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Efficacy of Over-the-Scope Clips Compared to Standard Therapy for Nonvariceal Upper Gastrointestinal Bleeding—A Systematic Review and Meta-analysis of Randomized Trials

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Abstract

The current standard of treatment for nonvariceal upper gastrointestinal bleeding (NVUGIB) includes endoscopic hemostasis with either through-the-scope clips or thermal therapy. However, they may be associated with rebleeding, especially in high-risk ulcers. Over-the-scope clips (OTSC) have been demonstrated in multiple recent studies to be an effective measure for NVUGIB. We aimed to analyze the current literature on standard therapy with OTSC to manage NVUGIB. A meta-analysis was performed by pooling the data from randomized studies obtained from a comprehensive search of Medline, Embase, and Scopus from inception to February 2023. The outcomes analyzed included rates of persistent bleeding, rebleeding, mortality, and duration of hospitalization. A total of five studies were included in the final analysis. There was no significant difference in the risk of persistent bleeding between the groups, with a risk ratio (RR) of 0.29 (95% confidence interval [CI]: 0.07–1.27). The use of OTSC was associated with a significantly lower risk of 7-day and 30-day rebleeding compared with standard therapy with RR of 0.30 (95% CI: 0.16–0.59) and 0.42 (95% CI: 0.24–0.72), respectively. There was no difference in the risk of 30-day mortality or the duration of hospitalization. There was no change in the effect on subgroup analysis of studies using OTSC as first-line therapy. The use of OTSC can reduce the rebleeding rates after endoscopic hemostasis. However, they may not reduce the risk of persistent bleeding or mortality. Future studies are required on the cost-efficacy of this modality.

Keywords

- upper gastrointestinal bleeding
- peptic ulcer bleeding
- over-the-scope clips
- through-the scope clips
- meta-analysis

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Introduction

First and recurrent bleeding from peptic ulcers and other lesions grouped as nonvariceal upper gastrointestinal bleeding (NVUGIB) is associated with significant morbidity and mortality. The current standard of care to treat such patients is standard endoscopic hemostasis via either single or combination therapy with local injection of adrenaline, through-the scope clip (TTS), or thermal therapy with coaptive coagulation.[1] However, in multiple recent trials, it has been demonstrated that standard endoscopic hemostasis was associated with high rates of clinically significant rebleeding.[2] A Doppler endoscopic probe can help decrease rebleeding rates, but it is expensive and often unavailable at many centers.[2] Also, applying conventional TTS clips becomes problematic in ulcers with a fibrotic base or in difficult locations. Hence, a novel method for endoscopic hemostasis was required.

Over-the-scope clips (OTSC) have been developed to manage GI perforations, leaks, and fistulas. This device provides firm tissue apposition with its more prominent jaw and superior strength due to its "bear-claw" design. Also, it can be deployed, keeping the scope much closer to the ulcer with the availability of the included distal attachment cap and tissue anchor. Using these clips for endoscopic hemostasis is relatively new, but it has shown impressive results in multiple recent cohort studies.[3–5] These studies suggest that OTSC clips can also be a first-line treatment for peptic ulcer bleeding.

However, data on the use of OTSC as first-line agents are sparse. Also, applying these clips is technically demanding and has a steep learning curve. Recent studies have shown conflicting results concerning the benefit of OTSC. Mangiafico et al reported significantly lower rebleeding with OTSC than standard therapy,[6] while two other studies reported no statistically significant difference in rebleeding rates.[7,8] Also, whether the application of these clips has a beneficial effect on reducing mortality is open to question. Hence, we aimed to compile and systematically review the existing evidence for the comparative efficacy of OTSC with standard therapy for managing NVUGIB.

Methods

Information Sources and Search Strategy

A comprehensive search of all randomized trials was conducted using the databases of MEDLINE, EMBASE, and Scopus from inception to February 2023. The keywords used were ("gastrointestinal hemorrhage" OR "gastrointestinal bleeding") AND ("over the scope clip" OR "OTSC"). Manual searching of reference lists of the included studies was also undertaken to ensure that no potentially relevant items were overlooked. The study methodology was designed and executed to adhere to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.[9]

Study Selection

The Population/Patient, Intervention, Comparator and Outcome (PICO) criteria used for included randomized studies were (a) *Patients*—patients with NVUGIB; (b) *Intervention*—OTSC; (c) *Comparison*—standard therapy including combination therapy with local injection of adrenaline and TTS or thermal therapy; (d) *Outcomes*—persistent bleeding, rebleeding, mortality, and duration of hospitalization. Per the selection criteria above, the titles and abstracts of all studies were independently reviewed by two authors. A third reviewer resolved any disagreements. The exclusion criteria used were nonrandomized studies, noncomparative studies, case series, and studies that do not report original data, including reviews, editorials, or opinions.

Data Extraction

Two independent reviewers performed the data extraction, and a third reviewer resolved any disagreement. Data were collected under the following headings: study author and year, country of study, study design, number of patients, age and sex distribution, details of the lesion, type of intervention used, technical success, clinical success, rebleeding, mortality, and duration of hospitalization.

Definition of Outcomes

Persistent bleeding was defined as bleeding at the conclusion of the index endoscopy, which may have been due to failure to control the active bleeding or active bleeding developing in a nonbleeding lesion. Rebleeding was defined as clinical or endoscopic evidence of bleeding after hemostasis during index endoscopy.

Risk of Bias in Individual Studies

After data extraction, the same two reviewers performed a risk of bias (quality) assessment using validated tools. The Cochrane risk-of-bias tool was used for randomized controlled trials (RCT).

Statistical Analysis

Risk ratios (RR) with 95% confidence intervals (CI) were calculated for all the dichotomous outcomes. Continuous variables were analyzed using mean difference (MD). A fixed-effect model was used for outcomes without significant heterogeneity, while the Mantel-Haenszel test for random effects was used in cases of considerable heterogeneity. A Cochran's Q test and I^2 statistics were used to determine the heterogeneity between the studies. A *p*-value of Q test less than 0.1 or the I^2 value more than 30% was considered significant. Visual inspection of funnel plots was used for publication bias assessment. The sensitivity analysis was performed using a leave-one-out meta-analysis. Sensitivity analysis was also performed using studies that used OTSC as first-line therapy. RevMan software (version 5.4.1, Cochrane Collaboration, Copenhagen) was used for statistical analysis.

Results

Study Characteristics and Assessment of the Risk of Bias

A total of five studies were included in the final analysis. ►**Fig. 1** shows the PRISMA flowchart for the study

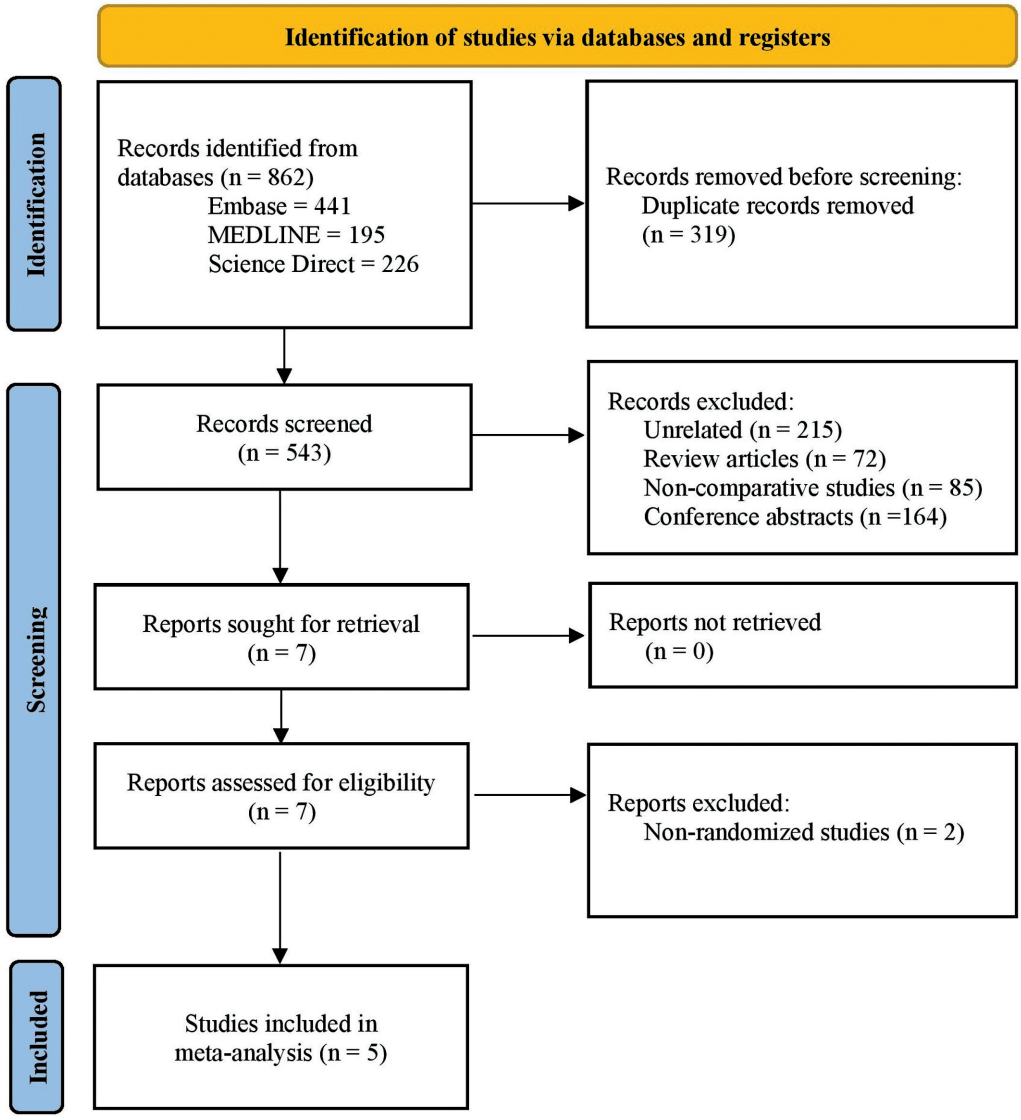

Fig. 1 Flow diagram for study retrieval and identification for meta-analysis as per the PRISMA 2020 statements.

selection and inclusion process. ►**Tables 1** and **2** summarize the baseline characteristics and outcomes of the included studies. Only one study used OTSC for secondary hemostasis after the failure of primary therapy,[10] while four studies used OTSC for primary hemostasis.[10–14] Two studies recruited patients exclusively with peptic ulcers,[10,13] while three recruited patients with all causes of NVUGIB.[11,12,14] Males constituted the predominant population in all studies. The proportion of patients using antithrombotics varied from 6 to 84%. ►**Fig. 2** shows the traffic-light plot to assess the risk of bias. The risk of bias was low in three[10,13,14] and medium in two studies.[11,12]

Persistent Bleeding

All the included studies reported the incidence of persistent bleeding in both groups. There was no significant difference in the risk of persistent bleeding between the groups with a RR of 0.29 (95% CI: 0.07–1.27; $I^2 = 59\%$). On subgroup analysis of patients undergoing placement of OTSC as primary therapy also, there was no difference in the risk of persistent bleeding with a RR of 0.38 (95% CI: 0.05–2.93; $I^2 = 63\%$) (►**Fig. 3**).

Rebleeding

All the included studies compared the incidence of rebleeding in patients achieving initial hemostasis with either of the interventions. The use of an OTSC was associated with a significantly lower risk of rebleeding compared with standard therapy at 7 and 30 days, with a RR of 0.30 (95% CI: 0.16–0.59; $I^2 = 0\%$) and RR of 0.42 (95% CI: 0.24–0.72; $I^2 = 0\%$), respectively. On subgroup analysis of patients undergoing placement of OTSC as primary therapy, OTSC was associated with a significantly lower risk of rebleeding compared with standard therapy at 7 and 30 days, with a RR of 0.29 (95% CI: 0.14–0.62; $I^2 = 0\%$) and RR of 0.43 (95% CI: 0.24–0.78; $I^2 = 3\%$), respectively (►**Fig. 4**).

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Table 1 Baseline characteristics of the studies included in the meta-analysis

Author, year	Country	Indication	Intervention	Number of patients	Age, in years	Male/female	Peptic ulcers	Antithrombotic use
Schmidt et al 2018[10]	Germany	Rebleeding from peptic ulcer within 7 days after initial successful endoscopic hemostasis	OTSC	33	77 (33–90)	20/13	100%	15 (45.5%)
			Standard	33	78 (44–93)	17/16	100%	12 (36.3%)
Jensen et al 2021[11]	USA	Primary treatment of severe[a] acute NVUGIB	OTSC	25	67.6 ± 16.5	19/6	22 (88%)	21 (84%)
			Standard	28	66.5 ± 14.8	24/4	22 (78.6%)	22 (78.6%)
Meier et al 2022[12]	Germany	Primary treatment of acute NVUGIB with a high risk of rebleeding (Complete Rockall Score ≥7)	OTSC	48	78 (42–92)	33/15	42 (87.5%)	19 (39.6%)
			Standard	52	79 (51–96)	37/15	42 (80.7%)	22 (42.3%)
Chan et al 2023[13]	Hong Kong, Taiwan, Thailand	Primary treatment of patients with high-risk peptic ulcers ≥15 mm	OTSC	50	72.41 ± 13.81	34/16	100%	7/50 (14%)
			Standard	50	70.74 ± 10.77	33/17	100%	3/50 (6%)
Lau et al 2023[14]	Hong Kong, China, Australia	Primary treatment of acute NVUGIB	OTSC	93	62.4 ± 18.9	74/19	86 (92.5%)	16 (17.2%)
			Standard	97	64.1 ± 17.2	75/22	87 (89.7%)	26 (26.8%)

Abbreviations: Hb, hemoglobin; NVUGIB, nonvariceal upper gastrointestinal bleeding; OTSC, over-the-scope clips; RBC, red blood cell.
[a]Severe UGI bleeding defined by clinical parameters (hypotension, shock, syncope, tachycardia, melena, hematemesis, and/or hematochezia), laboratory evidence (Hb ≤ 9 grams; or Hb decrease of ≥ 2 grams from baseline), and 1 or more units RBC transfusion (all 3 were required).

Table 2 Outcome of the studies included in the meta-analysis

Author, year	Intervention	Number of patients	Persistent bleeding	Rebleeding at 7 days	Rebleeding at 30 days	30-day mortality	Duration of hospitalization, in days
Schmidt et al 2018[10]	OTSC	33	2/33	3/31	3/31	2/33	29.75 ± 24.85
	Standard	33	14/33	5/19	5/19	4/33	19.5 ± 13.87
Jensen et al 2021[11]	OTSC	25	0/25	1/25	1/25	0/25	7.56 ± 8.17
	Standard	28	0/28	7/28	8/28	0/28	10 ± 16.19
Meier et al 2022[12]	OTSC	48	0/48	4/48	6/48	3/48	22 ± 18.7
	Standard	52	6/52	8/46	8/46	4/52	23.5 ± 19.65
Chan et al 2023[13]	OTSC	50	4/50	2/46	5/46	2/50	7.7 ± 5.3
	Standard	50	2/50	7/48	9/48	4/50	7.3 ± 5.4
Lau et al 2023[14]	OTSC	93	1/93	1/92	2/92	2/93	13.72 ± 24.33
	Standard	97	6/97	6/91	8/91	4/97	13.27 ± 16.13

Abbreviation: OTSC, over-the-scope clips.

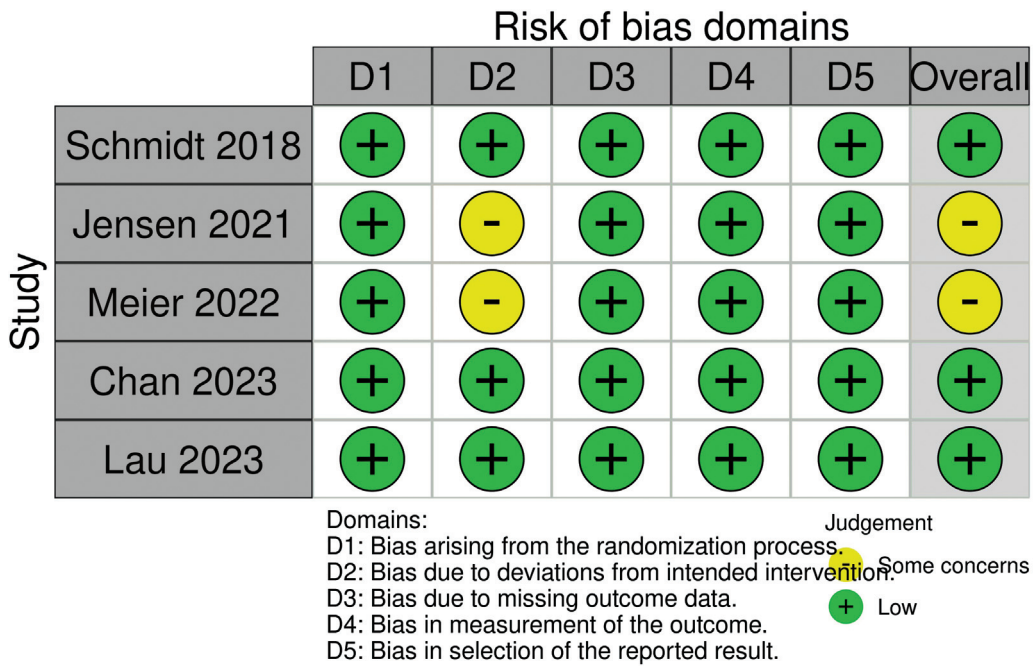

Fig. 2 Risk of bias assessment for the included studies.

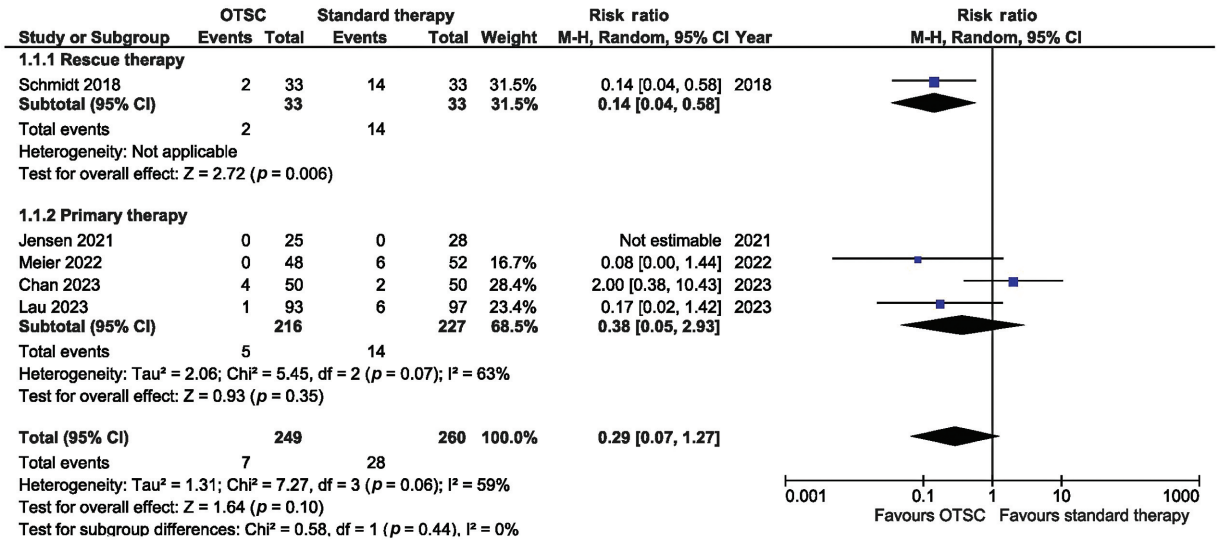

Fig. 3 Forest plot comparing the risk of persistent bleeding between standard therapy and OTSC with subgroup analysis based on the indication. CI, confidence interval; OTSC, over-the-scope clips.

30-Day Mortality

All five studies reported the incidence of 30-day mortality with either of the interventions. There was no difference in the risk of mortality at 30 days between both groups, on overall analysis or subgroup analysis, with a RR of 0.58 (95% CI: 0.26–1.28; $I^2 = 0\%$) and 0.61 (95% CI: 0.25–1.51; $I^2 = 0\%$), respectively.

Duration of Hospitalization

All five studies reported the duration of hospitalization with either of the interventions. There was no difference in the duration of hospitalization between both groups, on overall analysis or subgroup analysis, with an MD of 0.42 (95% CI: −1.00 to 1.84; $I^2 = 18\%$) and 0.21 (95% CI: −1.23 to 1.64; $I^2 = 0\%$), respectively (►**Fig. 5**).

Publication Bias, Sensitivity Analysis, and Certainty of the Evidence

Publication bias was not assessed as the number of studies was less than 10. On leave-one-out analysis, with the exclusion of the study by Chan et al, OTSC was associated with a lower risk of persistent bleeding with RR 0.14 (95% CI: 0.05–0.41; $I^2 = 0\%$). There was no significant change in the overall effect for other outcomes on leave-one-out analysis. ►**Table 3** shows the grade of evidence for various outcomes.

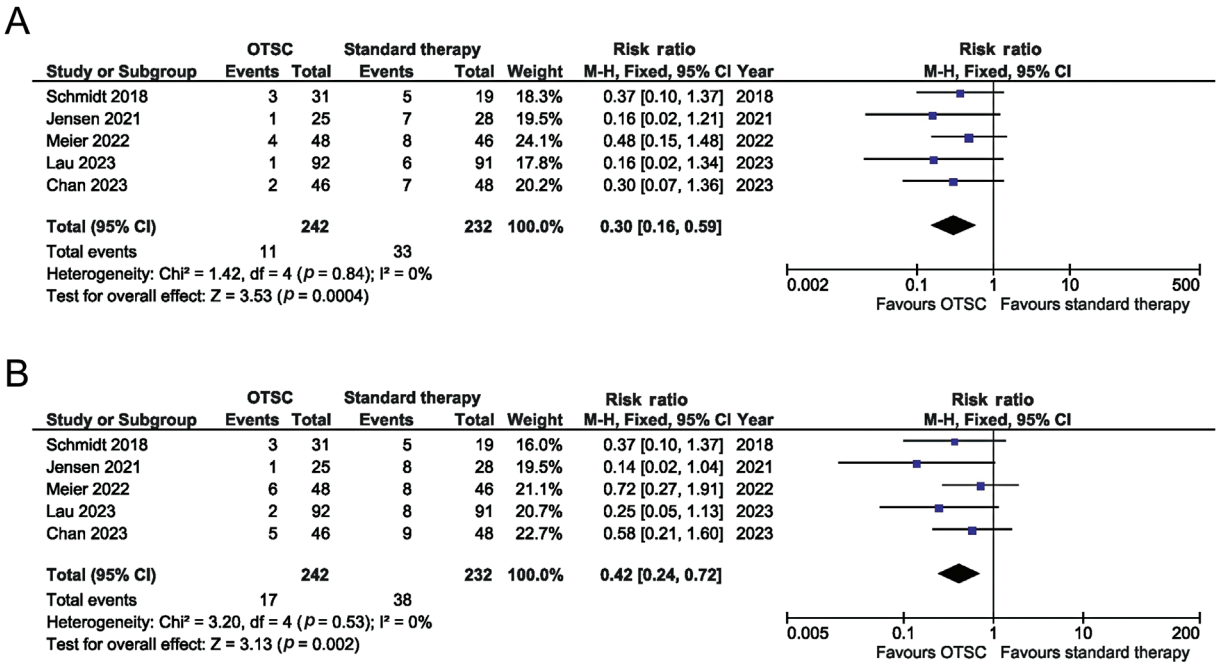

Fig. 4 Forest plot comparing the risk of rebleeding at (A) 7 days and (B) 30 days between standard therapy and OTSC. CI, confidence interval; OTSC, over-the-scope clips.

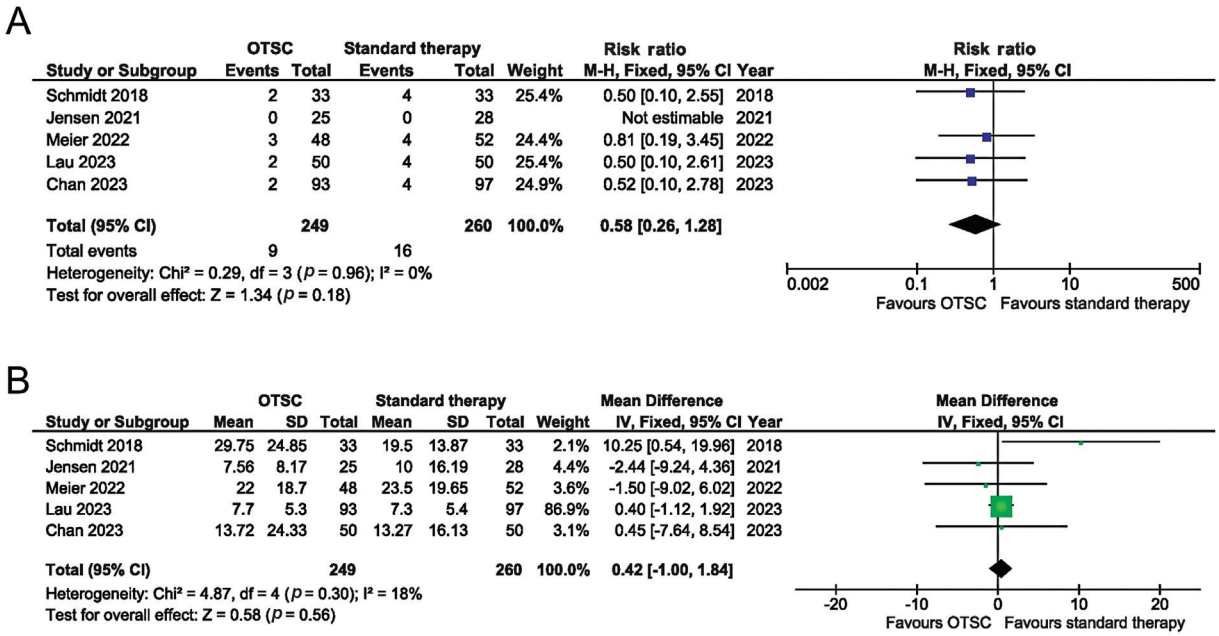

Fig. 5 Forest plot comparing the (A) risk of 30 days mortality and (B) duration of hospitalization between standard therapy and OTSC. CI, confidence interval; OTSC, over-the-scope clips; SD, standard deviation.

Discussion

The role of OTSC in managing NVUGIB as both first-line and second-line options for hemostasis is evolving. The present meta-analysis adds to the expanding literature on using OTSC clips for the management of NVUGIB. The present analysis reported a significantly lower risk of rebleeding at 7 and 30 days with OTSC compared with standard therapy. However, there was no difference in the risk of persistent bleeding, 30-day mortality, and duration of hospitalization between OTSC and standard therapy.

Both groups had no difference in the risk of persistent bleeding (failure to control bleeding). This was also seen in the subgroup analysis of patients where OTSC clips were used as a primary measure to achieve endoscopic hemostasis.

Table 3 Summary of findings with a grade of evidence

Population: Nonvariceal upper gastrointestinal bleeding
Intervention: OTSC
Comparison: standard therapy

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No. of patients (studies)	Certainty assessment				Overall certainty of the evidence
	Risk with standard therapy	Risk with OTSC			Risk of bias	Inconsistency	Indirectness	Imprecision	
Persistent bleeding	108 per 1,000	77 fewer per 1,000 (100 fewer to 29 more)	RR 0.29 (0.07–1.27)	509 (5 studies)	–	+	–	+	Low ●●○○
Rebleeding at 7 days	131 per 1,000	92 fewer per 1,000 (110 fewer to 54 fewer)	RR 0.30 (0.16–0.59)	424 (5 studies)	–	–	–	+	Moderate ●●●○
Rebleeding at 30 days	164 per 1,000	97 fewer per 1,000 (125 fewer to 46 fewer)	RR 0.42 (0.24–0.72)	424 (5 studies)	–	–	–	+	Moderate ●●●○
30-days mortality	61 per 1,000	26 fewer per 1,000 (45 fewer to 17 more)	RR 0.58 (0.26–1.28)	509 (5 studies)	–	+	–	+	Low ●●○○
Length of hospital stay	–	–	MD 0.42 (−1.00 to 1.84)	509 (5 studies)	–	+	–	+	Low ●●○○

Abbreviations: CI, confidence interval; MD, mean difference; OTSC, over-the-scope clips; RR, risk ratio.

Among studies using OTSC as a first-line therapy, including various lesion types and ulcer sizes, none of the individual studies reported any difference in the risk of persistent bleeding. However, in the study by Schmidt et al, where OTSC was used as a second-line therapy, persistent bleeding was seen in 42.4% of those receiving the standard therapy, compared with 6.1% in the OTSC group ($p = 0.001$). Thus, OTSCs may be a good option for hemostasis after the failure of standard therapy. However, based on the present literature, the benefit of OTSC for primary hemostasis is still debatable and requires further studies.

None of the individual studies reported any difference in the risk of rebleeding at 7 days, and two reported a lower risk of rebleeding at 30 days.[11,14] The pooled analysis of the data demonstrated a significantly lower risk of both early (day 7) and late (day 30) rebleeding as compared with standard therapy with RR of 0.30 (0.16–0.59), and RR of 0.42 (0.24–0.72), respectively. This may be because the individual studies were underpowered to show a statistically significant difference. A prior study utilizing a Doppler endoscopic probe demonstrated that OTSC more effectively obliterated effective arterial blood flow beneath the ulcer than standard therapy and was associated with a lower rebleeding rate.[15] Another recent study showed a lower cumulative 30-day rebleed rate in patients treated with OTSC clips compared with standard therapy (14.6 vs. 3.2%).[14] The authors proposed that using these clips as a primary line of management may be restricted to ulcers that are highly likely to rebleed. The predictors of rebleeding were active bleeding, large ulcer size, and posterior bulb or lesser curve gastric ulcers. They will likely erode into vessels from the gastroduodenal or left gastric arterial complexes.[14] Contrasting results were obtained in another study that specifically assessed the role of these clips in bleeding peptic ulcers more than or equal to 15 mm in size.[13] There was no statistically significant difference in rebleeding rates in the OTSC group. However, the caveat in this study was cases of OTSC failure were due to the highly technically demanding nature of the procedure due to the location of the lesion and the learning curve associated with deploying these clips. Also, subsequent salvage endoscopic measures were difficult due to the presence of large clips, and all of these patients required transarterial embolization to control the bleeding. A recent meta-analysis also demonstrated a significantly lower risk of rebleeding using OTSC clips.[16] These findings add to the data on using these clips, especially in cases with a high likelihood of rebleeding.

There are some disadvantages to the OTSC system. First, the scope must be removed after identifying the bleeding lesion to load the clip onto the scope. Second, applying in difficult locations like the posterior wall of the duodenal bulb or lesser gastric curvature is technically difficult. Also, technical expertise and training may be required to use them routinely. Lastly, the equipment cost is a cause of concern, especially in resource-limited settings. In a retrospective study using OTSC as first-line therapy, the procedural cost was significantly higher with OTSC compared with standard

therapy, but not hospitalization cost.[7] Another study on cost-effective analysis of the OTSC as second-line therapy reported comparable procedural costs as well as total costs with standard therapy.[17] Further studies are required to conduct a meta-analysis of the cost difference between the groups,

Chandrashekar et al published a systematic review on the use of OTSC clips in GI bleeding. However, most included studies were retrospective cohort studies and case series.[16] Also, they have not looked at the question of using OTSC clips as a primary measure in achieving hemostasis. The most recent meta-analysis by Bapaye et al[18] included 11 records (4 conference abstracts), out of which the majority were non-randomized studies associated with a significant bias. The present meta-analysis comprehensively reviews only RCTs that have examined the use of OTSC as a measure of hemostasis in NVUGIB. Hence, the current meta-analysis provides a better contemporary perspective on the role of OTSC in managing GI bleeding, along with a grade of evidence.

Despite this, there are some limitations to this study. First, in most of the studies, expert endoscopists used the OTSC system, which limits the generalizability of this modality in the community. Second, the number of included studies was small, with the majority having a small sample size, making the analysis underpowered. Third, there were differences in study protocols, especially in the selection criteria for the patients. Lastly, none of the studies looked at the cost-effectiveness of the use of OTSC clips for NVUGIB. Nevertheless, our analysis will serve as a helpful manual for clinical reference and a basis for further research, assisting clinicians by adding a new practice tool to their arsenal.

In conclusion, the present meta-analysis showed moderate evidence that OTSC could reduce the risk of rebleeding after endoscopic hemostasis. The possible benefit of OTSCs may be restricted to patients with failed hemostasis and those with a high risk of rebleeding. However, they have no benefit regarding initial bleeding control or 30-day mortality. Given the higher cost of OTSC, a cost-efficacy analysis needs to be conducted to analyze whether the reduced rebleeding risk may prove cost-effective.

Authors' Contributions

S.G. and S.H. conceptualized the study. S.G. and A.K. were involved in methodology. S.G., S.H., and M.K. contributed to formal analysis. A.K. and S.S. helped in Project administration. S.G., S.H., and V.J. were involved in visualization. S.G. helped in software. S.G., S.H., and V.J. validated the study. S.G., S.H., and M.K. wrote the original draft. S.G., S.H., V.J., and S.S. reviewed and edited the manuscript. All authors approved the final manuscript.

Conflict of Interest

None declared.

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