy, lower cost, and easy availability compared with talc.[1] Numerous studies have examined the efficacy, safety, and outcomes of these two agents concerning pleurodesis.[1,3,4] TP and povidone-iodine pleurodesis (PIP) have been evaluated for their effectiveness in managing MPE.[2,5] The debate primarily revolves around their comparative effectiveness, safety profile, recurrence rates, and cost-effectiveness in treating MPE. Studies have compared the outcomes and safety aspects of both interventions.[1,3] The comparison between talc and povidone-iodine in pleurodesis is crucial in resource-limited settings due to cost implications. Studies highlight povidone-iodine as a potentially cost-effective alternative to talc.[2] If both agents exhibit comparable efficacy in treating MPE, opting for povidone-iodine could be advantageous.[1,3] Povidone-iodine's lower cost and easy availability make it appealing, especially in areas with limited resources.[1] The potential to achieve similar therapeutic outcomes while minimizing expenses might notably benefit health care systems facing constraints in funding or availability of resources.

Materials and Methods

Registration and Protocol

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting the findings.[6] The study protocol was registered in PROSPERO: International Prospective Register of Systematic Reviews (registration number: CRD42023470930) before conducting the study.

Objectives

The research question for the systematic review is "What are the comparative efficacy and safety of TP and PIP in the management of MPE?" The research question was broken down into (population, intervention, comparison, and outcome) PICO format. The defined "population" was patients with MPE, without restriction on age, sex, and ethnicity. "Intervention" was patients treated with TP, whereas "comparator" was patients treated with PIP. The "outcome" measures assessed were efficacy and safety.

Eligibility Criteria

The studies were considered eligible to be included according to the following criteria.

Inclusion Criteria

(1) Interventional studies that include both TP and PIP in MPE patients.

Exclusion Criteria

(1) Interventional studies that include a study arm involving either TP or PIP with some other comparators; Any study lacking TP and PIP interventions will be ineligible for consideration.
(2) Animal studies.
(3) Nonretrievable articles or abstract-only papers.

Information Sources and Search Strategy

We have critically reviewed the literature to select relevant articles published in the electronic bibliographic databases from inception until December 30, 2023. We systematically performed an advanced electronic search in PubMed, Scopus, Web of Science, Cochrane, and Embase for eligible studies. The search strategy in the above database was performed using the keywords and Medical Subject Headings (MeSH) terms like "malignant pleural effusion," "Pleurodesis," "povidone iodine," "talc," using "AND" and "OR" (►**Supplementary File S1**, available in the online version). We limited the search to English publications.

Study Selection Process and Data Extraction

The studies were screened by title and abstracts followed by full-text articles based on predefined criteria. Two independent reviewers (D.B. and T.B.) performed the study selection, and disagreements were resolved by mutual consultation with a third reviewer (M.K.M). A well-defined data extraction sheet was employed for data extraction. Data from the final selected studies included authors' names, year of publication, study design, sample size, study groups, clinical outcomes, and adverse effects. One reviewer (T.B.) extracted the data in a standardized extraction sheet, and the other reviewer (D.B.) checked for accuracy. Any disagreement was resolved by a mutual discussion or consultation with a third reviewer (M.K.M).

Risk of Bias Assessment

The Cochrane risk of bias assessment tool was used to assess the methodological quality of the included studies.[7] Two

independent reviewers (D.B. and T.B.) performed the quality assessment, and any disagreements between the reviewers were settled through consensus or discussion with a third reviewer (M.K.M.).

Data Synthesis

A narrative synthesis was performed from the extracted data findings and presented in tabular form. The data synthesized in the review summarized the current evidence of efficacy and safety for TP and PIP in MPE. Subgroup analysis could not be performed due to insufficient available data.

Statistical Analysis

We used the Review Manager software (RevMan, version 5.3 for Windows; The Cochrane Collaboration, Oxford, United Kingdom) to conduct a meta-analysis, and odds ratio (OR) with 95% confidence interval (CI) values was calculated.[8] Statistical heterogeneity of data was assessed using the I^2 statistic, and the fixed-effects model was used for studies without significant heterogeneity ($I^2 \leq 50\%$ or $p \geq 0.10$). We could not create a funnel plot for assessing visual inspection of publication bias due to a lack of sufficient eligible studies.

Results

Study Selection

We identified 105 records by searching the MeSH terms from the abovementioned databases. We removed 54 duplicate records before the screening, leaving 51 unique records for further assessment. Out of these, 43 records were excluded, indicating the stringent application of predefined inclusion/exclusion criteria. Subsequently, efforts were made to retrieve eight reports for closer evaluation, although only six reports were successfully obtained and assessed for eligibility. Within this assessment, four reports were excluded, comprising two conference abstracts, one trial protocol, and one observational study that did not meet the desired comparator criteria. We employed a manual search strategy that resulted in the identification of two records. Subsequently, reports sought for retrieval and reports assessed for eligibility both amounted to two records each. However, one report was excluded due to being in a language other than the specified language criterion. Finally, we incorporated a total of three studies in the review.

Study Characteristics

All the final selected studies were randomized controlled trials (RCTs). We identified all research papers by the first author's last name and year (►**Table 1**). In tabular format, we recorded the extracted data from the three studies.[1,3,4] Among the included studies, two were conducted in Egypt[1,3] and one was conducted in India.[4] We extracted data from a study group consisting of patients with MPE who underwent pleurodesis with either povidone-iodine or talc. The flowchart for study selection according to the PRISMA guidelines is shown in ►**Fig. 1**. Among the three included studies, Agarwal et al had conducted their study by taking either benign or MPE.[4] Hence, according to our review criteria, we have extracted data about MPE only.

Overall Efficacy

To compare the efficacy of TP and PIP procedures, we identified and extracted the data on outcome measures, which were in terms of success rate, complete inflation, partial inflation, and failure rate (►**Table 2**).

Success Rate

In Ibrahim et al, the success rate was found to be 80.85% (17 out of 21) and 72.22% (13 out of 18) in the TP and PIP groups, respectively.[1] Similarly, Mohsen et al reported the success rate to be 90.90% (20 out of 22) and 85% (17 out of 20) in the TP and PIP group, respectively.[3] In the case of Agarwal et al, the success rate was high in the case of PIP. The success rate was reported to be 90% (16 out of 18) and 95% (17 out of 18) in the TP and PIP groups, respectively.[4]

Complete Inflation

Ibrahim et al[1] found the complete inflation to be high in the TP group, that is, 71.43% (15 out of 21) than in the PIP group, that is, 66.66% (12 out of 18). In the case of Mohsen et al,[3] the rate of complete inflation was almost similar, which was 86.36% (19 out of 22) and 85% (17 out of 20) in the TP and PIP groups, respectively.

Partial Inflation

The partial inflation rate was reported to be 9.52% (2 out of 21) and 5.55% (1 out of 18) in the TP and PIP groups, respectively, in Ibrahim et al.[1]

Failure Rate

Ibrahim et al reported the failure rate to be 19.04% (4 out of 21) and 27.77% (5 out of 18) in the TP and PIP groups, respectively.[1] A similar trend was observed by Mohsen et al, which was 9.09% (2 out of 22) and 15% (3 out of 20) in the TP and PIP groups, respectively.[3]

Adverse Events

To compare the occurrence of adverse events between the TP and PIP groups, we extracted the relevant data from the

Table 1 Characteristics of selected studies

Author/Year [Ref]	Regions	Study design	Study duration	Population
Ibrahim et al, 2015[1]	Egypt	RCT	Not available	Recurrent MPE
Mohsen et al, 2011[3]	Egypt	RCT	January 2002 to December 2005	MPE
Agarwal et al, 2011[4]	India	RCT	January 2006 to June 2007	MPE

Abbreviations: MPE, malignant pleural effusion; RCT, randomized controlled trial.

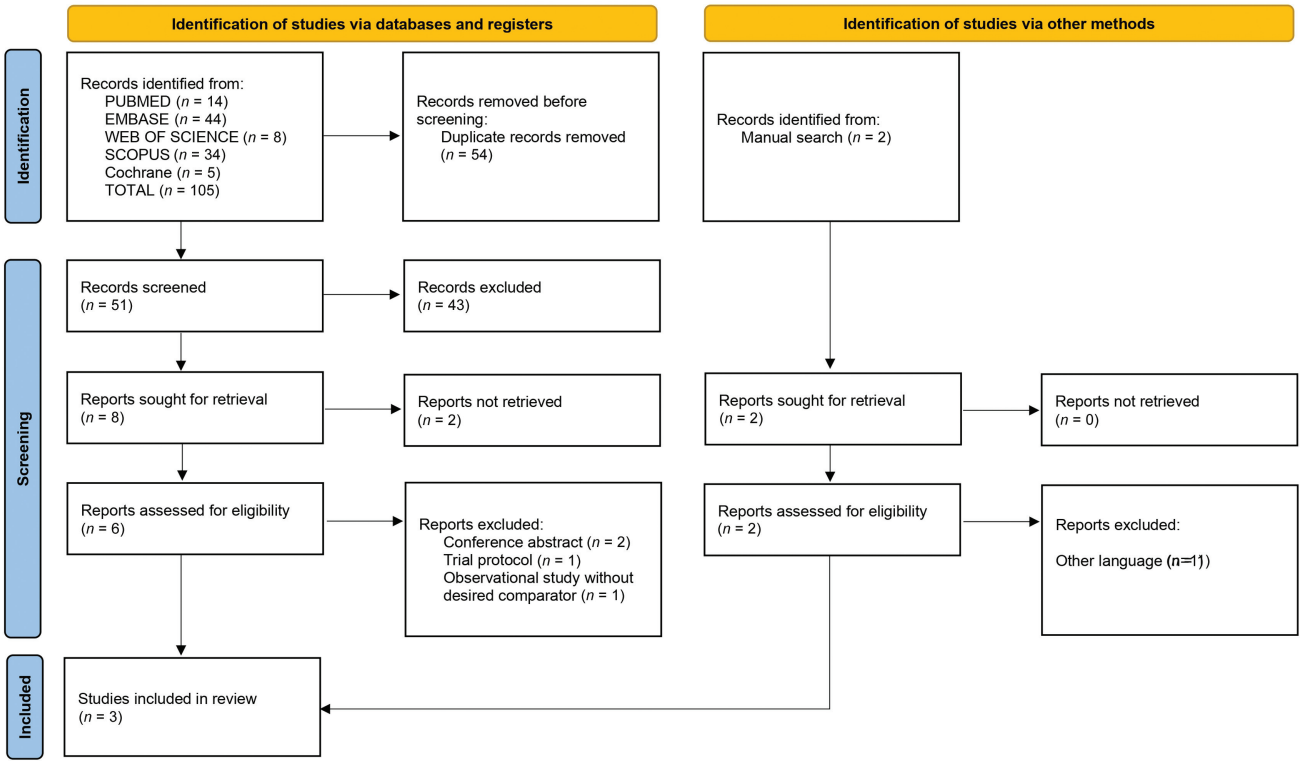

Fig. 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the screening and selection process.

selected studies for postprocedure pain, fever, recurrence of dyspnea, allergy, and death (►**Table 3**).

In the TP group, Ibrahim et al reported 66.66% (14 out of 22), 19.04% (4 out of 21), and 19.04% (4 out of 21) for pain, fever, and recurrence of dyspnea, respectively.[1] Whereas in the PIP group, 50% (9 out of 18), 22.22% (4 out of 18), and 27.77% (5 out of 18) for pain, fever, and recurrence of dyspnea, respectively. There were no adverse events reported for allergy and death in any of the pleurodesis groups.[1]

Mohsen et al reported 18.18% (4 out of 22) for pain and fever in TP.[3] They had reported for fever in 5% (1 out of 20) of the PIP group. There were no adverse events reported for pain and recurrence of dyspnea in the PIP group.[3]

Along with the above adverse events Mohsen et al reported the postprocedure hospital stay and mean survival rate among pleurodesis patients. The postprocedure hospital stay was reported to be 5.7 ± 2 and 4.5 ± 1.1 days in the TP and PIP groups, respectively. The mean survival rate was higher in the PIP group, which was 33.8 months, compared with TP, which was 27.7 months.[3]

Risk of Bias within the Studies

The methodological quality assessment of all three studies has been mentioned in ►**Table 4**. We have conducted the quality assessment for Cochrane risk of bias focused on the following domains: random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other biases.

We have omitted the two domains: blinding of participants and personnel as well as blinding of outcome assessment. Given the inherent differences in the interventions being studied, blinding of participants and personnel is challenging. Specifically, the TP intervention necessitates thoracoscopy, whereas the PIP intervention does not involve this procedure. Consequently, the nature of the interventions makes it impractical to blind participants and personnel to the treatment assignment due to the distinctive procedural requirements associated with each intervention.

The risk of bias in the mentioned domain in all included studies was categorized according to the following: high risk of bias, low risk of bias, unclear risk of bias, and not applicable.

Meta-Analysis

The success rate of TP was compared against PIP among MPE patients. ►**Fig. 2** represents the summary results of pooled data from all three RCTs on success rate.[1,3,4] The fixed-effect model was considered because of the lack of statistical heterogeneity among studies ($I^2 \leq 50\%$ or $p \geq 0.10$). The pooled analysis of the three studies having a total of 117 MPE patients showed a nonsignificant OR of 1.31 (95% CI: 0.46–3.72). The resulting I^2 value of 0% suggests that any heterogeneity might not be important among the included studies, which could be due to a small number of participants.[1,3,4]

Discussion

Our systematic review aimed to compare the efficacy and safety of TP versus PIP in managing MPE. We found that TP demonstrated a higher success rate in achieving pleurodesis than PIP.[1,3] However, one of the studies included in the

Table 2 Overall efficacy between talc pleurodesis and povidone-iodine pleurodesis

Study	Number of participants		Success rate		Complete inflation		Partial inflation		Failure	
	Talc, *n*	Povidone-iodine, *n*	Talc, *n* (%)	Povidone-iodine, *n* (%)	Talc, *n* (%)	Povidone-iodine, *n* (%)	Talc, *n* (%)	Povidone-iodine, *n* (%)	Talc, *n* (%)	Povidone-iodine, *n* (%)
Ibrahim et al, 2015[1]	21	18	17 (80.85)	13 (72.22)	15 (71.43)	12 (66.66)	02 (9.52)	01 (5.55)	04 (19.04)	05 (27.77)
Mohsen et al, 2011[3]	22	20	20 (90.90)	17 (85%)	19 (86.36%)	17 (85%)	01 (4.54%)	00 (0%)	02 (9.09)	03 (15)
Agarwal et al, 2011[4]	18	18	16[a] (90)	17[a] (95)	.	.	.	.	.	.

[a]Calculated from the given percentage value and total no. of participants in Agarwal et al.

Table 3 Adverse events between talc pleurodesis and povidone-iodine pleurodesis

Study[Ref]	Pain		Fever		Recurrence of dyspnea		Allergy		Death	
	Talc, *n* (%)	Povidone-iodine, *n* (%)	Talc, *n* (%)	Povidone-iodine, *n* (%)	Talc, *n* (%)	Povidone-iodine, *n* (%)	Talc, *n* (%)	Povidone-iodine, *n* (%)	Talc, *n* (%)	Povidone-iodine, *n* (%)
Ibrahim et al, 2015[1]	14 (66.66)	09 (50)	04 (19.04)	04 (22.22)	04 (19.04)	05 (27.77)	00 (0)	00 (0)	00 (0)	00 (0)
Mohsen et al, 2011[3]	04 (18.18)	00 (0)	04 (18.18)	01 (5)	00 (0)	.	.	.	.	.
Agarwal et al, 2011[4]	.	.	.	.	.	.	.	.	.	.

Table 4 Cochrane risk of bias assessment for selected studies

Studies[Ref]	Sequence generation	Allocation concealment	Incomplete outcome data	Selective reporting	Other bias
Ibrahim et al, 2015[1]	Low	High	Low	Low	Low
Mohsen et al, 2011[3]	Low	Low	Low	Low	Low
Agarwal et al, 2011[4]	Low	Low	Low	Low	Low

analysis presented differing results, leading to variability in findings.[4] While both interventions were generally well-tolerated, adverse events like pain and fever were reported less frequently in the povidone-iodine group, suggesting a superior safety profile for povidone-iodine. The clinical importance of these findings lies in the similar outcomes of TP and PIP in providing effective and sustained relief for patients with MPE. However, it is essential to consider the small sample size in all the included studies, which may impact the generalizability of these results. A retrospective observational study by Makkar et al showed a 79% success rate in pleurodesis with manageable pain and minimal complications.[9] In a meta-analysis, Muthu et al suggested that povidone-iodine is a cost-effective and widely available alternative, with a success rate of approximately 90%.[10] Their findings revealed no notable adverse effects like thyroid dysfunction or iodine toxicity, at standard doses. While talc poudrage may be superior according to a network meta-analysis, tube thoracostomy with povidone-iodine remains a practical option, especially in resource-constrained settings.[11] Another meta-analysis by Beltsios et al noted the potential superiority of TP over other mechanical approaches.[5] Comparatively better success rate associated with TP suggests that it may be a preferred option for more robust and sustained pleurodesis in patients with MPE. Clinicians may consider TP as a first-line intervention, particularly in cases where long-term efficacy is a primary concern. However, the superior safety profile of PIP, with fewer reported adverse events, presents an important alternative, especially in situations where minimizing complications is a priority. Clinicians should weigh the potential benefits of effective pleurodesis against the safety considerations when selecting the appropriate intervention for individual patients. Our findings align with the study by Muthu et al supporting the role of povidone-iodine as a cost-effective and widely available alternative with a pooled success rate of 90%.[10] A recent comprehensive review conducted by Bonser et al concluded that the current standard of care for pleurodesis in MPE is based on limited evidence.[12]

The study limitations hinder the generalizability of recommendations. However, the available evidence suggests that povidone-iodine is a safe, well-tolerated, and equally effective agent for achieving palliative pleurodesis in MPE. Povidone-iodine has several advantages including low cost, accessibility, and ease of administration, making it a suitable alternative to talc in certain clinical settings.[12] In resource-constrained settings, where talc may pose logistical challenges, povidone-iodine emerges as a practical option without compromising efficacy. Clinicians must consider the local context, patient preferences, and available resources when making decisions about pleurodesis interventions. While TP may be favored in settings with adequate resources and expertise, PIP can be a valuable alternative in situations where logistical constraints or safety concerns are paramount. The choice between TP and PIP should be made through shared decision-making involving the patient, considering individual factors such as comorbidities, treatment goals, and preferences. Additionally, ongoing monitoring for adverse events, patient response, and the need for repeat procedures should be integral components of post-pleurodesis care, irrespective of the chosen intervention. This nuanced understanding of the comparative effectiveness and safety profiles of TP and PIP should inform evidence-based decision-making in the clinical management of MPE. However, this systematic review has certain limitations. The primary constraint lies in the small sample size of the included studies, which may limit the generalizability of the findings. Additionally, variations in, the type of malignancy, and follow-up durations across the three RCTs might have influenced the heterogeneity. Also, including studies reporting no significant statistical differences between TP and PIP could have influenced the pooled results. However, their inclusion was necessary to reduce publication bias and provide a more balanced

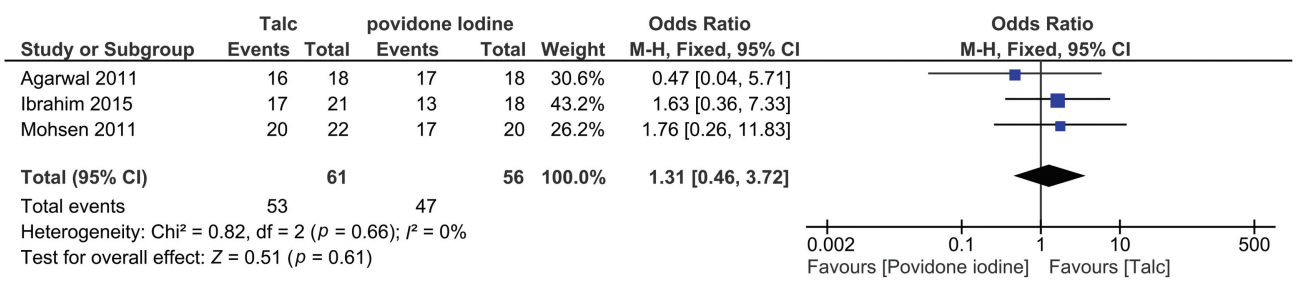

Fig. 2 The success rate in talc pleurodesis versus povidone-iodine pleurodesis.

and comprehensive analysis of the available studies on TP versus PIP in MPE patients. These warrant need for a larger, greater number of studies to strengthen the evidence base for informed clinical decision-making.

Future Directions

Future research should concentrate on conducting well-designed multicenter RCTs with larger sample sizes. Standardization of study protocols, including consistent outcome measures, will enhance the comparability of results across trials. Additionally, exploring patient-specific factors that may influence the choice of pleurodesis agent and conducting long-term follow-up studies are critical steps in advancing our understanding of the comparative effectiveness of TP and PIP. These may help to develop a prediction model for point care for MPE.

Conclusion

Although TP is more effective in achieving pleurodesis, the PIP treatment appears to have a better safety profile with fewer adverse effects. The importance of these results is that both treatments provide effective and long-lasting relief for patients with MPE. However, further research is needed, including larger and more standardized trials, to build on these findings and refine treatment guidelines in this clinical context.

Authors' Contributions

D.B. conceptualized the review question. D.B. and T.B. did the systematic search, data extraction, and risk of bias assessment. D.B. and T.B. interpreted the extracted data. T.B. performed the meta-analysis. D.B. and T.B. wrote the manuscript. M.K.M., S.S.M., and A.K.M. critically evaluated the manuscript. All the authors approved the final draft of the article.

Patient Consent

None declared.

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Conflict of Interest

None declared.

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