SYSTEMATIC REVIEW AND META-ANALYSIS

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Cold snare polypectomy versus cold endoscopic mucosal resection for small colorectal polyps: a meta-analysis of randomized controlled trials

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Cold snare polypectomy versus cold endoscopic mucosal resection for small colorectal polyps: a meta-analysis of randomized controlled trials

- **Cold snare polypectomy (CSP) is routinely performed for small colorectal polyps (≤ 10 mm). However, challenges such as insu cient resection depth and immediate bleeding, hindering precise pathological evaluation, have been reported.**
- **We aimed to compare outcomes of cold endoscopic mucosal resection (CEMR) with CSP for colorectal polyps ≤ 10mm, assessing data primarily from randomized controlled trials (RCTs).**
- **Multiple databases, including EMBASE, CENTRAL, MEDLINE, SCI, ESCI, PCI, SCOPUS, Clinical trial registers ClinicalTrials.gov and the International Clinical Trials Registry Platform were searched (till December 2023). We analyzed 7 RCTs reporting on outcomes of CSP versus CEMR for colorectal polyps ≤ 10 mm in size.**

Outcomes	Pooled proportions (95% confidence interval)		Pooled RR; *p*-value
	CSP	C-EMR	
Complete resection	91.8% (82.5–96.3)	94.6% (90.6–97.0)	30.94 (0.87–1.02); 0.0
En-bloc resection	98.9% (96.6–99.6)	98.3% (94.2–99.5)	1.01 (0.96–1.06); 0.06
Incomplete resection	6.7% (1.9–21.5)	4.8% (1.3–16.6)	1.60 (0.95–2.68); 0.15
Immediate bleeding	2.9% (1.0–7.8)	3.1% (1.7–4.9)	1.28 (0.64–2.55); 0.0
Delayed bleeding	1.3% (0.4–4.0)	1.4% (0.6–3.5)	0.94 (0.36–2.45); 0.90
Perforation	0.3% (0.1–1.2); 0%	0.3% (0.1–1.1)	1.27 (0.29–3.5); 1.0
Other complications	0.4% (0.1–2.1)	0.3% (0.1–1.5)	1.03 (0.2–4.1); 1.0
Mean resection rate (sec)	91.30±27.08	133.51±23.23	SMD 1.36 (0.69–1.96); <0.01

CSP, cold snare polypectomy; C-EMR, cold endoscopic mucosal resection; RR, relative risk; SMD, Standard mean difference

CSP vs. CEMR showed no statistical variance between the rates of complete resection, *en-bloc* resection, incomplete resection or adverse events. However, CEMR had a notably longer mean resection time.

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Background/Aims: Cold snare polypectomy (CSP) is routinely performed for small colorectal polyps (≤10 mm). However, challenges include insufficient resection depth and immediate bleeding, hindering precise pathological evaluation. We aimed to compare the outcomes of cold endoscopic mucosal resection (CEMR) with that of CSP for colorectal polyps ≤10 mm, using data from randomized controlled trials (RCTs).

Methods: Multiple databases were searched in December 2023 for RCTs reporting outcomes of CSP versus CEMR for colorectal polyps ≤10 mm in size. Our primary outcomes were rates of complete and *en-bloc* resections, while our secondary outcomes were total resection time (seconds) and adverse events, including immediate bleeding, delayed bleeding, and perforation.

Results: The complete resection rates did not significantly differ (CSP, 91.8% vs. CEMR 94.6%), nor did the rates of *en-bloc* resection (CSP, 98.9% vs. CEMR, 98.3%) or incomplete resection (CSP, 6.7% vs. CEMR, 4.8%). Adverse event rates were similarly insignificant in variance. However, CEMR had a notably longer mean resection time (133.51 vs. 91.30 seconds).

Conclusions: Our meta-analysis of seven RCTs showed that while both CSP and CEMR are equally safe and effective for resecting small (≤10 mm) colorectal polyps, the latter is associated with a longer resection time.

Keywords: Carcinoma; Colonic; Colonoscopy; Colorectal; Polyps

INTRODUCTION

In the year 2020, the global incidence of colorectal cancer (CRC) surpassed 1.9 million new cases, leading to more than 930,000 fatalities worldwide. By 2040, the annual incidence of CRC is estimated to rise to 3.2 million new cases, marking a 63% increase, and the annual mortality rate will escalate to 1.6 million, reflecting a 73% surge.[1,2] Colonoscopy remains an effective screening and diagnostic modality to identify and remove colorectal polyps, which are the precursor lesions for CRC.[3]

The optimal technique for colorectal polyp resection depends on the size, pathology, and location of the polyp, as well as operator experience. Endoscopic resection is recommended for polyps ≥6 mm in size, as they may harbor a higher risk of malignancy than polyps ≤5 mm in size.[4] Cold snare polypectomy (CSP) is an excision technique for colorectal polyps using a snare without electrocautery. Although diminutive polyps (lesions ≤5 mm in size) have low malignancy potential, they are still considered a premalignant state for which CSP is strongly recommended as a good resection method and is frequently performed in daily practice. According to the clinical guidelines of the European Society of Gastroenterology Endoscopy (ESGE), CSP is the preferred method for removing small polyps ≥5 mm because it is highly effective for complete resection, has low complications, and allows adequate histological samples (high-quality evidence, strong recommendation). The ESGE also suggests using CSP for sessile serrated polyps, which are 6 to 9 mm in size, since they have a better safety profile (moderate quality evidence, weak recommendation).[5] However, some challenges have been reported with CSP, such as insufficient resection depth and immediate bleeding, which hinder precise pathological evaluation.[6,7]

Cold endoscopic mucosal resection (CEMR), which includes submucosal saline injection in addition to the standard CSP technique, has been reported to be useful for delineating lesion margins and removing adenomatous tissue.[8] Several randomized controlled trials (RCTs) comparing CEMR to endoscopic mucosal resection (EMR) with diathermy have reported higher rates of histologic complete resection (>90%) in CEMR with submucosal injection for nonpedunculated colorectal polyps between 6 mm and 10 mm in size.[8,9] On the contrary, few studies have shown no significant difference in rates of complete mucosal resection but an increase in resection time as well as an increased risk of bleeding associated with the use of submucosal saline injections.[6,10] Hence, the use of submucosal injection in resection of colorectal polyps <10 mm remains debatable.

To delve deeper into the published literature, we performed a systematic review and meta-analysis to assess and compare the outcomes of CEMR with that of CSP for colorectal polyps ≤10 mm, gathering focused data from RCTs alone.

METHODS

Search strategy

A comprehensive search was conducted for RCTs reporting on outcomes of CSP versus CEMR for colorectal polyps ≤10 mm in size. Thereafter, a database search strategy was developed and deployed by a medical librarian. The Embase search query was reviewed by an independent medical librarian from the Mayo Clinic Libraries. Studies were identified via searching the databases Medline, Embase, and Cochrane Central Register of Controlled Trials—all via the Wolters Kluwer Ovid interface; Science Citation Index Expanded, Emerging Sources Citation Index, and Preprint Citation Index—all via the Clarivate Analytics Web of Science interface; Scopus; and clinical trial registers, ClinicalTrials.gov and the International Clinical Trials Registry Platform.[11] English language database limits were applied as available or built into the search strategy when possible. Controlled trial filters were applied to Embase, Medline, Science Citation Index Expanded, Emerging Sources Citation Index, Preprint Citation Index, and Scopus searches and are detailed in the Supplementary Materials 1 and 2.

The search strategy was written for Embase (Ovid) and manually translated across all databases using syntax, controlled vocabulary, and search fields. MeSH terms, Emtree terms, and text words were used for search concepts related to CSP, EMR, and colorectal polyps. Database and trial register searches were performed on 12/21/2023. All records were downloaded or manually added to EndNote 21 Desktop version and deduplicated using a method by Bramer et al.[12] The detailed literature search strategy is provided in Supplementary Material 1. Two investigators (VM, SM) independently examined the titles and abstracts of the studies retrieved through the initial search, discarding those not pertinent to the research question in line with predetermined inclusion and exclusion criteria. Subsequently, they scrutinized the full texts of the remaining studies to ascertain their relevance. Disagreements regarding study inclusion were resolved through a consensus-building process and, when necessary, through consultation with a third researcher (SC). To identify additional significant studies, the reference lists of the selected studies, as well as existing systematic and narrative reviews on the topic, were meticulously scanned.

Our methodology adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The checklists corresponding to the PRISMA guidelines can be found in Supplementary Material 2.[9]

Study selection

In our meta-analysis, we incorporated data from seven RCTs[6,13-17] that assessed the outcomes of CSP versus CEMR for the removal of colorectal polyps ≤10 mm. The inclusion criteria were broad, considering studies from any geographical location, and set in either an inpatient or outpatient context, provided that they supplied the necessary data for our analysis. Our exclusion criteria were as follows: (1) studies reporting outcomes for polyps >10 mm, (2) studies presented as conference abstracts, (3) studies conducted in the pediatric population (age: <18 years), (4) studies that were not published in English language, (5) observational/cohort studies, (6) individual case reports and case series, and (7) RCTs published before 2010. In instances of multiple publications pertaining to the same cohort or overlapping cohorts, we included data from the most current and/or most comprehensive report available. To reduce the risk of potential randomization bias for patients who had more than one polyp, the trials included in the study only accounted for the number of polyps per patient.

Data extraction and quality assessment

Data pertaining to study outcomes was extracted from the individual studies using a predefined template by at least two authors (VM, SC). In addition, two separate authors (DSD, PL) independently conducted the quality assessment. The quality of the studies was evaluated using the Jadad scale.[18] The specifics of the quality scores can be found in Supplementary Table 1.[6,9,12-16]

Outcomes assessed

Our primary outcomes were complete resection rate and *en-bloc* resection rate. Complete resection was defined by the absence of pathological evidence of disease in two subsequent biopsy specimens taken postinitial polypectomy. *En-bloc* resection was defined as removal of the lesion as a single specimen without any endoscopically detectable residual neoplastic tissue after resection.

The secondary outcomes were total resection time (seconds) and adverse events. The adverse events assessed included immediate bleeding, delayed bleeding, and perforation. The total time for resection was determined from the commencement of resection (beginning with the snare insertion in the CSP cohort or the injection needle in the CEMR cohort) to its completion (established upon verification of complete resection endoscopically and cessation of any immediate bleeding). Immediate bleeding was defined as bleeding during the procedure that persisted beyond 30 seconds and necessitated endoscopic intervention, while delayed bleeding was classified as postprocedural hematochezia that warranted urgent endoscopic hemostasis within 2 to 4 weeks following the procedure.

Statistical analysis

We used meta-analysis techniques for the computation of combined estimates, adhering to the DerSimonian and Laird method with a random effects model,[19] consistent with their guidelines for scenarios where effects are quantified by the probability of risk. In cases where an outcome's occurrence was zero in any study, we introduced a continuity correction of 0.01 to the number of events prior to the statistical evaluation.[20] Heterogeneity among the specific estimates from each study was quantified using Cochrane Q statistics and the I^2 statistic, where values less than 30% indicated low heterogeneity; 30% to 60%, moderate heterogeneity; 61% to 75%, substantial heterogeneity; and >75%, considerable heterogeneity.[21,22] Moreover, we computed the 95% prediction interval (PI) to account for the dispersion of effect sizes. An assessment for publication bias was not performed as the number of studies was <10. All analyses were conducted using the Comprehensive Meta-Analysis software, ver. 4 (BioStat).

RESULTS

Search results and population characteristics

Our initial search criteria yielded 2,779 citations. After deduplication, 1,721 citations remained. A total of 198 records were assessed after screening citations of interest and excluding conference abstracts. Of the 30 full length articles that were assessed, seven studies (1,560 patients: 771 in the CSP group and 789 in the CEMR group) were included in the final analysis.[6,13-17] The schematic diagram used for the study selection process is illustrated in Figure 1.

The mean ages in the CSP and CEMR groups were 60.1±11.8 and 60.2±10.2 years, respectively. The mean polyp size was 5.0±1.7 mm in the CSP group and 5.5±1.7 mm in the CEMR group. Tables 1 and 2 describe the study details, including population characteristics, polyp location, and pathology.[6,9,12-16]

Characteristics and quality of included studies

All the studies included were RCTs. Three of these studies were multicenter, and the rest were single-center analysis. Five of the included studies were of moderate quality, whereas two were of excellent quality. None of the studies were of low-quality. The submucosal lifting agents used in the studies were normal saline solution mixed with indigo carmine (0.04%) and epinephrine (1:10,000), saline solution mixed with methylene blue and epinephrine, methylene blue-tinted normal saline solution, or Everlift injection (a combination of hydroxypropyl methylcellulose, glycerol, and water). The types of snare used in all studies were CSP-dedicated snare (Boston CapCold; Boston Scientific), traditional oval snare (Exacto cold snare; Steris Corporation), SnareMaster Plus (Olympus Corp.), or open Exacto cold snare (Steris Corporation). A detailed assessment of the study quality is provided in Supplementary Table 1.

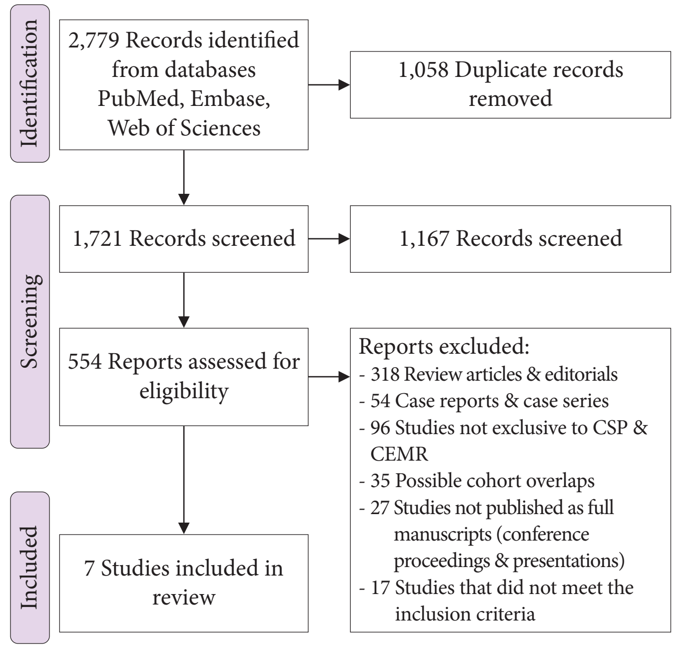


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses study selection flowchart. CSP, cold snare polypectomy; CEMR, cold endoscopic mucosal resection.

Meta-analysis outcomes

A total of 1,944 polyps in 1,560 patients (771 in the CSP group and 789 in the CEMR group) were assessed. The mean age in the CSP and CEMR groups were 60.0±11.8 and 60.2±10.2 years, respectively. The mean polyp size was 5.0±1.7 mm in the CSP group and 5.5±1.7 mm in the CEMR group.

Primary outcomes

1) Complete resection rates

The pooled rates of complete resection were comparable between the CSP and CEMR groups and were found to be 91.8% (95% confidence interval [CI], 82.5%–96.3%; I^2=67%) vs. 94.6% (95% CI, 90.6%–97.0%; I^2=51%); risk ratio (RR), 0.94 (0.87–1.02; p<0.01). No statistically significant difference was observed between the CSP and CEMR groups.

Table 1. Study and population characteristics

Study	Year published	Study details	Total patients		Age (mean±SD, y)		Male/female		Polyp number (total)		Polyp size (mean±SD, mm)		Polyp location		Polyp pathology		Type of snares (CSP & CEMR)	Type of injection used
			CSP	CEMR	CSP	CEMR	CSP	CEMR	CSP	CEMR	CSP	CEMR	CSP	CEMR	CSP	CEMR	(CSP & CEMR)	CSP
Kim et al.[15]	2023	Prospective, RCT, Jan. 2018 to Feb. 2021, multi-center, Korea	161	166	63.5±11.1	62.0±10.5	102/51	111/55	215 (6–8 mm, 155; 9–10 mm, 60)	210 (6–8 mm, 169; 9–10 mm, 41)	7.0±1.2	7.2±1.4	Cecum/ascending 63 (29.3); HFa/transverse/SFb 73 (34.0); descending/sigmoid 66 (30.7); rectum 13 (6.0)	Cecum/ascending 67 (31.9); HFa/transverse/SFb 50 (23.8); descending/sigmoid 80 (38.1); rectum 13 (6.2)	Tubular adenoma 196 (91.2); hyperplastic polyp 14 (6.5); serrated polyp 5 (2.3); adenocarcinoma 0 (0)	Tubular adenoma 186 (88.6); hyperplastic polyp 16 (7.6); serrated polyp 5 (2.4); adenocarcinoma 3	Traditional oval snare	Normal saline solution mixed with indigo carmine (0.04%) and epinephrine (1:10,000)
Katagiri et al.[14]	2023	Prospective RCT, Apr. 2019 to Apr. 2021, single-center, Japan	59	59	63.7±13.3	67.9±10.2	36/23	33/26	<5 mm, 76 (67.9%); ≥5 mm, 36 (32.1%)	<5 mm, 91 (61.1%); ≥5 mm, 58 (38.9%)	4.2±1.8	4.4±1.8	Right side 73 (65.2%); left side 39 (34.8%)	Right side 108 (72.5%); left side 41 (27.5%)	Low-grade adenoma 86 (76.8%); high grade adenoma 0 (0%); sessile serrated adenoma/polyp 10 (8.9%); hyperplastic polyp 13 (11.6%); inflammatory polyp 3 (2.7%); loss of tissue 0 (0%)	Low-grade adenoma 110 (73.8%); high grade adenoma 1 (0.7); sessile serrated adenoma/polyp 7 (4.7%); hyperplastic polyp 29 (19.5%); inflammatory polyp 1 (0.7%); loss of tissue 1 (0.7%)	NR	Epinephrine (0.001%) -added saline
Li et al.[16]	2020	Prospective, RCT, Jul. 2017 and Mar. 2019, single-center, China	131	135	51.63±14.40	51.77±14.55	77/52	73/59	244	252	11.95±3.35	12.03±3.36	Caecum and ascending colon 57/88; transverse colon 54/61; descending colon 46/50; sigmoid colon and rectum 42/45	Caecum and ascending colon 68/75; transverse colon 54/58; descending colon 57/59; sigmoid colon and rectum 57/58	Submucosal adenocarcinoma 0; advanced adenoma 123/159; adenoma 60/64; sessile/traditional serrated adenoma 16/21	Submucosal adenocarcinoma 1/1; advanced adenoma 160/171; adenoma 59/61; sessile/traditional serrated adenoma 17/19	Snares (Boston Scientific CAPTIVATORTM 13 mm; JHY-SD-23-230-15-AI 15 mm)	Normal saline solution, epinephrine (1:10 0000), and methylene blue
Mou et al.[13]	2023	RCT, Jul. 2020 to Sep. 2020, multi-center, China	150	150	53 (11, 18–79)	54 (10, 28–74)	90/60	92/58	216 (3–5 mm, 139 [64.4%]; 6–9 mm, 77 [35.6%])	150 (3–5 mm, 146 [62.4%], 6–9 mm, 88 [37.6%])	5 (2, 3–8)	5 (2, 3–9)	Cecum 7; ascending colon 27; hepatic flexure 14; transverse colon 41; splenic flexure 0; descending colon 24; sigmoid colon 72; rectum 31	Cecum 9; ascending colon 35; hepatic flexure 14; transverse colon 53; splenic flexure 3; descending colon 35; sigmoid colon 50; rectum 35	Tubular adenoma 136; villous/tubulovillous adenoma 6; sessile serrated lesion 4; hyperplastic polyp 53; inflammatory polyp 14	Tubular adenoma 146; villous/tubulovillous adenoma 6; sessile serrated lesion 8; hyperplastic polyp 51; inflammatory polyp 22	CSP-dedicated or traditional snares	Saline solution mixed with methylene blue and epinephrine

(Continued on the next page)

Table 1. (Continued)

Study	Year published	Study details	Total patients		Age (mean±SD, y)		Male/female		Polyp number (total)		Polyp size (mean±SD, mm)		Polyp location		Polyp pathology		Type of snares (CSP & CEMR)	Type of injection used
			CSP	CEMR	CSP	CEMR	CSP	CEMR	CSP	CEMR	CSP	CEMR	CSP	CEMR	CSP	CEMR	(CSP & CEMR)	CSP
Rex et al.[12]	2022	Prospective, RCT, Aug. 10, 2018 and Mar. 26, 2021, multi-center, USA	59	63	66.2 (9.9)	65.0 (8.0)	25/34	28/35	68	82	9.4±3.1	9.5±2.8	Ascending colon 24 (35.3); cecum 7 (10.3); descending colon 8 (11.8); hepatic flexure 5 (7.4); ileocecal valve 1 (1.5); rectum 2 (2.9); sigmoid colon 3 (4.4); transverse colon 18 (26.5)	Ascending colon 26 (31.7); cecum 8 (9.8); descending colon 13 (15.9); hepatic flexure 3 (3.7); ileocecal valve 0 (0); rectum 1 (1.2); sigmoid colon 6 (7.3); transverse colon 25 (30.5)	Adenoma 53 (77.9); hyperplastic 3 (4.4); normal mucosa 1 (1.5); sessile serrated lesion 10 (14.7); no tissue 1 (1.5)	Adenoma 61 (74.4); hyperplastic 2 (2.4); normal mucosa 0 (0); sessile serrated lesion 19 (23.2); no tissue 0 (0)	Dedicated cold snare (Boston CapCold [Boston Scientific] or Exacto Cold Snare [Steris Corporation)	Saline solution, hydroxyethyl starch, or any commercially available injection fluid
Shimodate et al.[6]	2020	Prospective RCT, Nov. 2017 to Sep. 2019, single-center, Japan	107	107	68 (median)	65 (median)	60/47	61/46	97	100	5 mm (median)	5 mm (median)	Cecum 4; ascending colon 23; transverse colon 23; descending colon 10; sigmoid colon 30; rectum 7	Cecum 5; ascending colon 24; transverse colon 15; descending colon 14; sigmoid colon 34; rectum 8	Low-grade adenoma 92; high grade adenoma 0; sessile serrated adenoma/polyp 2; hyperplastic polyp 1; inflammatory polyp 1; adenocarcinoma 1	Low-grade adenoma 95; high grade adenoma 1; sessile serrated adenoma/polyp 1; hyperplastic polyp 1; inflammatory polyp 2; adenocarcinoma 0	Cold polypectomy snare (Exacto cold snare) or Snare-Master plus	Normal saline solution mixed with indigo carmine (.04%) and epinephrine
Wei et al.[9]	2022	Prospective, RCT, Sep. 16, 2020, and May 31, 2021, single-center, USA	105	109	68.7 (7.8)	68.9 (7.9)	107/2	102/3	149	142	5.3 (1.5)	5.3 (1.5)	Cecum 13; ascending 42; hepatic flexure 7; transverse 50; descending 14; sigmoid 20; rectum 3	Cecum 13; ascending, 39; hepatic flexure 5; transverse 48; descending, 19; sigmoid 14; rectum 4	NR	NR	Open Exacto cold snare	Everlift injection

SD, standard deviation; CSP, cold snare polypectomy; CEMR, cold endoscopic mucosal resection; HFa, hepatic flexure area; SFb, splenic flexure band; NR, not reported; RCT, randomized controlled trial.

Table 2. Cumulative outcomes and adverse effects associated with CSP and CEMR

Outcome	Pooled proportions (95% CI) (%)				Pooled RR	*p*-value
	CSP	I^2	CEMR	I^2		
Complete resection	91.8 (82.5–96.3)	67	94.6 (90.6–97.0)	51	0.94 (0.87–1.02)	0.001
En-bloc resection	98.9 (96.6–99.6)	0	98.3 (94.2–99.5)	0	1.01 (0.96–1.06)	0.06
Incomplete resection	6.7 (1.9–21.5)	96	4.8 (1.3–16.6)	95	1.60 (0.95–2.68)	0.15
Immediate bleeding	2.9 (1.0–7.8)	0	3.1 (1.7–4.9)	40	1.28 (0.64–2.55)	0.001
Delayed bleeding	1.3 (0.4–4.0)	0	1.4 (0.6–3.5)	55	0.94 (0.36–2.45)	0.90
Perforation	0.3 (0.1–1.2)	0	0.3 (0.1–1.1)	0	1.27 (0.29–3.5)	1.00
Other complications	0.4 (0.1–2.1)	0	0.3 (0.1–1.5)	0	1.03 (0.2–4.1)	1.00

CSP, cold snare polypectomy; CEMR, cold endoscopic mucosal resection; CI, confidence interval; RR, relative risk.

2) *En-bloc* resection rates

The pooled rates of *en-bloc* resection were comparable between the CSP and CEMR groups (98.9% [95% CI, 96.6%–99.6%; I^2=0%] vs. 98.3% [95% CI, 94.2%–99.5%; I^2=0%]; RR, 1.0 [0.96–1.06; p=0.06]). No statistically significant difference was observed between both groups.

3) Incomplete resection rates

The pooled rates of incomplete resection between the two groups were 6.7% (95% CI, 1.9%–21.5%; I^2=96%) vs. 4.8% (95% CI, 1.3%–16.6%; I^2=95%); RR, 1.6 (0.95–2.68; p=0.15). No statistically significant difference was observed between both groups.

The corresponding forest plots to complete resection rates, *en-bloc* resection rates, and incomplete resection rates are illustrated in Figures 2–4. The corresponding forest plots illustrating the relative risk of each between CSP and CEMR are shown in Supplementary Figures 1–3.

Secondary outcomes

1) Immediate bleeding

No statistically significant differences were observed in the pooled rates of immediate bleeding (2.9% [95% CI, 1.0%–7.8%; I^2=0%] vs. 3.1% [95% CI, 1.8%–5.3%; I^2=40%]; RR, 1.28 [0.64–2.55; p<0.001]) between the CSP and CEMR groups.

2) Delayed bleeding

No statistically significant differences were observed in the pooled rates of delayed bleeding (1.3% [95% CI, 0.4%–4.0%; I^2=57%] vs. 1.4% [95% CI, 0.6%–3.5%; I^2=55%]; RR, 0.94 [0.36–2.45; p=0.91]) between the two groups.

3) Perforation

The pooled rates of perforation between the CSP and CEMR groups (0.3% [95% CI, 0.1%–1.2%; I^2=0%] vs. 0.3% [95% CI, 0.1%–1.1%; I^2=0%]; RR, 1.27 [0.29–3.50; p=1.0]) were not statistically significant.

4) Resection time

The mean resection time was significantly higher in the CEMR group than in the CSP group (133.51±23.23 seconds vs. 91.30±27.08 seconds; standard mean difference, 1.36 [0.69–1.96; p<0.01]).

The corresponding forest plots are illustrated in Supplementary Figures 4–7 along with the corresponding forest plots illustrating the relative risks of each for CSP and CEMR in Supplementary Figures 8–10.

Validation of meta-analysis results

1) Sensitivity analysis

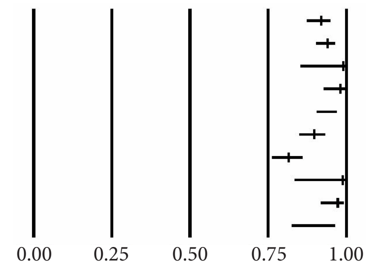
To evaluate whether individual studies exerted a disproportionate influence on the meta-analysis, we conducted a sensitivity analysis by omitting one study at a time and examining the impact on the overall summary estimate.[23] This analysis did not identify any single study that markedly altered the results of interest or the observed heterogeneity. No significant changes were observed in the combined rates noted.

2) Heterogeneity

We calculated the range of dispersion in our calculated rates using the PI and I^2 percentage values. The PI provides an estimate of the spread of effects, while the I^2 statistic indicates the proportion of variation due to heterogeneity rather than chance. Despite high I^2 values, the PIs for the pooled rates of complete and *en-bloc* resection, as well as total resection time, were narrow, indicating minimal dispersion of effects. The I^2 percentage values are detailed in Table 2, alongside the pooled rates.

Complete resection

Group by procedure	Study name	Statistics for each study			Event rate and 95% CI
		Event rate	Lower limit	Upper limit	
CEMR	Kim et al. 2023	0.919	0.874	0.949	
CEMR	Li et al. 2020	0.940	0.904	0.964	
CEMR	Rex et al. 2022	0.990	0.854	0.999	
CEMR	Wei et al. 2022	0.981	0.928	0.995	
CEMR	Pooled	0.946	0.906	0.970	
CSP	Kim et al. 2023	0.898	0.849	0.932	
CSP	Li et al. 2020	0.816	0.762	0.859	
CSP	Rex et al. 2022	0.988	0.836	0.999	
CSP	Wei et al. 2022	0.972	0.918	0.991	
CSP	Pooled	0.918	0.825	0.963	

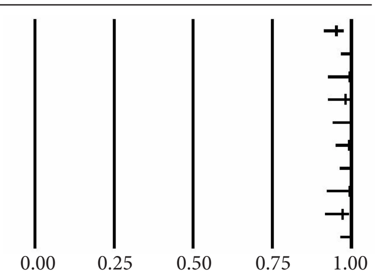


Meta analysis

Fig. 2. Forest plot showing complete resection rates of cold snare polypectomy (CSP) vs. cold endoscopic mucosal resection (CEMR). CI, confidence interval.

***En-bloc* resection**

Group by procedure	Study name	Statistics for each study			Event rate and 95% CI
		Event rate	Lower limit	Upper limit	
CEMR	Li et al. 2020	0.953	0.914	0.974	
CEMR	Mou et al. 2023	0.998	0.967	1.000	
CEMR	Shimodate et al. 2020	0.995	0.926	1.000	
CEMR	Wei et al. 2022	0.981	0.928	0.995	
CEMR	Pooled	0.983	0.942	0.995	
CSP	Li et al. 2020	0.993	0.951	0.999	
CSP	Mou et al. 2023	0.998	0.964	1.000	
CSP	Shimodate et al. 2020	0.995	0.924	1.000	
CSP	Wei et al. 2022	0.972	0.918	0.991	
CSP	Pooled	0.989	0.966	0.996	



Meta analysis

Fig. 3. Forest plot showing *en-bloc* resection rates of cold snare polypectomy (CSP) vs. cold endoscopic mucosal resection (CEMR). CI, confidence interval.

Complete heterogeneity was observed in the rate of incomplete resection for both CSP and CEMR (I^2=96% and 95%, respectively), possibly reflecting the low incidence of such events. No heterogeneity (I^2=0%) was detected in *en-bloc* resection, immediate bleeding rates with CSP, perforation, and other complication rates. Moderate heterogeneity was noted with both CSP and CEMR for complete resection rates (I^2=67% and 51%, respectively), immediate bleeding rates with CEMR (I^2=40%), and delayed bleeding rates (I^2=55%). The presence of substantial or moderate heterogeneity could be attributed to a range of factors, such as variations in polyp size, polyp location, types of submucosal injection, and the different snares used across the studies.

3) Publication bias

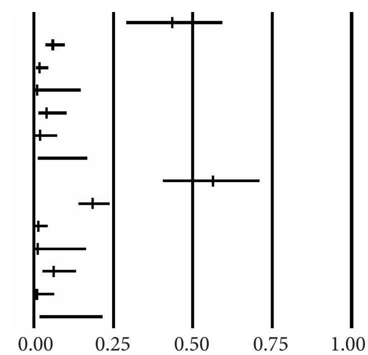
An assessment for publication bias was not conducted as the total number of studies incorporated into the final analysis did not exceed 10.

DISCUSSION

Our systematic review and meta-analysis of RCTs show comparable outcomes when CEMR was compared with CSP for colorectal polyps ≤10 mm. We found that the two techniques demonstrated similar outcomes for complete, *en-bloc*, and incomplete resection. Overall the pooled adverse event rates were not significantly different between the two. However, CEMR was associated with a longer resection time. These findings

Incomplete resection

Group by procedure	Study name	Statistics for each study: Event rate	Lower limit	Upper limit
CEMR	Kim et al. 2023	0.436	0.091	0.593
CEMR	Li et al. 2020	0.060	0.036	0.096
CEMR	Mou et al. 2023	0.017	0.006	0.045
CEMR	Rex et al. 2022	0.010	0.001	0.146
CEMR	Shimodate et al. 2020	0.040	0.015	0.102
CEMR	Wei et al. 2022	0.019	0.005	0.072
CEMR	Pooled	0.048	0.013	0.166
CSP	Kim et al. 2023	0.564	0.407	0.709
CSP	Li et al. 2020	0.184	0.141	0.238
CSP	Mou et al. 2023	0.014	0.004	0.042
CSP	Rex et al. 2022	0.012	0.001	0.164
CSP	Shimodate et al. 2020	0.062	0.028	0.131
CSP	Wei et al. 2022	0.009	0.001	0.062
CSP	Pooled	0.067	0.019	0.215



Meta analysis

Fig. 4. Forest plot showing incomplete resection rates of cold snare polypectomy (CSP) vs. cold endoscopic mucosal resection (CEMR). CI, confidence interval.

emphasize that submucosal injection may not be necessary for resection of sub-centimeter colorectal polyps.

For polyps <5 mm, CSP is associated with a higher complete resection rate than hot forceps polypectomy and cold-forceps polypectomy.[23] When addressing colorectal polyps that are ≤10 mm in size, although CSP and hot snare polypectomy (HSP) have the same efficacy, CSP is safer than HSP.[24] However, as compared with EMR, CSP had an inferior complete resection rate (91.5% vs. 98.5%).[24] A comprehensive meta-analysis of 32 RCTs demonstrated no significant difference in the rate of incomplete resections between CSP and HSP.[25] Furthermore, another large-scale RCT highlighted a notably lower rate of delayed bleeding in CSP than in HSP.[26] As a result of these findings, current international guidelines endorse CSP as the preferred method for managing small colorectal polyps under 10 mm.[5,27]

The advent of CEMR has been proposed to mitigate the challenge of incomplete resections seen in other techniques by allowing for a deeper and controlled removal of lesions. CEMR involves the use of a submucosal injection that lifts the lesion away from the muscular layer, which is then excised with a snare, and crucially, does not involve the use of electrocautery. It involves injecting a fluid, such as normal saline, sodium hyaluronate, succinylated gelatin, hydroxyethyl starch, or glycerol, into the submucosal layer beneath the lesion to create a cushion for safer snare resection. Growing evidence shows the benefit of fewer adverse effects in CEMR.[28] Large prospective studies have demonstrated CEMR as a safe, efficient, and cost-effective procedure.[29] Despite its advantages, recent discussions in the literature have centered on the potential issues, especially submucosal injection agents, as these agents may cause tissue alterations or artifacts that complicate histopathological interpretation, making it difficult to assess the depth of invasion of a lesion accurately.[30] Furthermore, some agents may interfere with the staining properties of tissues.[31]

Another potential issue is that the lifting effect of the agent may create an artificial separation between layers of the gastrointestinal tract wall, which could be misinterpreted as a deeper invasion by a neoplastic process leading to an overestimation of the tumor stage along with increasing the risk of specimen fragmentation.[31] Although CEMR potentially offers a more complete resection, it may be associated with longer procedure duration due to the preparation and injection of lifting agents as well as additional costs related to use of accessories and injections. This might also affect the preservation of the histological architecture, further complicating postresection pathological assessment.[32,33] In our meta-analysis we found that the mean resection time was significantly higher in the EMR group than in the CSP group (98.88 seconds vs. 43.96 seconds; standard mean difference, 1.21).

Adverse events remain a key metric in evaluating the safety of endoscopic procedures. CSP has been associated with low bleeding rates, with most complications being minor and manageable during the procedure itself.[24] Given the nonthermal and superficial nature of the resection, the risk of perforation with

CSP is almost negligible.[34] CEMR, in comparison, has been scrutinized for potentially higher complication rates due to the deeper resection and use of injections.[34] Rex et al.[17] showed that the risk of perforation was higher in CEMR than in CSP due to the depth of resection and the use of submucosal injections. However, this risk remains low and occurs infrequently. In our study, the pooled rates of immediate bleeding and delayed bleeding were similar between the CSP and CEMR groups with no statistically significant differences. No events of perforation in either procedure indicating comparable safety profiles were reported. The management of these events was within the expected standards of endoscopic practice, with no reports of serious complications that required surgical intervention or resulted in long-term morbidity.

The strengths of this review are as follows: systematic literature search with well-defined inclusion criteria, careful exclusion of redundant studies, detailed extraction of data, and rigorous evaluation of study quality. All the included studies are RCTs. Our study has a few limitations. First, our analysis included a small number of studies; therefore, our findings may not be generalizable. Second, bias may exist because only one randomization per patient was conducted for patients who had more than one polyp. Third, although the histological evaluation of specimens was performed in a blinded manner, patients and endoscopists knew the treatment methods. Finally, the type of submucosal agent and snares used in the trials varied, which likely contributed to the substantial heterogeneity in some of our outcomes. Despite these limitations, our study is still the best available estimate that may be used to compare CEMR with CSP.

In conclusion, based on a meta-analysis of seven RCT studies of 1,944 polyps in 1,560 patients (771 in the CSP group and 789 in the CEMR group), both CSP and CEMR are equally safe and effective for resecting small (≤10 mm) colorectal polyps; however, the latter is associated with a longer resection time. Our findings contribute to this ongoing discussion by suggesting that both CSP and CEMR have comparable safety profiles and are both viable options for the resection of small colorectal polyps. We observed no statistically significant differences in immediate or delayed bleeding, or perforation events between the two groups. However, CEMR involves a longer procedure time than that of CSP, which questions its use in clinical practice when compared to CSP. Considering the additional expenses associated with needles and injectates, further comparative trials may be needed to solidify the roles of these techniques in clinical practice.

Supplementary Material

Supplementary Material 1. Literature search strategy.

Supplementary Material 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist.

Supplementary Table 1. Study quality assessment.

Supplementary Fig. 1. Forest plot, risk ratio of complete resection in cold snare polypectomy vs. cold endoscopic mucosal resection. CI, confidence interval.

Supplementary Fig. 2. Forest plot, risk ratio of *en-bloc* resection in cold snare polypectomy vs. cold endoscopic mucosal resection. CI, confidence interval.

Supplementary Fig. 3. Forest plot, risk ratio of incomplete resection in cold snare polypectomy vs. cold endoscopic mucosal resection. CI, confidence interval.

Supplementary Fig. 4. Forest plot, rate of immediate bleeding in cold snare polypectomy vs. cold endoscopic mucosal resection. CI, confidence interval.

Supplementary Fig. 5. Forest plot, rate of delayed bleeding in cold snare polypectomy vs. cold endoscopic mucosal resection. CI, confidence interval.

Supplementary Fig. 6. Forest plot, rate of perforation cold snare polypectomy (CSP) vs. cold endoscopic mucosal resection (CEMR). CI, confidence interval.

Supplementary Fig. 7. Forest plot, rate of resection times cold snare polypectomy (CSP) vs. cold endoscopic mucosal resection (CEMR). CI, confidence interval.

Supplementary Fig. 8. Forest plot, risk ratio of immediate bleeding cold snare polypectomy vs. cold endoscopic mucosal resection. CI, confidence interval.

Supplementary Fig. 9. Forest plot, risk ratio of delayed bleeding cold snare polypectomy vs. cold endoscopic mucosal resection. CI, confidence interval.

Supplementary Fig. 10. Forest plot, risk ratio of perforation cold snare polypectomy vs. cold endoscopic mucosal resection. CI, confidence interval.

Supplementary materials related to this article can be found online at https://doi.org/10.5946/ce.2024.081.

Ethical Statements

Not applicable.

Conflicts of Interest

The authors have no potential conflicts of interest.

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Author Contributions

Conceptualization: VM, MB, AS, SC; Data curation: VM, SM, BPM, DR, DM, SC; Formal analysis: PL, MM, BPM; Investigation: SM, DSD, DR, BPM, MM, DM; Software: VM; Writing–original draft: SC, VM PL, DSD, MB, AS; Writing–review & editing: all authors.

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