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Targeted Versus NonTargeted Epidural Blood Patch for Spontaneous Intracranial Hypotension: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Spontaneous intracranial hypotension (SIH) is characterized by CSF leakage leading to orthostatic headaches and neurological deficits. In some cases, it can be extremely severe to cause nausea, vomiting, and vertigo. Despite conservative treatment, epidural blood patch remains the optimal approach for empiric resolution of symptoms. However, the medical community lacks consensus regarding the best approach to use: targeted epidural blood patch (TEBP) versus nontargeted epidural blood patch (NTEBP).

Methods: A systematic review and metanalysis was conducted on multiple databases with a two-step selection process in order to exclude studies with insufficient data, irrelevance, and lack of comparative analysis between the two procedures. From the included studies, we comparatively analyzed overall good outcomes, success at first attempts, and relapse rates between the groups of study.

Results: We included seven studies matching our inclusion criteria. No significant difference was noted between the TEBP and NTEBP groups concerning the improved overall outcome and success at first attempt. Similarly, comparable statistical significance was noted concerning the relapse rates.

Conclusion: TEBP and NTEBP are both effective treatments for SIH. However, given the lack of statistical difference between the interventions, along with considerations such as the patient risk profiles, physician expertise, and avoidance of invasive imaging procedures, the analysis suggests that NTEBP may be considered a viable initial approach, regardless of the identification of the leak.

1 | Introduction

Spontaneous intracranial hypotension (SIH), first described in 1938 by German neurologist Georg Schaltenbrand [1], is characterized by cerebrospinal fluid (CSF) leakage, resulting in orthostatic headaches and neurological deficits [2]. Often underdiagnosed, SIH can mimic other headache disorders, as patients commonly present with postural headaches that

Abbreviations: CSF, cerebrospinal fluid; DSM, digital subtraction myelography; NTEBP, nontargeted epidural blood patch; SIH, Spontaneous intracranial hypotension; TEBP, targeted epidural blood patch.

improve when lying down and worsen upon standing. While these postural headaches are the hallmark symptom, they can be accompanied by nausea, vomiting, vertigo, photophobia, blurred vision, phonophobia, tinnitus, neck stiffness, and pain with neck flexion [3–10].

MRI is the most accurate diagnostic tool for SIH. A recent meta-analysis of brain MRI findings revealed diffuse gadolinium pachymeningeal enhancement (73%), subdural collections (35%), brain sagging (43%), venous engorgement (57%), and pituitary gland enlargement (38%). Normal MRI results were observed in 19% of patients [11].

Historically, reduced CSF volume was attributed to decreased production, increased reabsorption, or leakage. Bell et al. initially proposed choroid plexus dysfunction and reduced CSF secretion as the primary cause in most cases, classifying low CSF pressure syndromes into five categories: spontaneous (primary), postoperative, post-traumatic, post-lumbar puncture/nerve sleeve tear, and secondary to other medical conditions like cerebral arteriosclerosis or dehydration [12]. However, compelling evidence from recent studies strongly supports direct CSF leakage as the primary cause of SIH [13–16].

Despite advances in high-resolution MRI for CSF leak detection, visualizing and surgically accessing the leak remains frequently impractical. This challenge has fostered the development of less invasive, indirect interventions like epidural blood patching (EBP), which promotes spontaneous healing [16, 17]. EBP offers a less invasive alternative to open surgery (dural repair or surgical ligation of CSF-venous fistulas) even when the leak location is known and includes both targeted (TEBP) and nontargeted (NTEBP) techniques. TEBP utilizes imaging to pinpoint CSF leaks, enabling direct blood injection, while NTEBP involves empirical injections at common leakage sites without prior imaging, relying on the patch's spontaneous spread. EBP's effectiveness stems from a dual mechanism: the injected blood spreads, creating a mechanical tamponade that physically seals the leak, and coagulation triggers an inflammatory and fibroblastic response, promoting fibrin seal formation and healing [17]. While TEBP offers greater precision, NTEBP remains more common, as studies have not demonstrated clear superiority for TEBP regarding symptom resolution, success rates, or complication risks [18–25].

This systematic review and meta-analysis aims to compare the clinical outcomes and complications of targeted versus nontargeted EBP in the treatment of SIH.

2 | Methods

This review was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines.

The PICO framework (Population: intracranial hypotension syndrome; Intervention: Targeted blood patch; Comparison: Nontargeted blood patch; Outcome: clinical improvement) was used to formulate the research question (Figure 1) [26].

2.1 | Search Strategy

Two authors (GT and MP) performed a comprehensive search on PubMed/MEDLINE and Scopus databases to identify relevant studies comparing TEBP versus NTEBP using the search terms: ("blood patch" OR EBP) AND (intracranial hypotension OR SIH OR spontaneous intracranial hypotension OR craniospinal hypotension OR low pressure headache OR low-pressure headache OR cerebrospinal fluid hypovolemia OR cerebrospinal fluid hypotension OR cerebro-spinal fluid hypotension OR CSF hypotension OR cerebrospinal fluid hypovolemia OR cerebro-spinal fluid hypovolemia OR CSF hypovolemia).

The search was updated to November 28, 2024, with no time limit. A forward search on references of the retrieved articles was also performed to increase the search power.

2.2 | Study Selection

The search was limited to peer-reviewed studies published in English. Only papers that contained quantitative data were included. Other inclusion criteria were as follows: papers comparing TEBP versus NTEBP; studies including more than five patients; follow-up of at least 6 months. Review papers and papers not presenting explicit data for each group (TEBP vs NTEBP) were excluded.

Two authors (CLS and MP) independently screened titles and abstracts of the articles retrieved by the search algorithm and selected studies according to the inclusion or exclusion criteria.

After the exclusion of ineligible articles, full texts of the remaining studies were assessed for eligibility according to the same criteria (Figure 1). Disagreements were resolved in a consensus meeting through a new reading of the article and collegial re-evaluation of the extracted data.

2.3 | Data Extraction

For each eligible study, we extracted author, year of publication, study design, total number of patients per treatment group, number of successful first tries for each group, number of individuals that required multiple EBPs, overall clinical outcomes, complications, and radiological findings. Clinical outcomes included global improvement of headaches post-intervention. Radiological outcomes reflected the eligibility to locate the leak by imaging.

2.4 | Presentation of Data and Statistical Analysis

Following a systematic review, we conducted a meta-analysis where sufficient data were available from multiple studies for a given outcome. This analysis calculated odds ratios (ORs) to compare TEBP with NTBP for a limited number of outcomes. OpenMetaAnalyst software (http://www.cebm.brown.edu/openmeta/), an R-based program funded by the Agency for

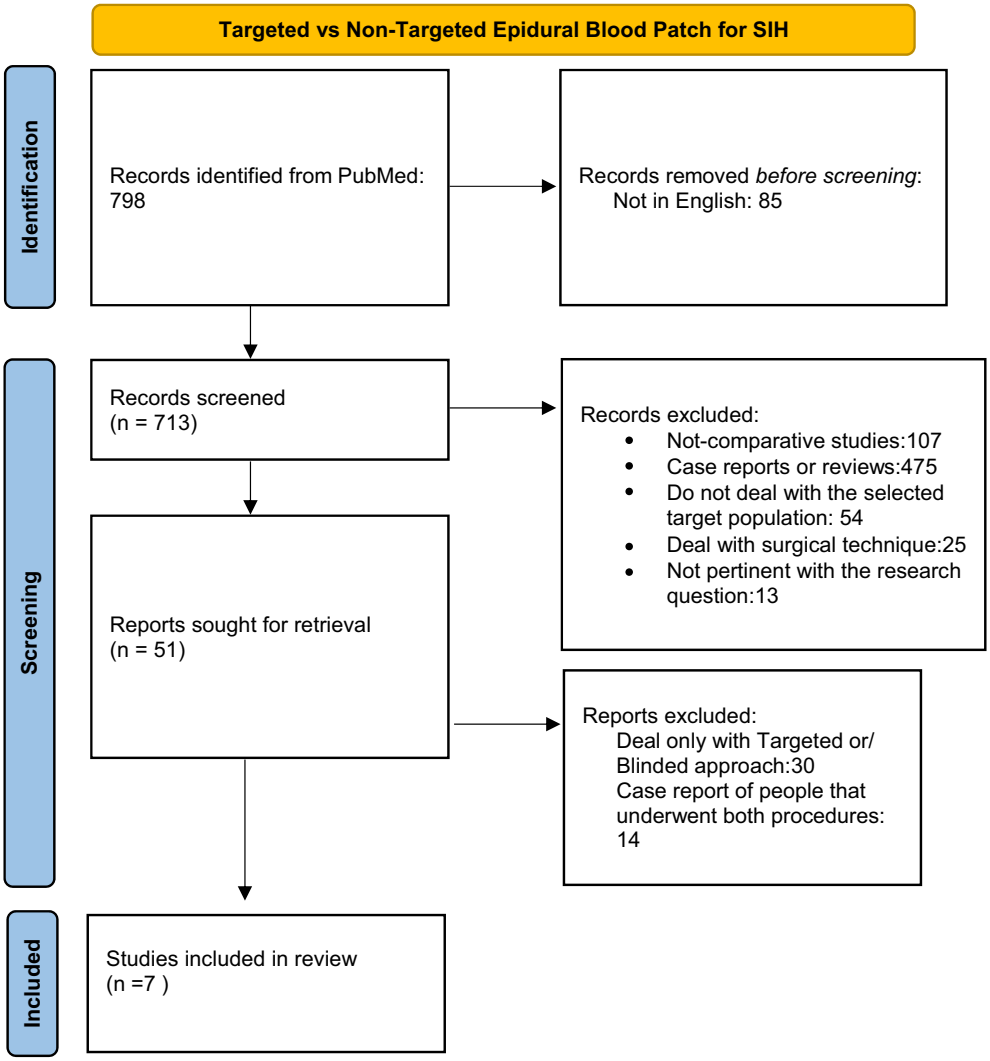

FIGURE 1 | PRISMA 2020 flow diagram for new systematic reviews.

Healthcare Research and Quality (Rockville, MD, USA), was used for all statistical analyses.

2.5 | Quality Assessment (Risk of Bias)

The ROBINS-I V2 (Risk Of Bias In Non-randomized Studies—of Interventions, Version 2) assessment tool along with the robins application (https://mcguinlu.shinyapps.io/robvis/) was used to evaluate study quality through visual representations (Figure 2).

3 | Results

The search algorithm retrieved 798 results. The initial screening process excluded the irrelevant articles based on predefined inclusion and exclusion criteria. Specifically, 85 articles were not in English, 107 were non-comparative studies, 475 were reviews and case reports, 54 did not deal with the selected population, 25 focused on surgical techniques, and 13 were not pertinent to the research question.

A secondary selection phase focused on identifying studies specifically comparing TEBP versus NTEBP. During this stage, articles with insufficient data and reviews were also excluded ($n = 44$).

Lastly, we included seven comparative studies in the final analysis (Figure 1; Table 1), whose quality was assessed using the ROBINS-I V2 tool for risk of bias evaluation (Figure 2).

The study selection process was documented using the PRISMA 2020 flowchart, outlining the stages of identification, screening, eligibility assessment, and final inclusion (Figure 1).

3.1 | Systematic Review

The procedural approaches for epidural blood patching varied across the seven included studies. For targeted epidural blood patch (TEBP), injection sites were chosen to directly address the identified CSF leak, which could be located at cervical, thoracic, or lumbar levels as determined by imaging. Nontargeted

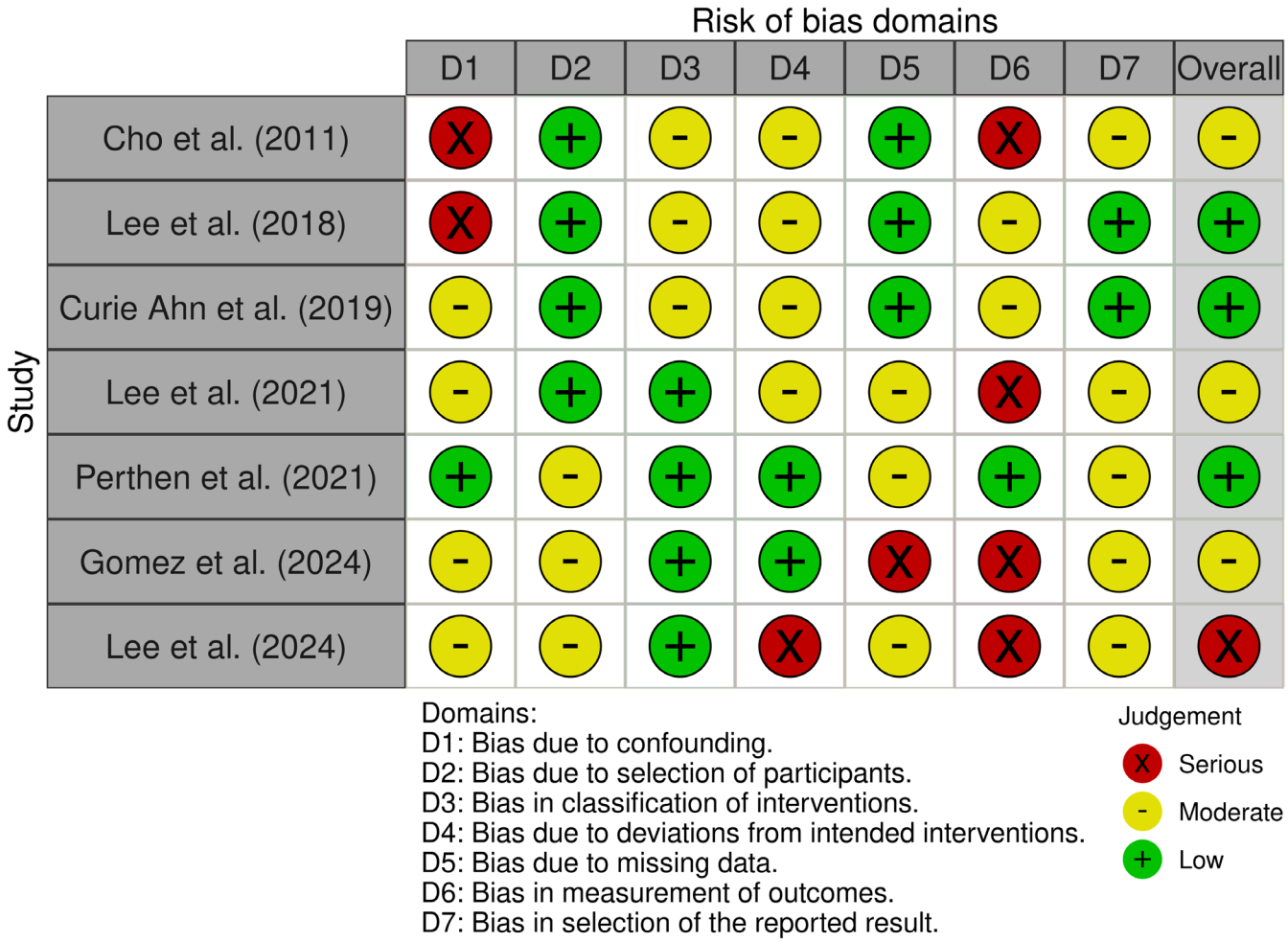

FIGURE 2 | ROBINS-I V2 (Risk Of Bias In Non-randomized Studies—of Interventions, Vers. 2).

epidural blood patch (NTEBP) techniques also demonstrated variability; some studies reported empirical lumbar injections (e.g., L3-L4 level [27, 32]), while others utilized specific multi-level protocols such as combined cervicothoracic (e.g., C7/T1) and thoracolumbar (e.g., T12/L1) injections [29], or targeted the cervicothoracic junction alone for unlocalized leaks [30]. Perthen et al. [31] also noted NTEBP typically being performed in the lumbar region [31].

An overview of the findings from the selected studies suggests that while both TEBP and NTEBP contribute to overall patient improvement, there is little to no significant difference in overall success rates between the two approaches.

Supporting this, Ahn et al. [29] found no significant difference in efficacy between the two groups, reporting that 71.4% of NTEBP patients and 69.3% of TEBP patients experienced complete relief after the first patch [29].

In contrast, both Cho et al. [27] and Lee et al. [31] reported notable differences in the effectiveness of the first patch between the two approaches [27, 30]. Cho et al. showed that patients in the TEBP (87.1%) experienced complete relief more often than the NTEBP (52%) group [27]. A decade later, Lee et al. confirmed those results, reporting 73.5% success for TEBP versus 45.8% for NTEBP at the first attempted patch [30].

The need for repeated EBP is a key factor assessed to address the long-term efficacy of the two approaches. Ahn et al. and Gomez et al. found no significant difference in the need for repeat blood patches between the two groups [29, 32]. However, Cho et al. noted that 63.2% of patients in the NTEBP required multiple repeat patches due to persistent headaches, compared to 12.9% of the TEBP group [27].

Long-term recurrence rates provide insight into the durability of symptom relief. Perthen et al. reported that TEBP has a higher relapse (23%) rate compared to NTEBP (10%) suggesting that while TEBP may provide an initial higher success, it may not always offer more durable relief [31]. In 2018, Lee et al. supported the findings of Perthen et al. stating the need for multiple patches regardless of the technique [28].

Finally, because of risks associated with spinal cord compression, chemical meningitis, iatrogenic epidural hematoma, and intrathecal blood injection, some authors advocate for NTEBP as a first-line treatment, reserving TEBP for refractory cases.

3.2 | Meta-Analysis

A meta-analysis was performed to evaluate the comparative effectiveness of TEBP and NTEBP in the treatment of SIH. The

TABLE 1 | Summary of the included studies.

Author and year	Study design	Patients treated (n)			Main details on EBP technique		Early symptoms relief		Need for retreatment		Overall outcome after treatment	
		Total	TEBP	NTEBP	TEBP imaging modality for leak detection	NTEBP site of injection	TEBP	NTEBP	TEBP	NTEBP	TEBP	NTEBP
Cho et al. [27]	R	56	31	25	Spine MRI, CT-M, Radionuclide Cisternography; Fluoroscopic confirmation	Lumbar (mainly L3-L4) or Upper Thoracic (mainly T4-T6)	27/31	18/25	27/31	12/25	27/31	18/25
Lee JY et al. [28]	R	62	19	43	MRI, CT Myelography (CT-M)	Not Specified	10/19	37/43	NR	NR	10/19	37/43
Ahn et al. [29]	R	116	88	28	CT Myelography (CT-M)	C7/T1 and T12/L1 junctions (two-site blind)	62/88	20/28	26/88	10/28	85/88	25/28
Lee HJ et al. [30]	R	68	60	8	Cisternography, Myelography	Cervicothoracic junction (for unlocalized SIH)	50/60	0/8	10/60	8/8	50/60	0/8
Perthen et al. [31]	R	89	23	66	Dynamic CT-M, Fluoroscopic Myelography (for localization); CT guidance (for injection)	Lumbar region	NR	NR	3/23	7/66	13/23	39/66
Gomez et al. [32]	R	36	11	25	MRI Spine, Digital Subtraction Myelography (DSM), MR Myelography, Cisternography	Lumbar (L3-L4 level)	9/11	3/25	11/11	18/25	NR	NR
Lee J et al. [33]	R	84	61	23	CT, MRI, CT-M (for localization); Fluoroscopic guidance (for EBP procedure)	Suspected leak/trauma site (often lumbar)	37/61	11/23	24/61	12/23	37/61	11/23

Abbreviations: C/T/L, Cervical/Thoracic/Lumbar; CT-M, CT Myelography; CT guidance, Computed Tomography guidance (for injection); DSM, Digital Subtraction Myelography; Fluoro., Fluoroscopy/Fluoroscopic; MR Myelography, Magnetic Resonance Myelography; MRI, Magnetic Resonance Imaging; NR, Not Reported (for outcome data); NTEBP, NonTargeted Epidural Blood Patch; R, Retrospective study; RC, Radionuclide Cisternography; TEBP, Targeted Epidural Blood Patch.

primary outcomes assessed were: (1) early symptom relief, (2) the need for retreatment due to symptom recurrence, and (3) overall outcome following one or more treatments. Pooled proportions and odds ratios were calculated. While TEBP appeared to be associated with numerically higher proportions of early symptom relief and overall positive outcome, and a lower proportion of retreatments, these differences were not statistically significant. Considerable heterogeneity was observed across the included studies for all outcomes. These results are summarized in Figure 3 and Table 2.

3.3 | Risk of Bias

The ROBINS-I V2 tool was used. Overall, four of the retrieved studies showed a low risk of bias [27, 28, 31, 33], while one paper was deemed at serious risk of overall bias [32]. In particular, the sixth domain of the ROBINS-I V2 tool, namely the risk of bias in measurement of outcomes, was judged as the domain at higher risk of bias across studies, as only one paper was judged at low risk of bias in this domain [31]. These results are summarized in Figure 2.

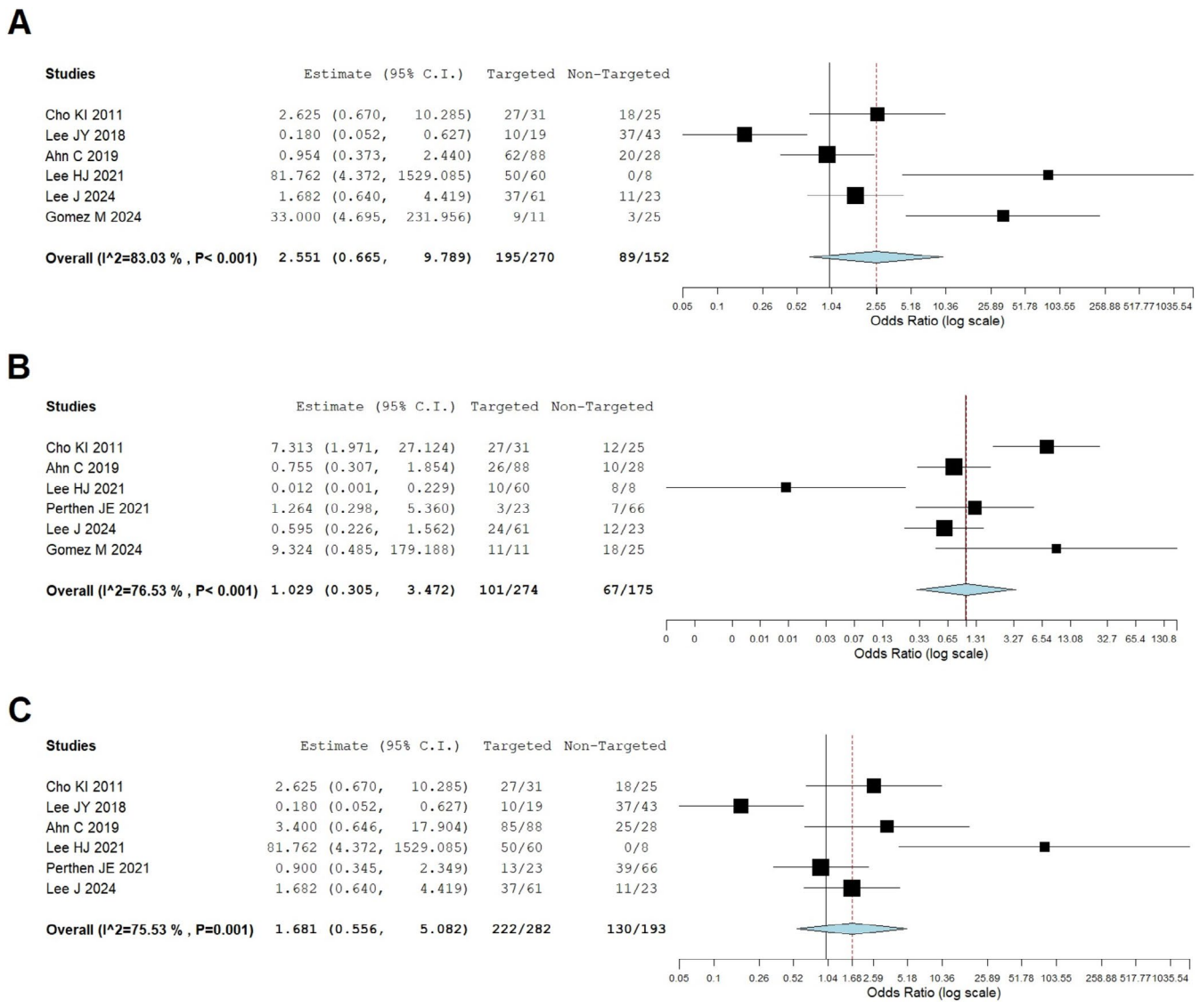

FIGURE 3 | Meta-analysis results. (A) Early symptom relief; (B) Need for retreatment; (C) Overall positive outcome after treatment.

TABLE 2 | Meta-analysis: Pooled proportions and odds ratios.

Outcomes	Proportion (95% CI)		OR (95% CI)	*p*	I^2
	TEBP	NTEBP			
Early symptoms relief	0.737 (0.637–0.837)	0.464 (0.210–0.717)	2.551 (0.655–9.789)	0.2	83%
Need for retreatment	0.469 (0.187–0.751)	0.519 (0.217–0.822)	1.029 (0.305–3.472)	0.96	76%
Overall positive outcome	0.747 (0.601–0.893)	0.569 (0.344–0.795)	1.681 (0.556–5.082)	0.3	75%

4 | Discussion

This meta-analysis aimed at comparing the effectiveness of TEBP compared with NTEBP. While conservative treatment with bed rest, hydration, caffeine, and steroids is often the initial approach, it proves effective in only about 28% of cases [3, 11]. Within these conservative strategies, corticosteroids have been noted for their potential therapeutic role. The clinical benefits in CSF hypotension may derive from several mechanisms as discussed in the literature, briefly including improving brain edema and inflammation from brain sag, inducing fluid retention, reducing CSF hyperabsorption, and facilitating reabsorption of extradural CSF to increase CSF volume [34].

For the remaining patients who do not respond, epidural blood patching (EBP) has become the most significant intervention for substantial symptom relief.

A targeted approach implicates a more sophisticated diagnostic workup often requiring MR myelography with intrathecal gadolinium, digital subtraction myelography (DSM), DSM in lateral decubitus, or dynamic CT myelography [35–41]. Consequently, despite its perceived advantages, TEBP is less frequently used in clinical practice, especially as an initial treatment strategy. Furthermore, medical literature does not currently support a clear superiority of TEBP over NTEBP. To address this gap, we analyzed and compared TEBP and NTEBP for SIH treatment, focusing on three primary endpoints: symptom relief after a single EBP, the need for subsequent retreatment, and the overall positive outcome achieved with one or more EBP procedures.

4.1 | Early Symptom Relief

The findings of this meta-analysis indicate that TEBP does not demonstrate superiority in short-term symptom alleviation compared to NTEBP. This observation supports the hypothesis that a nontargeted approach facilitates effective sealing, resulting in early symptom improvement. However, the long-term efficacy of both techniques is often compromised by the recurrence of symptoms necessitating further intervention.

4.2 | Reintervention

The relapse rate following EBP is a key factor to consider. Although TEBP could be perceived as more accurate and definitive, our meta-analysis (OR 1.029, 95% CI: 0.305–3.472, $p = 0.96$) demonstrates that it does not reduce the need for retreatment compared to NTEBP. However, in some studies such as Moriyama et al. Fei-Fang He et al. and Takai et al. almost all the patients in the TEBP achieved full recovery after a single treatment, highlighting the efficacy when precise imaging techniques were used to locate the leakage [7, 42, 43]. In particular, Fei-Fang He et al. reported an exceptionally high success rate, with all 165 patients experiencing good recovery after TEBP [7]. Differently, Maingard et al. and Rettenmaier et al. reported some cases where redo treatments were necessary after the first TEBP [44, 45]. These findings reinforce the non-superiority of the TEBP with respect to the NTEBP.

Some studies even suggest potentially higher relapse rates with TEBP due to undetected small leaks or the presence of more complex leak patterns in patients initially undergoing TEBP. This could be due to the difficulty in detecting small leaks during targeted procedures or because patients undergoing TEBP often present with more complex leak patterns initially [27].

Our meta-analysis, however, found similar retreatment rates between the two groups. This difference in findings likely reflects the influence of factors such as leak severity, location, and patient-specific anatomy, all of which can affect how long the treatment lasts.

4.3 | Overall Clinical Outcome

Overall, this meta-analysis confirmed the effectiveness of both TEBP and NTEBP in the treatment of SIH. At the conclusion of treatment, TEBP appeared to be associated with a greater proportion of positive outcomes. However, this difference was not statistically significant as determined by the odds ratio (OR). The substantial heterogeneity observed ($I^2 = 75.53\%$) suggests a significant influence of patient selection criteria, procedural variations, and institutional practices on the study results. Although a targeted approach is often advocated for its potential to reduce retreatment rates and improve clinical outcomes, this hypothesis was not supported by our meta-analysis. Our findings are consistent with the results reported by Lee JY et al. [28], Ahn et al. [29], and Lee J et al. [32], who also demonstrated comparable outcomes between targeted and nontargeted approaches, suggesting that the nontargeted approach may be optimal in the majority of clinical settings [28, 29, 33].

4.4 | Considerations

The results of this meta-analysis suggest that NTEBP may be considered as a suitable initial treatment approach for SIH in most clinical settings. Although TEBP showed trends toward higher first-attempt success rates and potentially better overall outcomes, the considerable heterogeneity among the included studies raises concerns about the reliability and generalizability of these findings. Indeed, the localization of CSF leaks for targeted approaches involved various imaging modalities, including MR myelography, CT myelography, and DSM, as reported in Table 1. However, the included studies generally did not stratify TEBP outcomes by the specific imaging technique used for guidance. Consequently, a sub-analysis to determine if certain targeting modalities are associated with better outcomes than others was not feasible and remains an area for future investigation. This heterogeneity underscores the need for further research to identify the specific patient populations that might benefit most from TEBP. In the interim, NTEBP offers a more readily accessible, cost-effective, and efficient option, particularly for patients with difficult-to-access or localized leaks. Furthermore, the noninvasive nature of NTEBP, avoiding the need for advanced imaging and targeted injections, potentially reduces the risk of complications. Therefore, while TEBP remains a viable alternative, this analysis suggests

the potential for broader application of NTEBP as a first-line intervention for SIH, based on its favorable safety profile and practical advantages, especially given the current uncertainties surrounding the true benefits of TEBP.

4.5 | Risk of Bias and Limitations

The substantial heterogeneity among the included studies significantly limits the generalizability of our findings. Beyond this, a key concern is the potential for overlapping patient cohorts in studies from the same institutions, specifically Cho et al. [27] and Lee JY et al. [28] from Samsung Medical Center [27, 28], and Ahn et al. [29] and Lee J et al. [32] from Seoul National University Bundang Hospital [29, 33]. The latter pair also had temporally overlapping study periods (Ahn: 2013–2017; Lee J: 2015–2019), increasing this risk. The extent of any such inter-study overlap could not be quantified from the published data, potentially biasing pooled estimates. Additionally, within-study patient crossover between NTEBP and TEBP arms in some primary studies, though handled as reported in primary studies, adds complexity. Furthermore, our risk of bias assessment highlighted that several included studies presented a considerable risk of bias. This was particularly evident concerning the measurement of outcomes, potential confounding, and deviations from intended interventions. Indeed, the definition and assessment of clinical outcomes, including "early symptom relief" and "overall positive outcome," varied substantially across the studies. These outcomes were generally based on patient-reported measures, such as changes in headache severity (e.g., Visual Analog Scale [VAS] or Numerical Rating Scale [NRS] scores, often with specific thresholds for improvement like $>50\%$ reduction) and qualitative assessments of symptom resolution (e.g., "complete relief," "partial relief," or categories such as "excellent," "good," and "fair"). The need for retreatment was also a common, though variably defined, metric. This significant variability in outcome definition and measurement directly contributed to the observed heterogeneity in our pooled results and represents a key limitation in comparing efficacy consistently. Lastly, while the risks associated with EBP procedures in general and the specific diagnostic interventions required for TEBP are recognized, the included studies did not consistently report comparative data on complication rates specifically distinguishing between the TEBP and NTEBP cohorts. This lack of granular, comparative safety data prevented a quantitative analysis of complications between the two techniques, which is a limitation of this review.

These limitations underscore the need for cautious interpretation of our results and highlight the importance of future research addressing these methodological concerns.

5 | Conclusion

This meta-analysis suggests that while TEBP may offer marginal trends toward higher rates of early symptom relief, improved overall outcomes, and a lower need for retreatment, these potential benefits are not statistically significant compared to NTEBP. Therefore, from a practical perspective, considering the comparable effectiveness of both approaches and the significant reduction in pretreatment investigations required for NTEBP, NTEBP appears to be a reasonable initial treatment strategy. This approach eliminates the need for invasive imaging, simplifies the procedure, and reduces associated risks, all while preserving therapeutic efficacy.

Author Contributions

Matteo Palermo: conceptualization, investigation, writing – review and editing, writing – original draft, data curation. **Carmelo Lucio Sturiale:** conceptualization, investigation, methodology, validation, writing – review and editing, visualization, writing – original draft, supervision. **Sonia D'Arrigo:** investigation, methodology, validation, formal analysis, visualization, writing – review and editing, supervision. **Gianluca Trevisi:** conceptualization, methodology, validation, software, formal analysis, visualization, writing – review and editing, data curation.

Ethics Statement

IRB approval was not required for a systematic review in our institute.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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