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EDITORIAL

MINIREVIEWS

META-ANALYSIS

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Contents

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EDITORIAL

Management of local recurrence after endoscopic resection of neoplastic colonic polyps

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Abstract

A proportion of neoplastic polyps are incompletely resected, resulting in local recurrence, especially after resection of large polyps or piecemeal resection. Local recurrences that develop after endoscopic resection of intramucosal neoplasms that lacked risk factors for lymph node metastasis or positive vertical margins are usually treated endoscopically. Endoscopic submucosal dissection (ESD) is indicated for local residual or recurrent early carcinomas after endoscopic resection. However, ESD for such recurrent lesions is technically difficult and is typically a lengthy procedure. Underwater endoscopic mucosal resection (UEMR), which was developed in 2012, is suitable for recurrent or residual lesions and reportedly achieves superior *en bloc* resection rates and endoscopic complete resection rates than conventional EMR. However, a large recurrent lesion is a negative independent predictor of successful *en bloc* resection and of complete endoscopic removal. We therefore perform UEMR for relatively small (≤ 10-15 mm) recurrent lesions and ESD for larger lesions.

Key words: Recurrence; Endoscopic management; Colon; Endoscopic submucosal dissection; Underwater endoscopic mucosal resection; Polyp; Endoscopic resection; Fibrosis; Non-lifting sign

Core tip: Local recurrences of neoplastic colonic polyps can occur, especially after resection of large polyps or piecemeal resection. Local recurrences that develop after endoscopic resection of intramucosal neoplasms that lacked risk factors for lymph node metastasis or positive vertical margins are usually treated endoscopically. We perform underwater endoscopic mucosal resection for relatively small (≤ 10-15 mm) recurrent lesions and endoscopic submucosal dissection for larger lesions.

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INTRODUCTION

Adenomatous polyps are the commonest neoplasms found during colorectal cancer screening[1]. Detection and removal of these cancer precursors may prevent many cancers and reduce mortality[2]. However, a proportion of neoplastic polyps are incompletely resected[3], resulting in local recurrence, especially after resection of large polyps (≥ 20 mm), in 4.3% to 36.7% of cases[4-10]. Not only size[4,6,8-10], but also piecemeal resection[7,9-11], histology of adenoma (compared with serrated polyp)[5,10], and intraprocedural bleeding[6,10] are also reportedly risk factors for local recurrence. A systematic review found that local recurrence after endoscopic mucosal resection (EMR) of non-pedunculated colorectal lesions occurs in 3% of *en bloc* resections and 20% of piecemeal resections; more than 90% of recurrences are detected 6 mo after EMR[12]. Periodic inspection by colonoscopy is desirable for early detection of local residual tumors/recurrences, and endoscopic management measures being suitable for many such lesions that are detected early[13]. The European Society of Gastrointestinal Endoscopy guideline recommends endoscopic follow-up within 6 mo of piecemeal resection of adenomas larger than 10 mm[14]. Local recurrences that develop after endoscopic resection of intramucosal neoplasms that lacked risk factors for lymph node metastasis or positive vertical margins are usually treated endoscopically. Here we review and summarize the management of local recurrence after endoscopic resection.

MANAGEMENT OF LOCAL RECURRENCE AFTER ENDOSCOPIC RESECTION

Several groups have reported their management of local recurrences. Hotta *et al*[11] reported performing additional endoscopic resection in 32 of 34 recurrent lesions (94%), the remaining two patients (6%) undergoing additional surgery. In a multicenter prospective study of 1000 consecutive wide-field EMRs, 93% (135 of 145) of local recurrences were successfully resected endoscopically, the remaining 10 being referred for surgery[6]. Knabe *et al*[7] reported a prospective two-center study of 243 consecutive patients with 252 adenomas resected endoscopically. Seventy-seven residual tumors and recurrences were all treated by endoscopic resection and/or argon plasma coagulation. Sakamoto *et al*[15] have reported a retrospective study of 60 consecutive patients with locally recurrent or residual tumors after endoscopic resection. Of 69 lesions in 60 patients, 67 were treated endoscopically, whereas two required surgical treatment. *En bloc* resection rates were 39% (23/58) with EMR (39%) and 56% (5/9) with endoscopic submucosal dissection (ESD)[15].

According to the Japan Gastroenterological Endoscopy Society guidelines for colorectal ESD/EMR[13], ESD (Figure 1) is indicated for local residual or recurrent early carcinomas after endoscopic resection. Although most local recurrences can be treated endoscopically, additional endoscopic resection is technically challenging because of severe fibrosis at the original resection site because such fibrosis results in the non-lifting sign with submucosal fluid injection. Thus, ESD for such recurrences is technically difficult and typically a lengthy procedure.

Underwater EMR (UEMR) was developed and described by Binmoeller *et al*[16] in 2012. In this procedure, air is evacuated from the affected segment of lumen and water infused until the lumen is complete full, at which stage hot snare polypectomy is performed without submucosal injection. This procedure is reportedly effective for resecting large polyps[16,17]. It is also suitable for recurrent or residual lesions. Kim *et al*[18] reported a retrospective, cross-sectional study of patients with recurrent adenoma after piecemeal EMR of colorectal laterally spreading tumor (≥ 2 cm). The *en bloc* resection rate (47% *vs* 16%, $P = 0.002$) and complete resection rate (89% *vs* 32%, $P < 0.001$) were significantly higher in the UEMR group ($n = 36$) than that of the conventional EMR ($n = 44$)[18]. Argon plasma coagulation of visible residual lesions during the salvage procedure was less frequently required in the UEMR than the EMR group (11% *vs* 66%, $P < 0.001$). The recurrence rate at follow-up colonoscopy was significantly lower in the UEMR group (10% *vs* 39%, $P = 0.02$). In this trial, UEMR was an independent predictor of *en bloc* resection and complete resection, whereas a large recurrent lesion is a negative independent predictor of successful *en bloc* resection and complete endoscopic removal. We therefore perform UEMR for relatively small (≤ 10-15 mm) recurrent lesions (Figure 2) and ESD for larger lesions.

Even with the technical advances of ESD and development of UEMR, endoscopic treatment of recurrent lesions is still challenging. We therefore recommend precise diagnosis of the extent of naïve lesions by careful examination using indigo carmine and/or narrow band imaging endoscopy. We also recommend close follow-up after

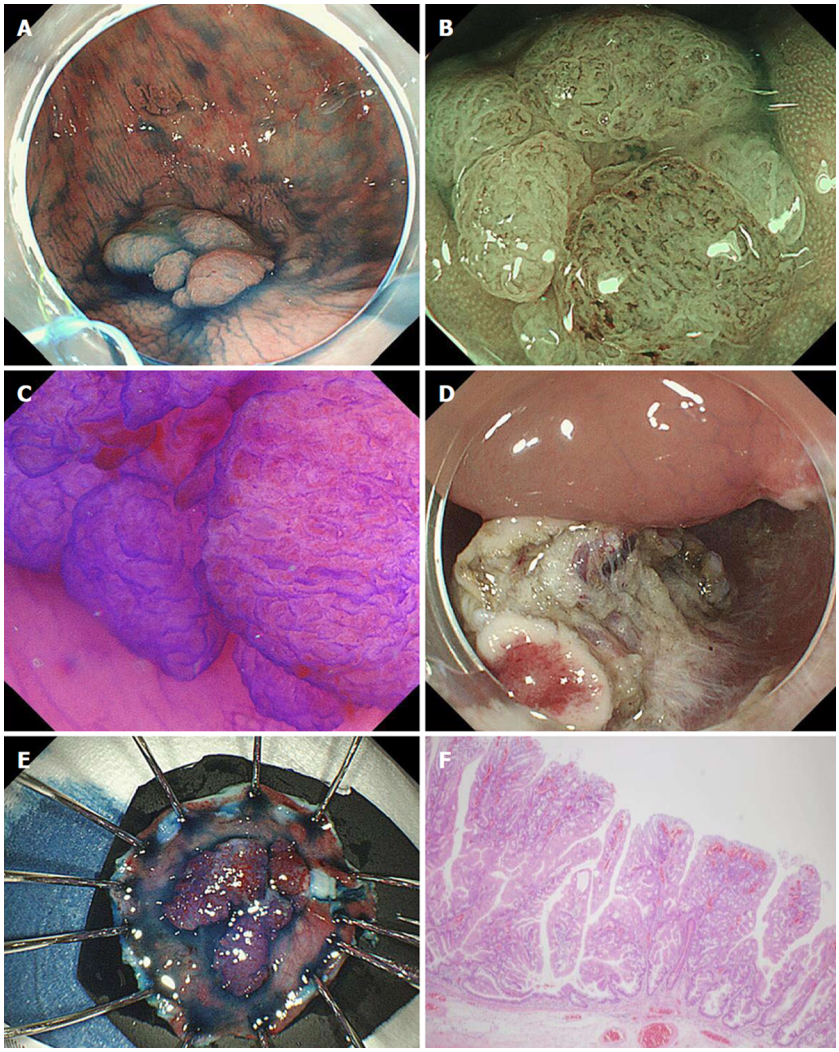

Figure 1 Endoscopic submucosal dissection of recurrent lesion in the cecum. A: A Local recurrence (laterally spreading tumor, granular type) was identified in the cecum 18 mo after piecemeal endoscopic mucosal resection; B: The Japan Narrow-band imaging Expert Team classification was type 2B[19]; C: Kudo's pit pattern was V_I[20]. The laterally spreading tumor was diagnosed as an intramucosal lesion and ESD performed; D, E: Although there was severe fibrosis in the submucosal layer, *en bloc* resection was achieved; F: The pathological diagnosis was adenocarcinoma arising from a sessile serrated adenoma/polyp, type 0-IIa, 16 × 15 mm, pTis, pHM0, pVM0; ER0, Cur EA; pap > tub1, ly0, v0.

piecemeal resection or resection of large polyps.

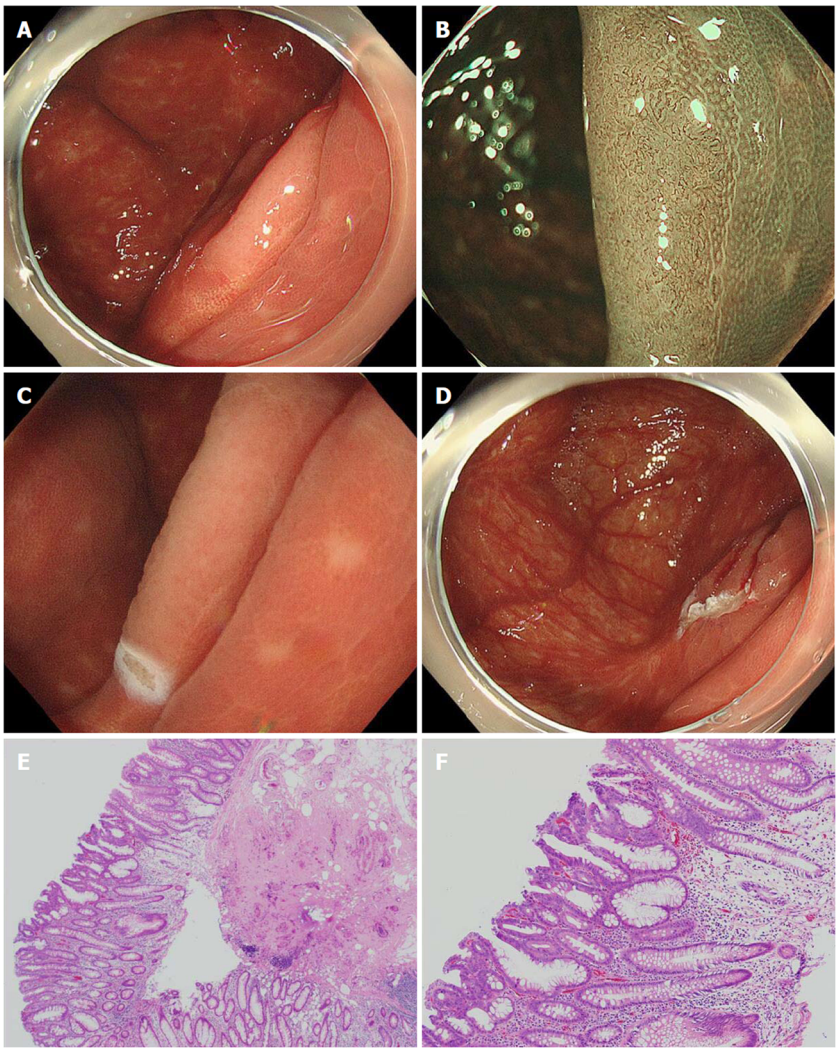

Figure 2 Underwater endoscopic mucosal resection of a recurrent lesion in the cecum. A: A local recurrence was identified in the cecum 12 mo after *en bloc* endoscopic mucosal resection; B: Magnified endoscopy with narrow band imaging revealed Japan Narrow-band imaging Expert Team classification type 2A; C: Underwater endoscopic mucosal resection was performed after marking; D: Complete resection was achieved. E, F: The pathological diagnosis was low grade adenoma.

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MINIREVIEWS

Long term oncological outcome of laparoscopic techniques in pancreatic cancer

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Abstract

The laparoscopic technique in distal pancreatic resection (LDP) has been widely accepted, and outcome data support the hypothesis that survival is improved, partly due to improved postoperative safety and recovery, thus optimizing treatment with adjuvant chemotherapy. But laparoscopic pancreaticoduodenectomy (LPD or Whipple-procedures) has spread more slowly, due to the complexity of the procedure. Surgical safety has been a problem in hospitals with low patient volume, resulting in raised postoperative mortality, requiring careful monitoring of outcome during the surgical learning curve. Robotic assistance is expected to improve surgical safety, but data on long term oncological outcome of laparoscopic Whipple procedures with or without robotic assistance is scarce. Future research should still focus surgical safety, but most importantly long term outcome, recorded as recurrence at maximal follow up or - at best - overall long term survival (OS). Available data show median survival above 2.5 years, five year OS more than 30% after LDP even in series with suboptimal adjuvant chemotherapy. Also after LPD, long term survival is reported equal to or longer than open resection. However, surgical safety during the learning curve of LPD is a problem, which hopefully can be facilitated by robotic assistance. Patient reported outcome should also be an endpoint in future trials, including patients with pancreatic ductal adenocarcinoma.

Key words: Chemotherapy; Endpoint; Imaging; Laparoscopic surgery; Long term outcome; Overall survival; Pancreatic cancer; Robotic assistance

Core tip: Laparoscopic techniques have profoundly altered oncological gastrointestinal surgery, also resectional treatment of pancreatic ductal adenocarcinoma. Long term outcome of distal resections has been gradually improved. Median survival is more than 2.5 years, five year overall survival above 30%, whereas outcome of laparoscopic

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pancreaticoduodenectomy needs further evaluation before the technique can be widespread. It is an open question how wide this spread ought to be, but robotic assistance is expected to improve surgical safety.

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INTRODUCTION

Improved survival after laparoscopic resection of gastrointestinal carcinoma was expected after elimination of the initial failures in surgical performance during the nineties. A randomized controlled trial (RCT) from Barcelona[1], comparing survival after laparoscopic and open colectomy (n = 219) supported this concept. But subsequent multicenter RCTs with comprehensive patient numbers could not verify any survival difference[2]. In patients with ductal pancreatic adenocarcinoma (PDAC), no RCT comparing long term outcome of laparoscopic and open distal resection was identified in the Cochrane review 2016[3]. In 2017, a small series from India was published with shorter hospital stay after laparoscopic resection[4]. Nevertheless, laparoscopic distal pancreatectomy (LDP) has become a widespread technique, and selection of relevant clinical parameters for assessment of long term oncological outcome is ever more underlined[5]. Also increasing numbers of laparoscopic pancreaticoduodenectomy (LPD/Whipple procedures) have been reported with good outcome[6], and oncological advantages over an open approach have been suggested[7].

The clinical benefit of adjuvant chemotherapy after open resectional surgery in pancreatic cancer (PC) patients is well documented[8,9], whereas the question of upfront surgery *vs* neoadjuvant chemotherapy is unsettled. These questions have never been investigated, focusing only laparoscopically operated patients, but fair rationales indicate that evidence generated from PC patients operated openly, is transferable to laparoscopic practice. This minireview updates current evidence on long term oncological outcome of laparoscopic resection combined with applied chemotherapy in PDAC patients. The intention of the analysis is first to improve selection of endpoints in future clinical trials, second to guide the choices of surgical methodological development.

Methods (search strategy and data management)

Search in PubMed was performed with the key words: PC, combined with chemotherapy, laparoscopy, morbidity, outcome, safety, survival. Reports were selected, based on publication date and comprehended internal validity in each paper. Cochrane reviews, meta-analyses and review articles, relevant to the scope of this review were prioritized. Data on long term survival was particularly focused. Core information from the most relevant publications was selected for presentation in two summary tables.

DISTAL RESECTIONS

The laparoscopic technique was introduced in distal resections during the nineties, concurrent with ongoing diagnostic improvements generated from increasing use of abdominal CT, MRI and ultrasound examination. Concomitantly, awareness of the malignancy potential of mucinous cysts[10] enables surgical removal of premalignant tumors/early invasive carcinoma, thus improving postoperative survival after any surgical technique. In the first report from our department on 50 PDAC patients, undergoing LDP[11], five year survival was above 30%, which was very much better than in our previous series, obviously due to earlier diagnosis, but the early skepticism aligned with laparoscopic techniques in PDAC patients was opposed by those data. In 2012, Mitchem, Strasberg *et al*[12] published a modified open technique for resection of adenocarcinoma of the body/tail of the pancreas; the Radical Antegrade Modular Pancreaticosplenectomy Procedure (RAMPS), underlining new technical aspects, including the necessity of removal also of the left adrenal gland in numerous cases; "posterior RAMPS". In 47 patients, operated by the RAMPS

technique, median postoperative survival was 26 mo, 5 year overall actuarial survival (OS) 35.5%, mean lymph node count was 18 and rate of R0 resection (free margin) 81%. Survival in the 50 PDAC patients, operated with LDP in our department, was similar but lymph node count in our specimens was significantly lower. This observation initiated investigation of the putative impact on lymph node count of improved pathology examination, focusing specimens from patients undergoing LDP during ten years (January 2007-January 2017). The lymph node count and the number of positive glands increased significantly when specimens underwent a strictly, standardized examination[13]. Accordingly, comparison of lymph node count in the specimens from different centers is associated with significant uncertainty, thus also comparison of oncological outcome of surgical methods, based on lymph node count. Also the rate of R0 resections is an unsafe oncological quality indicator, first because of various R0 definitions[14,15], second because neoadjuvant chemotherapy is used increasingly and R0 status has not been clearly defined in this situation. Due to spot wise death of tumor tissue during chemotherapy in PDAC, the R0 concept must be redefined. Overall survival/cancer related death rate are the most appropriate clinical parameters for evaluation of long term oncological outcome of resectional surgical methods, subsidiary, recurrence rate at maximal follow up.

In a Pan-European, retrospective study (DIPLOMA), oncological outcome was compared between LDP and open distal pancreatectomy (ODP). Among 1212 patients, operated from 2007-2015 in 34 centers, distributed between 11 countries, propensity score matching was possible in 340. Postoperative survival was median 31 and 28 mo after ODP and LDP respectively[16]. Data registration was not standardized between the participating 34 centers, and the uncertainty of these data is substantial. In another recent report from two centers (Oslo/Norway and Seoul/South Korea) who standardized their registration, 207 patients with histologically confirmed PDAC underwent LDP from 2002-2016. Median overall and recurrence-free survival were 32 and 16 mo, five year OS and recurrence-free survival was 38, 2% and 35, 9% respectively[17]. Adjuvant chemotherapy was given according to national guidelines in Norway and Korea during the inclusion period, which later has been shown to be suboptimal, as the ESPAC 4 study documented improved survival of Gemcitabine plus Capecitabine[9]. Accordingly, even better long term oncological outcome of LDP is probably achievable, when the procedure is combined with the best adjuvant regimen. These data are in line with comparative studies from single centers in Asia. Shin *et al*[18] compared median OS and recurrence rate at maximal follow-up in PDAC patients, 70 operated with LDP, 80 ODP between December 2006 and August 2013. Five year OS was 32.5% *vs* 27.6%, recurrence after maximal follow-up was found in 50% *vs* 60%, respectively, but there was no statistically significant difference after propensity score matching. Hu *et al*[19] reported recurrence after maximal follow-up in 18% after LDP *vs* 48% after ODP, but total patient number was only 34, and hence no significant difference. In a Cochrane review 2016[3], the authors conclude that short time outcome (hospital stay, recovery, postoperative morbidity, *etc*.) seems improved after LDP (medium strong evidence), whereas evidence favoring better long term oncological outcome is still weak.

PANCREATICODUODENECTOMY (WHIPPLE PROCEDURES)

The first international State-of-the-Art conference on Minimally Invasive Pancreatic Resection took place in Sao Paulo, Brazil on April 20th, 2016, and a comprehensive summary of the proceedings have been published[20]. A systematic review on best-evidence of outcome after LPD identified 582 publications, 26 comparative studies[21]. Information from the National Cancer Data Base (NCDB) comparing short term outcome of LPD with open pancreaticoduodenectomy (OPD) describes 4421 patients, operated 2010-2011; 4037 (91%) underwent OPD, 384 (9%) LPD, and no difference was found in 30 day mortality, 5.2% *vs* 3.7% respectively[22]. This report gives no information on long term oncological outcome. Another paper based on the Nationwide Inpatient Sample Database identified 15574 Whipple procedures performed from 2000-2010; 681 of these (4.4%) laparoscopically[23]. The main conclusion is that even during the learning curve of laparoscopic surgeons, safety seems acceptable, short term outcome is equal or better than OPD, but no information on long term oncological outcome is given. A report from the Mayo Clinic on outcome in 108 patients after LPD, compared to 214 after OPD found no significant survival difference[7], but delay of recovery due to postoperative morbidity resulted of no adjuvant chemotherapy in 12% after OPD *vs* 4% after LPD (P = 0.04). However, at a national level, this difference could not be verified, in a report from NCDB in 7967 subjects[24]. Kendrick[21] mentions number of lymph nodes retrieved and margin status

as relevant endpoint parameters for assessment for oncological outcome and lists five publications with this information, but only two of these reports have information on local recurrence and survival at the time of maximal follow up. A comparative study from France[25], gives only data on short term outcome, but in a recent combined report from the United States and France, favorable survival was found after LPD[26]. After propensity score matching median OS was 35.5 mo after LPD *vs* 29.6 after OPD; 1-, 3 and 5-year survival was 80.5% *vs* 49.2%, 77.7% *vs* 39.7%, and 46.4% *vs* 30% respectively. However, a recent metaanalysis shows that the immediate risk of postoperative morbidity may influence OS, as introduction of LPD in hospitals with low patient volume, resulted in more than doubling of postoperative mortality, 7.5% *vs* 3.4%[27]. Also a Pan European report from 14 centers having performed more than ten LPD, found increased morbidity after minimally invasive procedures[28]. All centers should obviously not introduce this procedure. Information from core papers on oncological long term outcome of distal resections is put together in Table 1, pancreaticoduodenectomy in Table 2.

ROBOTIC ASSISTANCE

Robotic surgery was first utilized for pancreatic resection in 2003[29], and is becoming increasingly utilized[30], even though the number of operated patients is still limited. Robotic assistance in distal resections has been evaluated in a metaanalysis from 2016[31], reporting nine comparative studies with all together 246 robotic *vs* 391 laparoscopic procedures. Short term outcome in terms of postoperative morbidity, hospital stay and recovery were similar. An updated metaanalysis 2017[32], including 813 patients, verified this but conversion rate was lower in RDP than LDP. Information about long term oncological outcome is missing in both these papers, but is reported in two small series: In ten PDAC patients median OS was 15, range 7-29 mo[33], in 72 other patients[34] mean OS was 15.6 mo ± 5.8 mo, and only 26% of the latter cases received adjuvant chemotherapy, *i.e.*, there is a potential for further increased survival.

Safety aspects

The complexity of Whipple procedures and the resulting risk of postoperative severe morbidity and mortality are well known. Robot-assistance may possibly result in more precise dissection and safer construction of anastomoses. Institutions gaining experience with robot assisted pancreaticoduodenectomy (RPD)[31], underline that standardization of key element of the learning curve of RPD is mandatory[35]. A good model for this has been published from Pittsburgh, where quality outcomes of the first consecutive 200 RPD procedures have been monitored in subgroups of 20 cases, reviewing the learning curve during the implementation phase[36]. This program was developed also to adjust the introduction of a robotic platform to the ongoing paradigm shift in healthcare; a move from fees for service to payment for performance, thus achieving better value from available resources[37]. This is particularly relevant for RPD-procedures, as a major downside is high costs. Nevertheless, a recent comparative study found comparable surgical and oncological safety, median OS was 23 mo *vs* 22 mo after RDP and ODP respectively, and even costs were equal[38]. The robotic platform is expected to improve recovery significantly after major pancreatic surgery, thus obtaining better patient outcome/satisfaction for used resources.

ADJUVANT AND NEOADJUVANT CHEMOTHERAPY

Adjuvant chemotherapy has been utilized in PC patients for more than twenty years, and selection of regimens is continuously improving, based on well accomplished RCTs. In Scandinavia, Gemcitabine plus capecitabine have been standard of care in unselected cases after the ESPAC 4 trial[9], but it has already been documented that Folfirinox is more potent[39]. Selection of patients tolerating regimens with significant toxicity leads to five year survival far above 30% after open pancreatic surgery - this probably applies also for laparoscopic techniques. So far, no prospective trials have been conducted, investigating these questions. Current knowledge stem from observational studies of patients, receiving regimens which were inferior to the present standard of care. Accordingly, a reasonable presumption is that there is room for further improvement of postoperative survival after laparoscopic pancreatic surgery, when combined with updated adjuvant treatment.

Neoadjuvant chemotherapy attracts increasing interest, and numerous RCTs are

Table 1 Core information on distal pancreatic resection in pancreatic cancer patients

Ref.	No. of patients reported	Study	Median survival (mo)	
			Open	Laparoscopic
Van Hilst *et al*[16], 2017	680	Comparative, 34 centers (propensity score matching) retrospective	28	31
Mitchem *et al*[12], 2012	47	Non comparative, single center retrospective	26	NA
Sahakyan *et al*[17], 2017	207	Non comparative, two centers retrospective	NA	32
Shin *et al*[18], 2015	150	Comparative, single center (propensity score matching) retrospective	29	33
Grossman *et al*[40], 2016	78	Non comparative, single center retrospective	25	NA

NA: Not applicable.

ongoing, including resectable and borderline resectable patients undergoing open pancreatic resections. Also considerations on putative benefit and/or harm of neoadjuvant treatment algorithms in laparoscopic pancreatic surgery have to await results from these trials.

DISCUSSION

Five year OS above 30%-35% after LDP has recently been reported from numerous centers, illustrating that increasing evidence show good long term oncological outcome. Comparison with outcome of ODP favors the laparoscopic technique, even though data from RCTs are still lacking. In recent reports, five year OS is 25% after the RAMPS procedure[40,41]. Patients with PDAC in the pancreatic body or tail should therefore be offered laparoscopic resection if the HepatoPancreaticoBiliary (HPB) center possesses the required expertize. But pancreatic head tumors are still resected openly in most HPB-centers, as the role of LPD is not at all clear and long term oncological outcome is mostly unknown. The international State-of-the-Art conference on Minimally Invasive Pancreatic Resection in 2016 concluded that the small number of comparative studies of LPD *vs* OPD is also of low quality, Newcastle-Ottawa score (NOS) < 6[21]. This score is a risk of bias assessment tool for observational studies[42]. During the State-of-the-Art conference 2016, a specific session evaluated what would be the future most essential scientific contributions in this field, underlining that numerous important questions need valid answers[43]. Even though RCT is the reference standard for clinical comparative research according to the traditional pyramid of evidence level, the applicability of this study design is limited and numerous clinical questions cannot be solved by any randomized trial. A critical question in any trial is selection of primary and secondary outcome variables (clinical endpoints). The importance of adequate choice of endpoint is clearly illustrated by finalized or ongoing RCTs comparing outcome of open and laparoscopic techniques in pancreatic surgery. The PLOT trial[4] randomized 60 Whipple operated patients, focusing hospital stay, and found median 13 d after OPD *vs* 7 d after LPD, $P = 0.001$, which is relevant and interesting, but marginally important. In the Netherlands, the LEOPARD 1 study[44] includes patients in need of distal resection, randomizing between open and laparoscopic technique with time to functional recovery as primary endpoint. Similarly, the LEOPARD 2 studies[45] randomize upfront resectable patients between OPD and LPD with the same endpoint. These studies represent relevant clinical research, and valid answers might be generated, but it is already well known from numerous prospective observational studies that LPD is associated with rapid recovery in most centers, and it would be more interesting to investigate whether or not robotic assistance could further improve recovery, safety and particularly long term OS.

In trials focusing outcome of any Whipple procedures focus on safety aspects, especially postoperative mortality, is critically important. This is emphasized in comprehensive registry studies[22] and single center reports[46]. In the State-of-the-Art conference 2016[21], an important "take home messages" to HPB-centers on their way to introduce LPD was; "Surgeons should assess their level of commitment with a clear understanding of the procedure complexity, expected learning curve, and requirements to achieve proficiency". This message is further underlined by recent information from the Leopard 2 study. The data monitoring board has recommended early termination of the trial because of too high 90-d complication-related mortality

Table 2 Core information on pancreaticoduodenectomy/Whipple-procedures in pancreatic cancer patients

Ref.	No. of patients reported	Study	Overall survival		
			Open	Laparoscopic	*P* value
Croome *et al*[7], 2014	322 LPD 108 OPD214	Comparative, retrospective single center	Median 21.8 mo	Median 25.3 mo	0.22
Nussbaum *et al*[24], 2016	7967 LPD 1191 OPD 6776	Comparative Registry (NCDB) Retrospective	Two year 47%	Two year 43%	NS
Conrad *et al*[26], 2017	65 LPD 40 OPD 25	Comparative, retrospective two centers	Median 29.6 mo	Median 35.5 mo	NS

LPD: Laparoscopic pancreaticoduodenectomy; OPD: Open pancreaticoduodenectomy; NCDB: National Cancer Data Base; NS: Not significant.

in the laparoscopic arm, *i.e*., 10% *vs* 2% in the open arm[47] .

The implementation of laparoscopic techniques in oncological surgery has put focus on the traditional pyramid of evidence level, raising the question: how should surgical methods be developed, evaluated and broadened? Both internal and external validity of published investigations are highly relevant, as prospective data, documenting increased survival will probably be reproducible in the publishing center. However, the same outcome data cannot be presupposed transferable to other centers if core conditions differ. Methodological considerations should also be developed across surgical subspecialties, illustrated by a recent report on 10597 patients with lung cancer stage 1, included in a propensity match study, comparing long term oncological outcome of minimally invasive (MI) and open lung resection[48]. Four year survival was 68.6% after MI procedures *vs* 64.8% after open lung resection (P = 0.003). For patients with lung cancer, these data is a significant contribution to evidence based guidance of surgical methodological development.

Finally, the lack of patient reported outcome (PRO) in the literature is a major problem, raising the uncertainty concerning short- and long term outcome in patients with PDAC. There are numerous explanations for the scarcity of data on health related quality of life (HQoL) in this group of patients. One important problem is that disease specific QoL measures are comprehensive, including irrelevant questions which result in low response rates from patients included in prospective trials[49]. This problem has recently been solved by development of the PC Disease Impact (PACADI) score[50]. This is a brief, disease specific measure, and item selection was based on the patients' priorities of which dimensions of PRO had greatest impact on their everyday QoL. In our opinion, every trial evaluating laparoscopic techniques in PC patients should also include PRO as an endpoint. Prospective comparative studies with long follow-up of OS as primary outcome parameter, longitudinally recorded PRO as secondary endpoint, are strongly warranted.

CONCLUSION

The potential for clinical benefit from laparoscopic techniques in pancreatic surgery is great, but available evidence is still limited. Outcome of LPD and RPD is associated with great uncertainty. For all Whipple procedures, surgical safety is a particular concern, which probably can be improved by robotic assistance.

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MINIREVIEWS

Endoscopic evaluation of immunotherapy-induced gastrointestinal toxicity

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Abstract

Immunotherapy is any treatment aimed at boosting or enhancing the immune system. It includes a wide range of options, from vaccines to treatment for conditions such as allergy and cancer. In the case of cancer, unlike other available treatments, immunotherapy is not aimed at destroying the tumor cells but at stimulating the patient's immune system so that it attacks the tumor. In cancer, immunotherapy provides a series of advantages. Nevertheless, immunotherapy administered for treatment of cancer is associated with immune-mediated enterocolitis. Colitis mediated by monoclonal anti-cytotoxic T lymphocyte–associated antigen 4 and to programmed cell death protein 1 and its ligand PDL1 shares characteristics with chronic inflammatory bowel disease (IBD), and similar findings have been reported for both the endoscopy images and the segment involved. The most frequent lesions on endoscopy are ulcer and erythema, and the most frequently affected site is the sigmoid colon. A segmental pattern has been reported to be slightly more frequent than a continuous pattern. In addition, upper gastrointestinal lesions have been reported in up to half of patients, with the most frequent findings being gastritis and erosive duodenitis. As is the case in IBD, systemic corticosteroids and immunosuppressive treatment (anti-TNF agents) are the approaches used in patients with a more unfavorable progression. Immunotherapy must be suspended completely in some cases.

Key words: Enterocolitis; Ipilimumab; Immunotherapy; Immune-related adverse event; Nivolumab; Toxicity; Endoscopy

Core tip: Widespread use of immunotherapy in various types of cancer has led to reports of new associated adverse effects resulting from increased stimulation of the immune system, which can confuse the body's own tissues and organs with foreign matter, thus leading it to attack the body's healthy tissue. The most frequent immune-mediated adverse effects include asthenia, general malaise, fever, gastrointestinal toxicity (abdominal pain, diarrhea, and colitis), cutaneous toxicity, hypothyroidism and

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hepatitis. This review of the endoscopic evaluation of immunotherapy-induced toxicity presents the most typical endoscopic images, the differential diagnosis based on these images, and the initial management.

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WHAT DO WE UNDERSTAND BY THE TERM "IMMUNOTHERAPY"?

Immunotherapy is any treatment aimed at boosting or enhancing the immune system. It includes a wide range of options, from vaccines to treatment for conditions such as allergy and cancer. In the case of cancer, unlike other available treatments, immunotherapy is not aimed at destroying the tumor cells but at stimulating the patient's immune system so that it attacks the tumor. In cancer, immunotherapy provides a series of advantages, such as targeted treatment, which only acts on tumor cells without damaging healthy cells, and immunological memory, which can subsequently be reactivated to recognize and attack the tumor once the immune system is stimulated. Immunotherapy is also subject to disadvantages, such as the time necessary for it to take effect-the immune response is not immediate but gradual- and the associated adverse effects. There are 2 main types of immunotherapy: Specific immunotherapy, which causes a response to a specific cell or antigen and includes vaccines and adaptive cell therapy; and nonspecific immunotherapy, which is aimed at stimulating the whole immune system and includes cytokines and regulatory proteins such as antibodies to cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) or the programmed cell death protein 1 and its ligand PDL1 (PD1/PDL1) pathway. Also of interest are monoclonal antibodies, which are included in another group, known as passive immunotherapy, and comprise molecules designed to recognize tumor cells or substances that the tumor needs for growth. These are administered intravenously and can destroy tumor cells or deprive them of the essential components they require for growth. They are sometimes combined with other treatments in order to enhance their effect[1,2].

Ipilimumab is a monoclonal anti-CTLA-4 immunoglobulin 1 (IgG1) antibody that activates destruction of regulatory T cells by stimulating antibody-mediated cytotoxicity, thus halting the immunosuppressive effect. Ipilimumab is currently approved for the treatment of advanced melanoma (unresectable or metastatic) in monotherapy or in combination with nivolumab (anti-PD1)[3-8].

The most advance therapy attempts to inhibit the PD-1/PD-L1 checkpoint pathway. The PD1 receptor is found in lymphocytes and acts as an inhibitory-type checkpoint by interacting with its ligands PDL1 and PDL2. Tumor cells are capable of expressing PDL1, thus inhibiting the action of the cytotoxic T cell on them and generating tolerance. In this way, anti-PD1 drugs (nivolumab, pembrolizumab, durvalumab) and anti-PDL1 drugs (avelumab, atezolizumab) overcome tumor immune tolerance and enable the action of cytotoxic T cells. Anti-PD1 and anti-PDL1 agents have several indications in various scenarios, both in monotherapy and in combination therapy in patients with melanoma, lung cancer, renal cell carcinoma, urothelial carcinoma, classic Hodgkin lymphoma, and head and neck tumors[9].

PATHOPHYSIOLOGY OF GASTROINTETINAL TOXICITY

Toxicity of the various types of immunotherapy, or immune-related adverse effects, is closely associated with the mechanism of action of the different treatments, for example, the toxicity of interleukin 2 (IL-2) results from release of nitric oxide, IL-1, tumor necrosis factor alpha, and interferon gamma. In adoptive cell therapy, the initial toxicity is caused by lymphodepleting chemotherapy. After T-cell infusion, immunotoxicity manifests as fever, tachycardia, vascular hyperpermeability followed by multiorgan failure. In the most severe cases, this is due to cytokine release syndrome[10]. Blockade of CTLA-4 suppresses the function of regulatory T cells, which

contribute to local inflammation in the gastrointestinal mucosa. It has been suggested that colitis associated with CTLA4 could result, in part, from this immunosuppressive function[11]. PD-1 and CTLA-4 blockade can generate toxicity that mimics autoimmune diseases[12].

HOW TOXIC IS IMMUNOTHERAPY FOR THE GASTROINTESTINAL TRACT?

Adverse effects involving the digestive system are recorded in around one-third of all patients receiving immunotherapy, specifically monoclonal anti-CTLA-4 IgG1 and anti-PD1 IgG4 antibodies[13].

Immune-mediated enterocolitis is one of the most common adverse effects, especially with ipilimumab. Up to one-third of patients treated with ipilimumab experience diarrhea, and immune-mediated colitis is observed in 7%-22% of cases[14]. In contrast, immune-mediated enterocolitis associated with nivolumab is less common, affecting around 10% of all patients who receive it[15]. The combination of ipilimumab and nivolumab is even more toxic than when each agent is used separately[8].

ENDOSCOPY

When should it be performed?

Colonoscopy with biopsies is the standard diagnostic approach for patients with lower digestive symptoms (*e.g.*, diarrhea, hematochezia). It is recommended in patients who receive immunotherapy and have persistent diarrhea or associated poor prognostic factors (hospitalization due to oral intolerance or absence of response to corticosteroids). Upper gastrointestinal symptoms (*e.g.*, dysphagia, gastroesophageal reflux, epigastralgia) are not uncommon and necessitate gastroscopy[16].

Which are the main endoscopy findings?

In the colon: In their series of 39 patients receiving anti-CTLA-4, Marthey *et al*[17] reported the most common lesions in endoscopy to be ulcer (79%) (Figures 1 and 2), erosion (13%), and erythema (8%) (Figure 3). The rectum and/or sigmoid colon were involved in 97% of cases, with extensive colitis being observed in 66% of patients. The distribution of the lesions was patchy in 55% of cases. The ileum was affected in only 5 patients.

In their study of 40 patients receiving treatment with anti-CTLA-4 agents who developed diarrhea and underwent flexible sigmoidoscopy or colonoscopy, Beck *et al*[18] reported findings for 36 cases. Again, the most common findings were erythema and ulcer (in 63% of patients). Endoscopy revealed inflammation several months after onset of enterocolitis, thus suggesting that in some cases, enterocolitis induced by anti-CTLA-4 agents can progress to inflammatory bowel disease (IBD).

We can find similar results for the type of involvement in immune-mediated colitis caused by anti-PD1 agents, which is less frequent than that associated with anti-CTLA-4 agents. Collins *et al*[15] studied a series of 20 patients with diarrhea who were receiving treatment with anti-PD1 agents and in 12 of whom colonoscopy findings were abnormal. The most frequent location was the descending colon (83%), and a patchy pattern, rather than a continuous pattern, was the most common (found in approximately 73% of patients). The most common lesions are also the same as those described above, namely, erythema, erosion, and ulceration.

Esophagus-stomach-duodenum: In their study of 22 patients who underwent gastroscopy, Marthey *et al*[17] found lesions in 13 (60%), the most common being gastritis (Figures 4 and 5) and erosive duodenitis.

Similar results were reported by Collins *et al*[15], who found that 63% of patients also presented upper gastrointestinal lesions. Erythematous gastritis was reported in most cases.

Biliary tract: The scientific literature also contains references to biliary involvement, more specifically in cases of extrahepatic cholangitis[19] and toxic hepatitis[20]. In such cases, endoscopy can be based on retrograde cholangiopancreatography or cholangioscopy. To our knowledge, no endoscopic images of the biliary tract obtained by cholangioscopy have been reported.

Small intestine: To our knowledge, there are no published capsule endoscopy-based

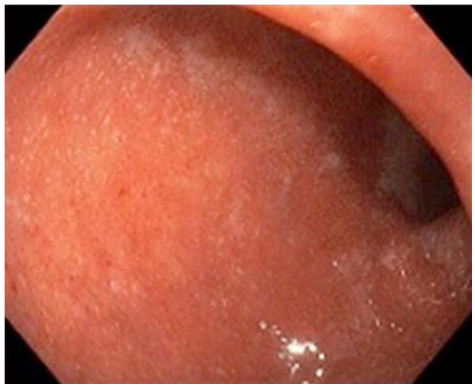

Figure 1 Mucosa at the rectosigmoid junction with mild erythematous spots and no erosions or ulcers.

data on involvement of the small intestine as a result of toxicity induced by immunological therapy.

Other aspects associated with endoscopy

Other lesions seen in endoscopy include exudates, granularity, and loss of vascular pattern. These findings are similar to those of IBD (ulcerative colitis and Crohn disease). Endoscopy findings from the first 2 wk of treatment with the drug and before the onset of symptoms have not been shown to predict the development of immune-mediated colitis. Endoscopy-confirmed involvement and the need for infliximab are not more common in patients receiving high-dose anti-CTLA-4 agents, thus suggesting that the severity of enterocolitis is not dose-dependent[21,22].

WHICH DIFFERENTIAL DIAGNOSIS SHOULD BE MADE?

Suspicion of toxicity due to immunotherapy should be based on the presenting complaints, of which diarrhea is the most common. Therefore, immune-mediated colitis should be taken into consideration in any patient receiving treatment with anti-CTLA-4 and/or anti-PD1 agents and who presents compatible symptoms. Other possible presenting complaints are abdominal pain, vomiting, hematochezia, weight loss, and/or fever. Onset of symptoms may be at any time during treatment and even several months after the last dose. The main conditions in the differential diagnosis are tumor progression, the infectious causes of diarrhea, and the development of IBD (Table 1). Therefore, imaging tests should also form part of the extension study for the primary tumor. Feces should also be tested for parasites and *Clostridium difficile*, and other tests, such as diagnostic colonoscopy, should be performed[21].

The main laboratory abnormalities in patients receiving immunotherapy are anemia, increased C-reactive protein, and low levels of serum albumin, all of which are nonspecific and play no role in the differential diagnosis. Therefore, endoscopy is the key to diagnosis. However, the result of a macroscopically normal endoscopy does not rule out the diagnosis, and biopsy specimens should be taken throughout the colon and assessed according to the segment they came from. Furthermore, infection by cytomegalovirus should also be ruled out by immunohistochemical staining of the biopsy specimens.

Histopathology findings are compatible with acute colitis, which is characterized by a marked inflammatory cellular infiltrate in the lamina propria consisting of neutrophils, lymphocytes, plasma cells, and eosinophils. Occasional findings include foci of neutrophilic cryptitis, crypt abscess, gland destruction, and erosions of the mucosal surface[23].

The histological characteristics of immune-mediated colitis are often nonspecific and may mimic those of other types of colitis. However, a variety of histologic characteristics that can act as useful pointers have been reported. Active colitis, together with major apoptosis of the epithelial cells in the crypt, has been recognized as the most useful characteristic. Other, less common associated patterns include lymphocytic and collagenous colitis. The correlation with the clinical history and, in particular, exposure to the drug plays an essential role in enabling the pathologist to differentiate immune-mediated colitis from infectious colitis, IBD, and drug-related colitis[24].

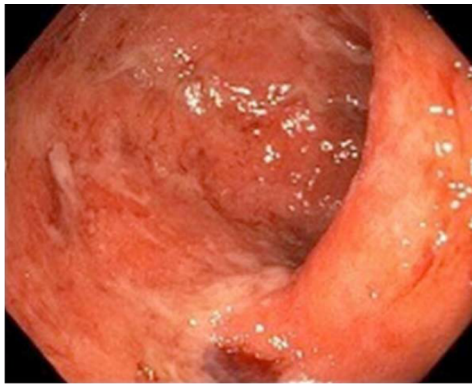

Figure 2 Mucosa at the rectosigmoid junction with erythema and fibrin-covered superficial erosions.

HOW SHOULD THE DISEASE BE TREATED?

Management of the patient with suspected immune-mediated enterocolitis should be multidisciplinary, involving oncologists, gastroenterologists, endoscopists, and the intensive care unit.

Treatment is mainly medical, and endoscopy is used only for diagnosis. Treatment of mild diarrhea (fewer than 3 watery stools per day) is based initially on oral antidiarrheal drugs together with fluid-electrolyte replacement. In moderate cases or absence of response, treatment should be started with oral corticosteroids (prednisone or equivalent at 0.5-1 mg/kg per day). In cases of severe diarrhea (more than 6 watery stools per day), treatment with anti-CTLA-4 and/or anti-PD1 agents should be suspended permanently, and intravenous corticosteroids should be started (methylprednisolone or equivalent 1-2 mg/kg per day). Patients who do not have a clinical response to intravenous corticosteroids after 3 d of treatment should start biologics (infliximab in a single dose of 5 mg/kg). The response to infliximab is generally fast, although some patients may require a second dose after 2 wk[21,25]. Marthey *et al*[17] reported that 37% of patients were treated successfully with corticosteroids. Biologic therapy was necessary owing to resistance to corticosteroids in 30% of cases (12 of 39 patients); infliximab was successful in 83% of cases (10 of 12 patients). Given the favorable response to infliximab, this therapy should be intensified rapidly in patients who do not respond to corticosteroids and whose clinical course is indolent. Treatment with corticosteroids during the first 5 d after onset of symptoms can enable more rapid resolution of symptoms than later initiation of treatment[26].

Perforation of the colon, while potentially fatal, is uncommon (< 1%). However, when surgery is necessary, colectomy should be subtotal and not segmental, since in most cases, enterocolitis induced by anti-CTLA-4 agents affects the whole colon[27-29].

CONCLUSION

Immune-mediated colitis is an emerging condition, given that the indications for immunotherapy, specifically anti-CTLA-4 and anti-PD1 agents, are expected to increase over time and for different types of tumor. Therefore, it is important to know the symptoms and determine the degree of involvement of immune-mediated colitis using endoscopy in order to initiate appropriate treatment early. The differential diagnosis should be based on infection, tumor progression, and IBD, with which the disease shares symptoms, endoscopy-confirmed lesions, and treatment.

The most common endoscopy-confirmed lesions of immune-mediated colitis are ulcers and erosions on edematous and erythematous mucosa. The most common location is the sigmoid colon, and a segmental pattern is slightly more common than a continuous pattern. Although histopathology is not specific in immune-mediated colitis, a biopsy must be taken to rule out other diseases and make a definitive diagnosis. Treatment includes systemic corticosteroids, although biologic therapy with infliximab may be necessary in some cases. Lastly, we believe that it is of the utmost importance to perform new studies that provide a detailed description of the adverse effects of regulatory proteins and of new, forthcoming agents in order to improve recognition and treatment of immune-mediate colitis in daily clinical practice.

Table 1 Differential diagnosis

Disease	Endoscopy findings	Clinical characteristics
IBD	UC: Continuous and circumferential mucosal inflammation starting in the rectum	Rectal bleeding, abdominal pain, diarrhea, chronic anemia
	CD: Deep fissures, cobblestoning, segmental distribution, relative rectal sparing, and terminal ileal involvement	
Radiation colitis	Similar to IBD	Rectal bleeding, chronic anemia
Infectious colitis	Diffuse effects on the colon	Dysentery-like diarrhea, different agents, *Clostridium difficile* and CMV to be ruled out
Colitis associated with diverticulosis	Segmental distribution, peridiverticular, sigmoid colon affected, rectum and proximal colon are normal	Rectal bleeding, abdominal pain, diarrhea
NSAID-induced colitis	Any part of the intestine, isolated lesions	Recurrent abdominal pain, obstruction, perforation, hemorrhage, chronic anemia
Microscopic colitis	Normal endoscopy findings	Watery diarrhea
Ischemic colitis	Segmentary colitis (sigmoid /left colitis)	Acute onset of abdominal pain and rectal bleeding

IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease; CMV: Cytomegalovirus; NSAID: Nonsteroidal anti-inflammatory drug.

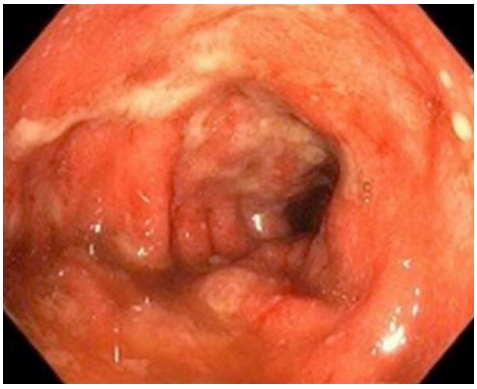

Figure 3 Mucosa in the descending colon with extensive erythema and deep fibrin-covered ulcers.

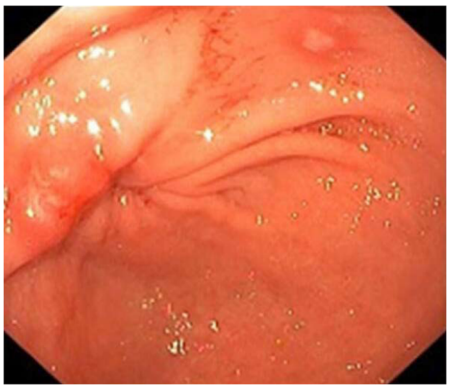

Figure 4 Erosion on the mucosa of the gastric antrum with generalized erythema.

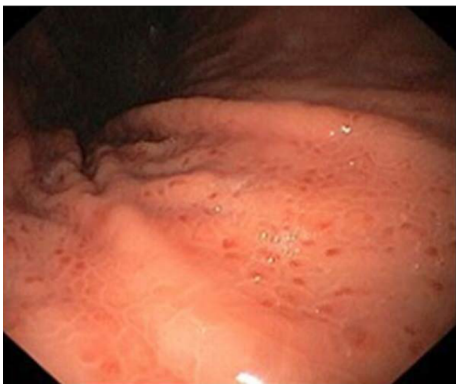

Figure 5 Petechiae on the mucosa of the gastric fold.

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META-ANALYSIS

Video capsule endoscopy *vs* double-balloon enteroscopy in the diagnosis of small bowel bleeding: A systematic review and meta-analysis

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Hélcio Pedrosa Brito, Igor Braga Ribeiro, Diogo Turiani Hourneaux de Moura, Wanderley Marques Bernardo, Dalton Marques Chaves, Rogério Kuga, Robson Kiyoshi Ishida, Eduardo Turiani Hourneaux de Moura, Eduardo Guimarães Hourneaux de Moura, Department of Endoscopy of Clinics Hospital of São Paulo University, São Paulo 05403-00, Brazil

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Abstract

AIM

To compare the diagnostic accuracy of video capsule endoscopy (VCE) and double-balloon enteroscopy (DBE) in cases of obscure gastrointestinal bleeding (OGIB) of vascular origin.

METHODS

MEDLINE (*via* PubMed), LILACS (*via* BVS) and Cochrane/CENTRAL virtual databases were searched for studies dated before 2017. We identified prospective and retrospective studies, including observational, cohort, single-blinded and multicenter studies, comparing VCE and DBE for the diagnosis of OGIB, and data of all the vascular sources of bleeding were collected. All patients were subjected to the same gold standard method. Relevant data were then extracted from each included study using a standardized extraction form. We calculated study variables (sensitivity, specificity, prevalence, positive and negative predictive values and accuracy) and performed a meta-analysis using Meta-Disc software.

RESULTS

In the per-patient analysis, 17 studies (1477 lesions) were included. We identified 3150 exams (1722 VCE and 1428 DBE) in 2043 patients and identified 2248 sources of bleeding, 1467 of which were from vascular lesions. Of these lesions, 864 (58.5%) were diagnosed by VCE, and 613 (41.5%) were diagnosed by DBE. The pretest probability for bleeding of vascular origin was 54.34%. The sensitivity of DBE was 84% (95%CI: 0.82-0.86; heterogeneity: 78.00%), and the specificity was 92% (95%CI: 0.89-0.94; heterogeneity: 92.0%). For DBE, the positive likelihood ratio was 11.29 (95%CI: 4.83-26.40; heterogeneity: 91.6%), and the negative

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likelihood ratio was 0.20 (95%CI: 0.15-0.27; heterogeneity: 67.3%). Performing DBE after CE increased the diagnostic yield of vascular lesion by 7%, from 83% to 90%.

CONCLUSION
The diagnostic accuracy of detecting small bowel bleeding from a vascular source is increased with the use of an isolated video capsule endoscope compared with isolated DBE. However, concomitant use increases the detection rate of the bleeding source.

Key words: Small bowel bleeding; Hemorrhage; Upper gastrointestinal bleeding; Obscure hemorrhage; Enteroscopy

Core tip: We performed a systematic review and meta-analysis comparing the diagnostic accuracy of video capsule endoscopy and double-balloon enteroscopy (DBE) in cases of obscure gastrointestinal bleeding of vascular origin. This is the first systematic review in this setting. We observed that the diagnostic accuracy of detecting small bowel bleeding from a vascular source is increased with the use of an isolated video capsule endoscope compared with isolated DBE. However, concomitant use increases the detection rate of the bleeding source.

Brito HP, Ribeiro IB, de Moura DTH, Bernardo WM, Chaves DM, Kuga R, Maahs ED, Ishida RK, de Moura ETH, de Moura EGH. Video capsule endoscopy *vs* double-balloon enteroscopy in the diagnosis of small bowel bleeding: A systematic review and meta-analysis. *World J Gastrointest Endosc* 2018; 10(12): 400-421
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INTRODUCTION

Approximately 5% of gastrointestinal bleeding occurs between the ligament of Treitz and the ileocecal valve[1-3] and can be classified as occult when there is no overt bleeding or overt bleeding with melena or hematochezia. Obscure gastrointestinal bleeding (OGIB) includes both definitions[1,2,4].

The most common sources of OGIB in older patients are small bowel angioectasias (30% to 40%), whereas tumors (17%) are more frequent in patients under 50 years old[5,6]. Other causes include Meckel's diverticula, radiation enteropathy, Dieulafoy's lesions, small-bowel varices, nonsteroidal anti-inflammatory drug enteropathy and inflammatory bowel disease[7-10].

Although prior evaluation of proximal and distal parts of small bowel with upper and lower endoscopy is recommended, it is occasionally not possible to identify the bleeding source with these methods. In these cases, newer endoscopic evaluation techniques are recommended, such as video capsule endoscope (VCE) and deep enteroscopy [which encompasses spiral, single, and double-balloon enteroscopy (DBE)].

The advent of VCE in 1998 enabled direct and painless visualization of small-bowel mucosa[4,11]. DBE, which has been on the market since 2003, allows for the endoscopic scrutiny of the entire small intestine, but it has the disadvantage of being an invasive procedure.

The diagnostic and therapeutic yield of these technologies has been compared with conventional approaches of push enteroscopy (PE), intraoperative enteroscopy and radiologic methods, revealing greater diagnostic yield[12]. Few studies comparing the diagnostic success of VCE and DBE are inconclusive in determining which of these two methods is superior. Thus, we decided to compare these methods in this review.

Although numerous meta-analyses have compared the efficacy of VCE and DBE in detecting an OGIB, this is the first systematic review and meta-analysis comparing OGIBs specifically in vascular origins. The objective of this study is to compare the diagnostic accuracy of VCE and DBE in cases of OGIB of vascular origin.

MATERIALS AND METHODS

Protocols and registration

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) recommendations and registered on PROSPERO international database (www.crd.york.ac.uk/prospero/) under number CRD42017078046.

Eligibility criteria

Types of studies: transversal studies from which it was possible to extract information necessary to calculate using only directly or indirectly supplied data. No abstracts or data from unpublished research were accepted. There were no restrictions in terms of language or date of publication.

Types of participants: patients with overt or occult OGIB from a vascular source. There were no restrictions regarding sex, age, risk factors, or anemia level in the study participants.

Types of interventions: VCE and DBE. Only studies that completed both exams, *i.e.*, VCE followed by DBE, were included regardless of where the procedure was performed, the type of colon cleaning, and the brand of the capsule or enteroscope.

Outcome measures: the main outcomes were sensitivity, specificity, pretest and posttest probabilities, positive and negative predictive values, and the accuracy of DBE.

Information sources

To identify articles, searches were conducted using MEDLINE (*via* PubMed), LILACS (*via* BVS) and Cochrane/CENTRAL virtual databases. Databases were searched from March 2017 to April 2018 with no restriction regard the idiom or the year of publication.

Search

The search used varied strategies depending on the database, and these strategies are specified below: (A) PubMed/MEDLINE: (angiodysplasias OR arteriovenous OR malformation OR hemorrhage OR gastrointestinal OR hemorrhages OR hematochezia OR angioectasia OR intestines OR small bowel bleeding OR intestine OR duodenum OR duodenal OR jejunum OR jejunal OR ileum OR ileal OR bleeding OR intestinal OR occult OR obscure phlebectasias) AND (double balloon OR enteroscopy OR enteroscopes OR enteroscopies OR double balloon endoscopy OR capsule endoscopy OR capsule endoscope OR full enteroscopy OR deep enteroscopy) AND (diagnosis/broad[filter]); and (B) LILACS and Cochrane/CENTRAL: enteroscopy AND capsule endoscopy AND obscure bleeding.

Study selection

Articles were initially selected after an assessment of the titles and abstracts to assess the relevance of the full text. Then, abstracts were read, and those that did not fit the inclusion criteria were excluded. Two independent reviewers performed eligibility assessment and study selection. Disagreements between reviewers were resolved by consensus.

Data collection process

The method of data extraction from each included study consisted of completing information sheets after the paper was read. Relevant data were then extracted from each included study using a standardized extraction form. One review author extracted data from the included studies, and a second author checked the extracted data. Disagreements were resolved by discussion between the two review authors.

Data items

The selected data included age, gender, total number of patients, study design, VCE and DBE models, intestinal preparation, interval time between VCE and DBE, number of patients with diagnoses of small-bowel bleeding using VCE and DBE and number of vascular lesions found. Only bleeding from vascular lesions was considered true positive diagnostically. We classified "vascular lesions" as angiodysplasias, varices, hemangiomas, red spots, and Dieulafoy lesions. Bleeding from tumor, ulcer, erosions, polyps and masses were not classified as vascular lesions but were considered bleeding from alternative sources.

Risk of bias in individual studies

To evaluate the risk of bias and the applicability of primary diagnostic accuracy studies, we used the QUADAS-2 tool (Table 1), which is structured in four domains.

The first domain is patient selection, which we described in terms of risk of bias. The second domain is a description of the index test, including analysis of how it was conducted and interpreted. The third domain is the reference standard, namely its description, conduction and interpretation. The fourth domain is flow and timing, where we recorded any patient who did not receive the index test(s) and/or reference standard, patients who were excluded from the analysis, and the time interval or any interventions that occurred between the index test(s) and the reference standard.

Summary measures

The sensitivity, specificity, pretest probability, positive and negative predictive values, and accuracy of DBE were the primary outcome measures and calculated using data provided from the original papers. Analysis was performed using capsule endoscopy as the gold standard for detection of small bowel lesions. We also created a summary receiver operating characteristic curve (sROC). All of these variables were subjected to per-lesion analyses. I-square was used to evaluate heterogeneity. Studies that remained under 50% of the sROC curve were removed.

Data were organized, and averages and standard deviations were calculated using Microsoft Excel Software 2013. Analysis was performed using the Meta-Disc 1.4 software.

RESULTS

In the per-patient analysis, 17 studies (1477 lesions) were included (Figure 1). In 3150 exams (1722 VCE and 1428 DBE) performed in 2043 patients, 2248 sources of bleeding were identified, of which 1467 were found to be vascular lesions and 781 were related to other sources, including tumor, ulcer, erosions, polyps and mass. Eight hundred and sixty-four (58.5%) lesions were diagnosed by VCE, and 613 (41.5%) by DBE. Of these, 605 (40.9%) were angiodysplasia; 5 (0.33%) were varices; 160 (10.8%) were described as blood and clots/bleeding, active bleeding or bleeding; 11 (0.74%) were red spots; 45 (3.04%) were described as arteriovenous malformation; 10 (0.67%) Dieulafoy lesions; 7 (0.47%) angiomas; and 74 (5.01%) were described generically as vascular lesions. Some patients were subjected to the same exam twice, and some of the sources of bleeding were identified by both exams.

The sensitivity of DBE was 84% [95% confidence interval (CI): 0.82-0.86; heterogeneity: 78.00%] (Figure 2), and the specificity was 92% (95%CI: 0.89-0.94; heterogeneity: 92.0%) (Figure 3). The positive likelihood ratio was 11.29 (95%CI: 4.83-26.40; heterogeneity: 91.6%) (Figure 4), and the negative likelihood ratio was 0.20 (95%CI: 0.15-0.27; heterogeneity: 67.3%) (Figure 5).

The posttest probability was 41.6% for DBE in the studied population and 85% for VCE. The area under the sROC curve was 0.9469 for DBE (Figure 6) and 0.9526 for VCE (Figure 7). The difference between the areas under independent ROC curves was 0.006, and the *P*-value was 0.41 (two-tailed).

Performing DBE after CE increased the diagnostic yield to vascular lesion by 7% from 83% to 90%

STUDY CHARACTERISTICS

Information extracted from each paper included characteristics of trial participants (including age, gender), study design, VCE and DBE models, intestinal preparation, interval time between VCE and DBE, number of patients with diagnoses of small-bowel bleeding using VCE and DBE, number of vascular lesions found, and the source of obscure gastrointestinal bleeding (Table 2).

All studies had similar characteristics; they studied the use of VCE and DBE in the diagnoses of OGIB sources, listing the sources separately. None of the studies classified vascular lesions according to the Yano[13] or Saurin[14] classification for vascular lesions of the small bowel.

A retrograde and/or anterograde route was decided based on VCE findings. Full enteroscopy using DBE was not always performed. The interval time was different in all studies based on institutional protocols. There were different definitions for vascular lesions. Every study reported a positive predictive value greater than 90%, except Fujimori[2] (33.33%) and Zhang[15] (53.31%).

Fujimori[2] exhibited high heterogeneity in poll specificity and sensitivity in addition to a poll accuracy under the medium media on SROC curve. Therefore, we excluded this paper.

Table 1 QUADAS-2. Risk of bias in individual studies

Study	Hadithi *et al*, 2006[4]	Hermans *et al*, 2017[11]	Hollerman *et al*, 2014[37]	Kaffes *et al*, 2007[34]	Kalra *et al*, 2015[16]	Kamalapor *et al*, 2008[30]	Kameda *et al*, 2008[27]	Li *et al*, 2010[35]	Lin *et al*, 2007[40]	Maeda *et al*, 2015[32]	Marmo *et al*, 2009[23]	TianMin, *et al*, 2013[39]	Nakamura *et al*, 2006[29]	Rahmi *et al*, 2013[33]	Chu *et al*, 2016[17]	Zhang, *et al*, 2015[15]
Was a consecutive or random sample of patients enrolled?	YES	UNCLEAR	UNCLEAR	YES	UNCLEAR	UNCLEAR	YES	YES	YES	YES	YES	YES	YES	YES	YES	UNCLEAR
Was a case-control design avoided?	YES	YES	NO	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Did the study avoid inappropriate exclusions?	YES	YES	YES	YES	UNCLEAR	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO
Could the selection of patients have introduced bias?	LOW	MODERATE	HIGHT	LOW	HIGH	HIGH	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	HIGH
Are there concerns that the included patients do not match the review question?	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	HIGH

Were the index test results interpreted without knowledge of the results of the reference standard?	YES	NO	YES	NO	YES	NO	YES	UNCLEAR	UNCLEAR	UNCLEAR	YES	NO	YES	NO	NO	UNCLEAR
If a threshold was used, was it prespecified?	YES LOW	YES MODERATE	YES LOW	YES MODERATE	NO MODERATE	YES MODERATE	YES LOW	YES MODERATE	NO MODERATE	YES MODERATE	YES LOW	NO HIGH	YES LOW	YES MODERATE	YES MODERATE	YES MODERATE
Could the conduct or interpretation of the index test have introduced bias?	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	HIGH
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	UNCLEAR
Is the reference standard likely to correctly classify the target condition?																

Were the reference standard results interpreted without knowledge of the results of the index test?	YES	NO	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	UNCLEAR
Could the reference standard, its conduct, or its interpretation have introduced bias?	LOW	MODERATE	LOW	MODERATE	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	HIGH	HIGH
Are there concerns that the target condition as defined by the reference standard does not match the review question?	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	HIGH	HIGH
Was there an appropriate interval between index test(s) and reference standard?	YES	NO	NO	NO	NO	NO	YES	YES	YES	YES	YES	YES	YES	NO	YES	UNCLEAR

Did all patients receive a reference standard?	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Did all patients receive the same reference standard?	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Were all patients included in the analysis?	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Could the patient flow have introduced bias?	MODERATE	LOW	LOW	LOW	LOW	MODERATE	LOW	LOW	LOW	LOW	LOW	LOW	LOW	MODERATE	LOW	LOW

Risk of bias within studies

Most studies (thirteen) had a low risk of bias. In 3 studies, DBE was performed after VCE, which could introduce bias in the route used (antegrade/retrograde). QUADAS-2 revealed that most studies did not exhibit bias. All studies followed the same pattern of inclusion: positive findings for VCE with posterior use of DBE performed in the same center.

Kalra[16] used Medtronic, Duluth, and the United States VCE, whereas Chu[17] used the OMOM capsule endoscopic device. All other studies were performed using the given imaging device.

Complementary analysis

Analyzing DBE as the standard procedure resulted in the following metrics for VCE: sensitivity of 93% (95%CI: 0.91-0.95; heterogeneity: 89.0%); specificity of 82% (95%CI: 0.79-0.84; heterogeneity: 87.3%); positive likelihood ratio of 5.44 (95%CI: 3.22-9.21; heterogeneity: 88.0%); negative likelihood ratio of 0.07 (95%CI: 0.03-0.18; heterogeneity: 91.3%) and accuracy of 86.75%.

DISCUSSION

VCE and DBE were developed as new examination techniques for the small intestine and have the potential to overcome conventional enteroscopy[11]. The small bowel is difficult to inspect with endoscopic methods. Prior to evaluation of the small bowel, it is recommended to repeat an upper digestive endoscopy and a colonoscopy[18]. Although intraoperative enteroscopy is the best for observing the entire small bowel, it is the most invasive procedure.

This is the first systematic review with meta-analysis to analyze the accuracy of DBE combined with VCE in diagnosing vascular lesions as a source of small bowel bleeding. The studies selected exhibited homogeneous intervention in a large number of patients. Eligibility criteria were strict, and selection and analysis were performed using international recognized protocols to avoid bias.

Saurin *et al*[14] divided the small bowel lesions into three distinct groups:

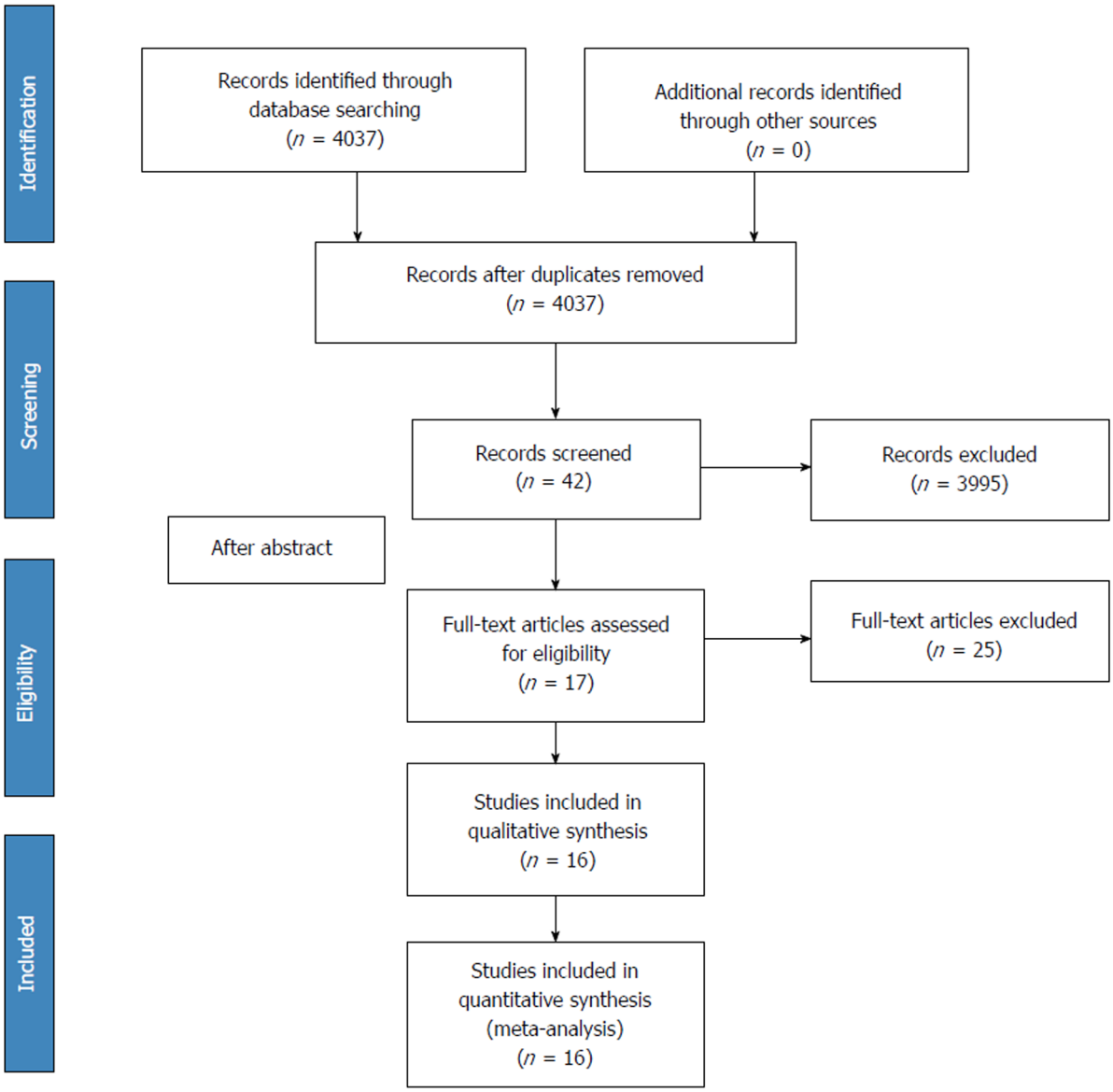

Figure 1 Flow diagrams - PRISMA[36].

submucosal veins, diverticula and nodules are included in the P0 lesions group; red spots and small or isolated erosions are considered P1 lesions; and angioectasias, varices, ulcerations and tumors represent P2 lesions. Yano *et al*[13] divided vascular small bowel lesions into 4 types depending on their characteristics and the presence or absence of bleeding. None of the studies in this meta-analysis divided the vascular lesions according to these classifications. Many sources of obscure bleeding were of vascular origin. When an endoscopic capsule or enteroscopy examination is performed and a source of bleeding is not identified, the cause is considered to be vascular by default. Thus, flash blood and clots/bleeding, active bleeding, and bleeding were considered as vascular sources in our study.

The benefits of VCE include the noninvasive nature of the test, patient acceptance, safety and diagnostic yield. However, it is limited by the inability to perform conventional endoscopic procedures, such as air insufflation, local reexamination, rinsing, biopsy, therapeutic intervention and precise identification of lesions. However, in DBE, a complete small bowel examination is typically not possible using only one route, so it often requires combined oral and rectal approaches. Diagnostic algorithms to identify gastrointestinal bleeding have suggested that VCE is best used initially to identify the lesion. DBE is best used for performing a therapeutic procedure after VCE. Thus, VCE was chosen as the gold standard in this review.

The diagnostic yield of VCE, DBE and single balloon enteroscopy (SBE) appears highest for patients with ongoing overt bleeding[19-21]. Comparing VCE and SBE, Shiani *et al*[19] reported a strong degree of concordance between VCE and SBE for active

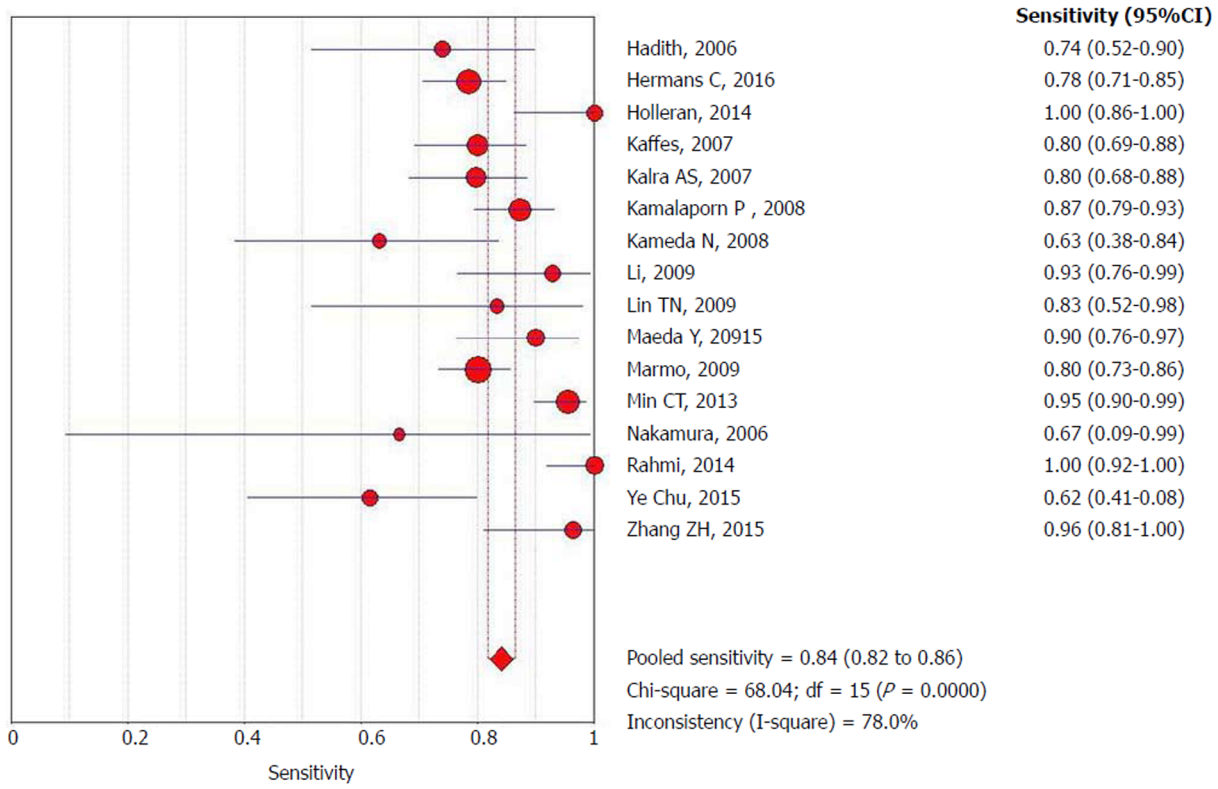

Figure 2 Forrest plot: Double-balloon enteroscopy sensitivity per-lesion analysis.

bleeding and clots but only moderate concordance for vascular lesions and fair concordance for ulcers. The diagnostic yield of VCE is increased if performed within 2 wk (greatest in 48 to 72 h). The timing of capsule endoscopy can influence the diagnosis and outcomes in patients with small bowel bleeding by identifying patients for early intervention, leading to endoscopic or surgical interventions or changes in medical management[22]. A study reported a high diagnostic and therapeutic yield (90%) with early (within 24 h) DBE in 10 patients with overt small bowel bleeding[23].

Regarding emergency ongoing overt OGIB, European Society of Gastrointestinal Endoscopy suggests that small bowel capsule endoscopy or device-assisted enteroscopy should be considered as a first-line approach[24]. Studies included in this meta-analysis did not differentiate the cause of bleeding as emergency or nonemergency. However, our results revealed increased accuracy of VCE to identify the vascular source of bleeding compared with DBE. This result demonstrates the ability of VCE to exclude lesions and to demonstrate the direction of the DBE. These results allow us to recommend the capsule as the first-line approach in these cases.

In the evaluation of OGIB, Martínez *et al*[25] demonstrated that the overall diagnostic yield of antegrade DBE is roughly equivalent to VCE; however, the diagnostic yield of DBE is increased when pre-DBE imaging is positive. A lesion source is frequently identified when pre-DBE imaging is negative or not performed. In a systematic review with 9 articles, Westerhof *et al*[26] reported that the diagnostic yields of CE and DBE for OGIB varied between 38% and 83% for CE and between 43% and 75% for DBE. The concordance between findings of CE with those of DBE varied between 29% and 92%, and the most frequent diagnosis was angiodysplasias. Our review reveals that DBE is reasonably sensitive and exhibits high specificity; however, it performs worse than VCE. Performing DBE after the CE increases the vascular lesion detection index by 7% from 83% to 90%.

This study is helpful for selecting the best initial diagnostic procedure in patients in whom vascular bleeding is suspected, such as cases of vascular syndromes, elderly patients and patients using anticoagulants. In many locations, these procedures are associated with high costs and are not always available at the same center. Although suggestions for the use of DBE as the first choice in obscure bleeding are reported, we have demonstrated that VCE would be the best and safest choice based on a 7% increase in diagnostic yield of DBE regardless of the severity of the case.

Variables that have been associated with an increased detection rate includes earlier VCE, inpatient status, overt GI bleeding with transfusion requirement, male sex, increasing age, use of warfarin and liver comorbidity[24]. Unfortunately, the articles

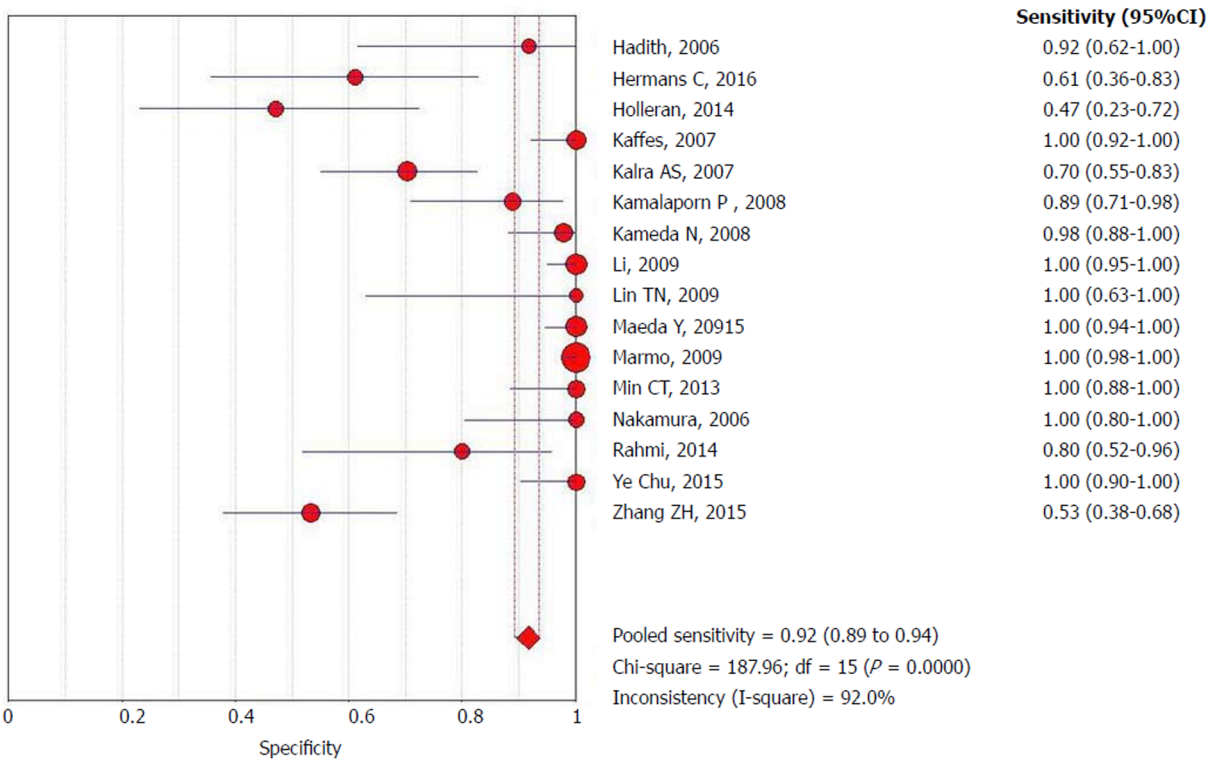

Figure 3 Forrest plot: Double-balloon enteroscopy specificity per-patient analysis.

did not stratify the findings according to these variables but according to the findings of the examinations, preventing very interesting data from being collected and analyzed.

A greater sensitivity of DBE in small bowel OGIB after using the VCE as the initial examination was observed. Considering the high sensibility of VCE in relation to DBE (93% × 84%), we suggest its use for suspicion of vascular lesions. Despite the low specificity noted when using VCE after DBE, its posttest result is double that of DBE (85% × 41.6%), prompting us to suggest using this feature after DBE with a negative finding. In this meta-analysis, we included studies in which VCE was performed before enteroscopy, and the route was chosen according to the possible location of the finding in the VCE. This procedure leads to an increased probability of finding the lesion with DBE. On the other hand, some enteroscopies were not completed because they only used one of the insertion pathways.

In one study[27] that attempted complete small bowel examination, all patients underwent both an antegrade and retrograde DBE procedure, whereas the DBE strategy varied in the other studies. In two studies, the antegrade or retrograde approach of DBE was chosen based on the VCE findings[2,28]. One study[29] chose the route of DBE based on the medical history. One study[4] chose the antegrade route of DBE in all cases followed by an alternate approach if considered necessary. In many studies, the decision to perform an additional DBE using the alternate route was made after considering several factors, including the results of the initial procedure, clinical indication, and patient consent. Two studies[29,30] had a single-blinded design.

The mean age of our study was 57.2 years. Angiectasias accounts for 20% to 30% of small bowel bleeding and are more commonly observed in older patients. In addition, bleeding in those who use nonsteroidal anti-inflammatory drugs and proper intestinal preparation facilitates lesion identification. The analyzed studies did not stratify the findings in the examinations regarding age, use of medications (nonsteroidal anti-inflammatory drugs), urgency/emergency indications, and bowel preparation, which prevents us from analyzing more data that would provide valuable information[31].

Although studies have assessed the diagnostic yield of VCE, PE, and device-assisted enteroscopy in OGIB, the precise significance of lesions identified and the impact on clinical outcome have not been consistently evaluated for those modalities. In the case of OGIB, a positive patient outcome should be either cessation of bleeding or resolution of anemia. Several studies have demonstrated a change in patient management and improved outcomes following VCE and device-assisted enteroscopy[32].

Of the included manuscripts, seven included patient follow-up. The mean duration

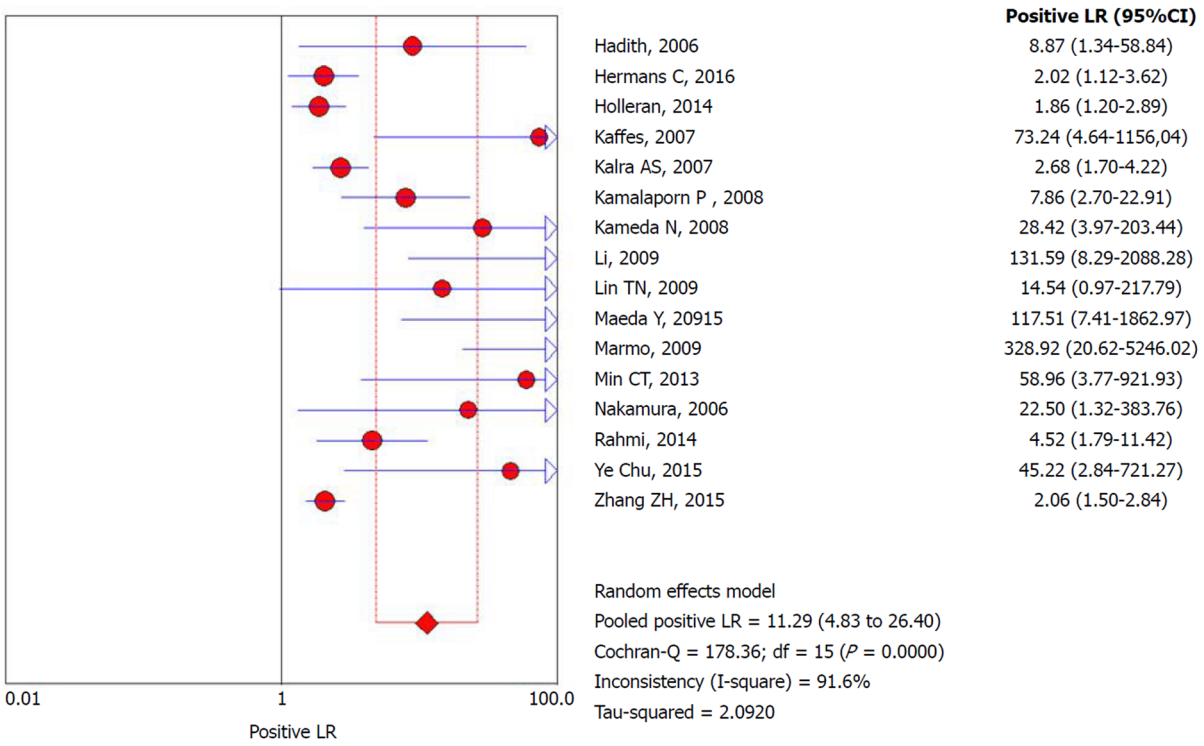

Figure 4 Forrest plot: Double-balloon enteroscopy positive likelihood ratio per-patient analysis.

of follow-up varied from 5 to 12 mo. Patients continued to exhibit bleeding in most of these studies, ranging from 65% to 81% including those whose findings were external of the small bowel[4,25,27,31,33-35].

Our study has some limitations, including nonstandardized follow-up of the patients after the exams, no standardized bowel preparation between the studies and no standard interval time between the exams. Additionally, performing DBE after a VCE exam facilitates the decision of the insertion route for enteroscopy (Figure 8). All of these limitations appear to favor DBE. The analyzed studies did not stratify the findings in the examinations regarding age, use of medications (nonsteroidal anti-inflammatory drugs), urgency/emergency of the indication, and the preparation, which prevents us from analyzing more data that would provide valuable information. These are data that would enrich the revision; however, they depend on the particularities of conduct of each author.

In conclusion, the diagnostic accuracy of detecting small bowel bleeding from a vascular source is greater with the use of an isolated VCE compared with isolated DBE. However, concomitant use increases the detection rate of the bleeding source.

Table 2 Studies characteristics

	Median age; range	Patient total	Study design	VCE Model	DBE Model	Preparation	Interval CE × DBE	No. of patients with diagnoses of SBB by CE/total CE performed	No. of patients with diagnoses of SBB by DBE/total DBE performed
Fujimoto *et al*[28], 2007	64 (38-93)	45 M: 25 F: 20	Prospective study	Pillcam (Given Imaging, Yoqneam, Israel).	EN-450P5 DBE diagnostic model and/or the EN-450T5	CE: 12 h fast + 1 L sodium sulfate/sodium bicarbonate DBE: 72 h after CE in 36 pct	72 h	18/45 Angiodysplasia: 6 Varices: 2 jejunal	18/36
Hadithi *et al*[4], 2006	63.2 (19-86)	35 M:22 F: 13	Prospective blinded study	Given M2A, Given Imaging Ltd., Yoqneam, Israel	Fuji Photo Optical Incorporated Company Fujinon Inc., Japan	CE: fast overnight after the ingestion of 1 L of sodium sulfate/sodium bicarbonate solution DBE: fast overnight after ingestion of 1 L clean prep. for the antegrade approach and bowel cleansing as for colonoscopy (4 L Klean prep)	7 to 14 d	21/35 AVM: 19 Fresh blood and clots: 5	28/35 AVM: 16 Fresh blood and clots: 2
Hermans *et al*[11], 2017	69 (18-91)	146 M: 91 F: 55	Retrospective observational study.	Olympus VC (Olympus EndoCapsule; Tokyo, Japan) and Pillcam VC (Covidien plc, Dublin, Ireland)	Fujinon Double-Balloon Enteroscopy System (Fujinon GMBH, Germany), EN-450T5	CE: 2 L PEG in a single or split dose DBE: 1 L PEG divided into two doses to be used twice	111 (1–1091) days	105/134 Angiodysplasias: 70 active bleedings without visible focus : 35	93/146 Angiodysplasias: 19
Holleran *et al*[37], 2013	54 (16-90)	246 M: 130 F: 116	Retrospective comparative study	SB1 or SB2 pillcam (Given imaging, Yokneam, Israel)	Fujinon double-balloon enteroscope (EN-450P5/20, Fujinon, Inc., Saitama, Japan)	CE: No preparation was required other than an overnight fast. Anterograde DBE: overnight fast Retrograde DBE: PEG the day prior	NR*	40/46 Angiodysplasia: 10 Active bleeding: 3	116/246 Angiodysplasias: 44
Kaffes *et al*[34], 2007	62 ± 18	60	Prospective cohort study	M2A; Given Imaging Ltd, Yoqneam, Israel)	Fujinon	CE, DBE: fasting period of 8 h before the oral procedure and a bowel preparation with a sodium (Picoprep; Pharmatel, Thornleigh, Australia)	NR*	45/60 Angiectasia:28 Red spots: 9 Blood: 8	45/60 Angioectasia: 21 Red spots: 9 Blood: 8

Kalra, A *et al*[16], 2015	66.6 ± 13.2	116 M:65 F: 51	Retrospective review	Medtronic, Duluth, GA, the United States	Fujifilm Medical System, Stanford, CT, the United States	Retrograde DBE: bowel preparation the night before the procedure.	1 yr	/69	29/69 AVM: 29
Kamalaporn *et al*[30], 2008	64.1 (34-83)	195 M: 26 F:25	Retrospective review	Given M2A CE system (Given Imaging Ltd, Israel)	Fujinon DBE system (Fuji Photo Optical Incorporated Company, Fujinon Inc., Japan)	CE: 2 to 4 L PEG and fasted overnight, at least 8 h before the procedure DBE: 4 L PEG and fasted overnight	139 (40 to 335) d	181/202 studies Angiodysplasia: 33 Bleeding: 22	56/56 Angiodysplasia: 36 Bleeding: 9
Kameda *et al*[27], 2008	62.4 (27-84)	32 M: 13 F: 19	Prospective single-blind trial	Pill Cam capsule (M2A, Given Imaging, Yoqneam, Israel)	DBE system (FujinonToshiba ES System, Saitama, Japan)	CE: fasting after midnight on the evening before the examination (minimum 8 h) DBE: overnight fasting and ingestion of 1 l of electrolyte lavage preparation (Niflec, Ajinomoto Pharma, Tokyo, Japan) in the morning.	1-7 d	29/32 Angiodysplasia: 8 bleeding: 6	21/32 Angiodysplasia: 7 bleeding: 6
Li *et al*[35], 2010		190	Prospective study	M2A, Given Imaging, Ltd. (Yoqneam, Israel)	Fujinon EN-450P5/ 20 and EN-450P5/28 (Fujinon Inc., Saitama, Japan)	CE: 1 L of PEG electrolyte 12 h before the procedure Anterograde DBE: fasted for 8 h. Retrograde DBE: PEG electrolytes preparation 4 h before the examination	5.8 d (1-18)	165/190 AVM: 7 Fresh blood or clots: 8	34/51 AVM: 9 Bleeding: 0 Angioma: 4
Lin *et al*[40], 2007	63.5 ± 22.7 (11-87)	10 M:3 F:7	Prospective study	Pill Cam SB capsule (Given Imaging, Yoqneam, Israel)	DBE: EN-450P5 and the EN-450T5	CE: fast overnight for 8-12 h Anterograde DBE: fasting for 6-8 h Retrograde DBE: bowel cleansing as in a colonoscopy.	7 d	9/10 Angiodysplasias: 3 Bleeding: 3	8/10 Angiodysplasias: 3 Varices: 1 Dieulafoy's lesion: 1
Maeda *et al*[32], 2010	70 (30-92)	89 M: 48 F: 41	Retrospective analysis	PilCam SB® (SB1, SB2, or SB3) (Covidien, Irvine, CA, the United States).	(EN-450 T5/W or EN-580 T, Fujinon Inc., Saitama, Japan)	NR*	24 h	58/89 Angioectasia: 8 AVM : 3 Dieulafoy lesion: 9 Varices: 2	29/37 Angioectasia: 8 AVM: 3 Dieulafoy lesion:6 Varice: 1
Marmo R *et al*[23], 2008	61.6 ± 16.2	193 M: 119 F: 74	Prospective study	Pillcam SB	Fujinon Double-Balloon Enteroscopy System	Anterograde DBE: fasting period of 8 h Retrograde DBE: 4 L PEG-based preparation	2 wk	175/193 Vascular lesions: 74 Blood or clot: 34	132/193 Vascular lesions: 72

Tian Min *et al*[39], 2013	55.4 (23-78)	62 M: 34 F:28	Prospective study	Pill Cam SB capsule	EN-450P5 and the EN-450T5 (Fujinon)	CE: 2 L to 4 L PEG and fasted overnight Anterograde DBE: fasting for 6-8 h before the procedure. Retrograde DBE: bowel cleansing as in a colonoscopy.	15 (4-60) d	44/62 Angiodysplasia: 26 Bleeding: 26	48/62 Angiodysplasia: 27 Bleeding: 30
Nakamura *et al*[29], 2006	58.5 (25 ± 85)	32 M: 21 F: 11	Prospective and blinded	M2A, Given Imaging,	Fuji EN−450 T5/20	CE: fluid diet for 12 h and observed a fasting period starting at midnight Anterograde DBE: fasted for 12 h Retrograde DBE: clear liquid diet on the day before the examination and PEG electrolyte lavage solution on the morning of the examination	48 h	19/32 Angiodysplasias: 4 Red spots: 2	12/28 Angiodysplasias: 2 Red spots: 2
Rahmi *et al*[33], 2013	67 ± 11	383 M: 114 F: 269	Prospective, multicenter study	PillCam SB device	EN-450P5 and EN-450T5; Fujinon	CE: residue-free diet 2 d before VCE ingestion; 2 L PEG solution the night before the examination; patients then fasted overnight Anterograde DBE: No bowel preparation Retrograde DBE: 4 L of a PEG solution was given the day before the procedure	4.1 ± 6.3 mo	266/383 Angiodysplasia: 266	205/266 Angiodysplasia: 190
Chu *et al*[17], 2016	51.1 ± 17.1	121 M: 60 F: 61	Study Cohorts	OMOM capsule endoscopic device (Jinshan Science and Technology Group Co., Ltd, Chongqing, China)	Fujinon EN-450P5/20	CE: 2 L polyethylene glycol-based electrolyte solution 12 h prior to the test, followed by an overnight fast for bowel preparation fast Retrograde DBE: bowel preparation used for CE procedure the day before the examination	1 wk	115/121 Angiodysplasia: 86% Active bleeding: 6	29/46 Angiodysplasia: 9

Zhang *et al*[15], 2015	47.19 (16-78)	88 M: 64 F: 24	Prospective study	Pill Cam SB	Fuji DBE system	CE: 3 liters of PEG (2 liters at 10:00 pm the night before the procedure, and 1 L with the simethicone at 4:00 am on the morning of the procedure) Anterograde DBE: fast for 6-8 h Retrograde DBE: 2 L of PEG	NR	53/88 MAV: 14 Hemangioma: 0 Diverticulum with a Bleeding: 1	52/88 MAV: 10 Hemangioma: 3 Diverticulum with a Bleeding: 7

M: Male; F: Female; SBB: Small bowel bleeding; PEG: Polyethylene glycol solution; AVM: Arteriovenous malformation; VC: Video capsule; NR: Not related; DBE: Double-balloon enteroscopy; VCE: Video capsule endoscope.

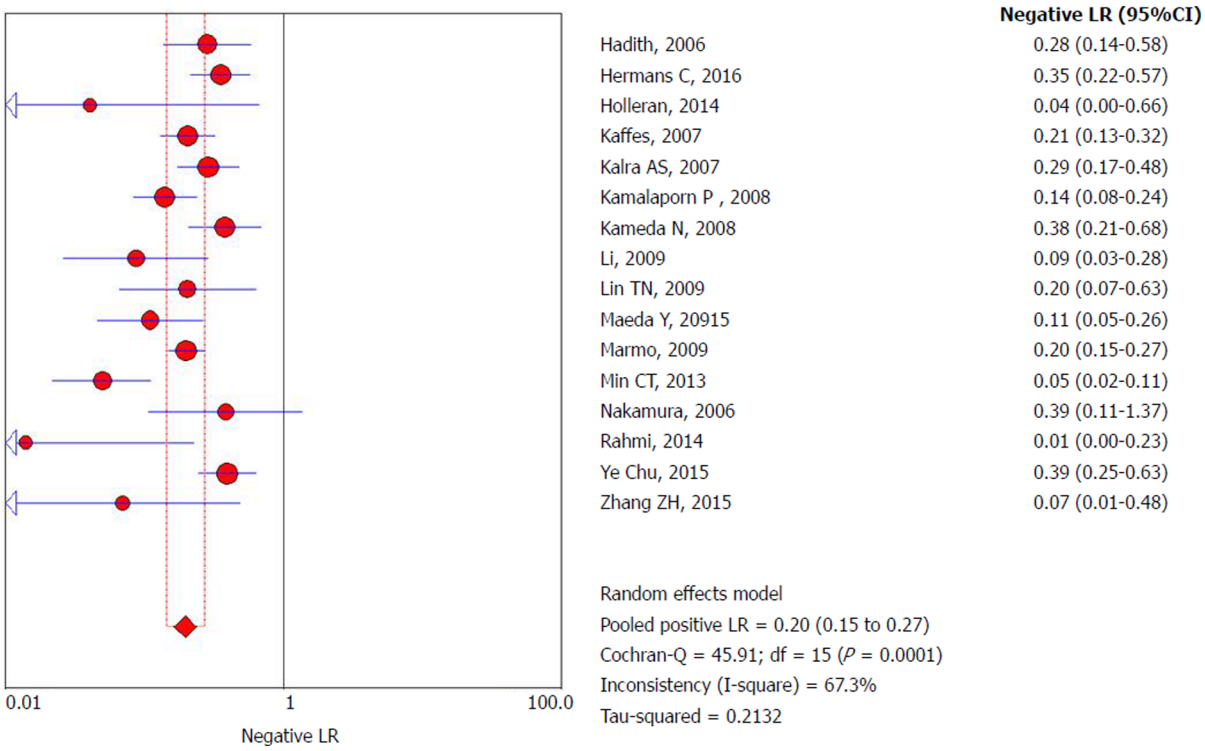

Figure 5 Forrest plot: Double-balloon enteroscopy negative likelihood ratio per-patient analysis.

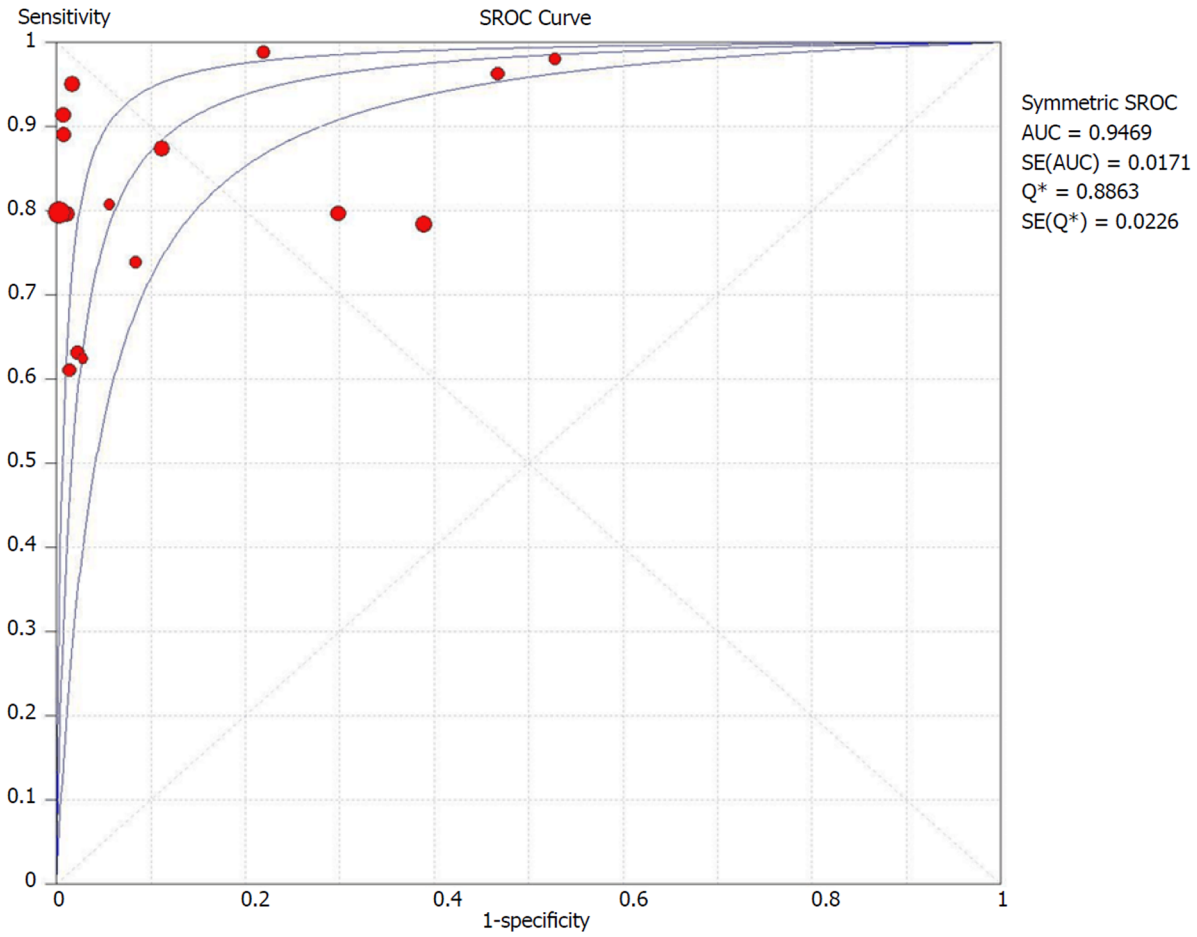

Figure 6 Summary receivers operating characteristic curve for double-balloon enteroscopy in per-patient analysis. sROC: Summary receiver operating characteristic.

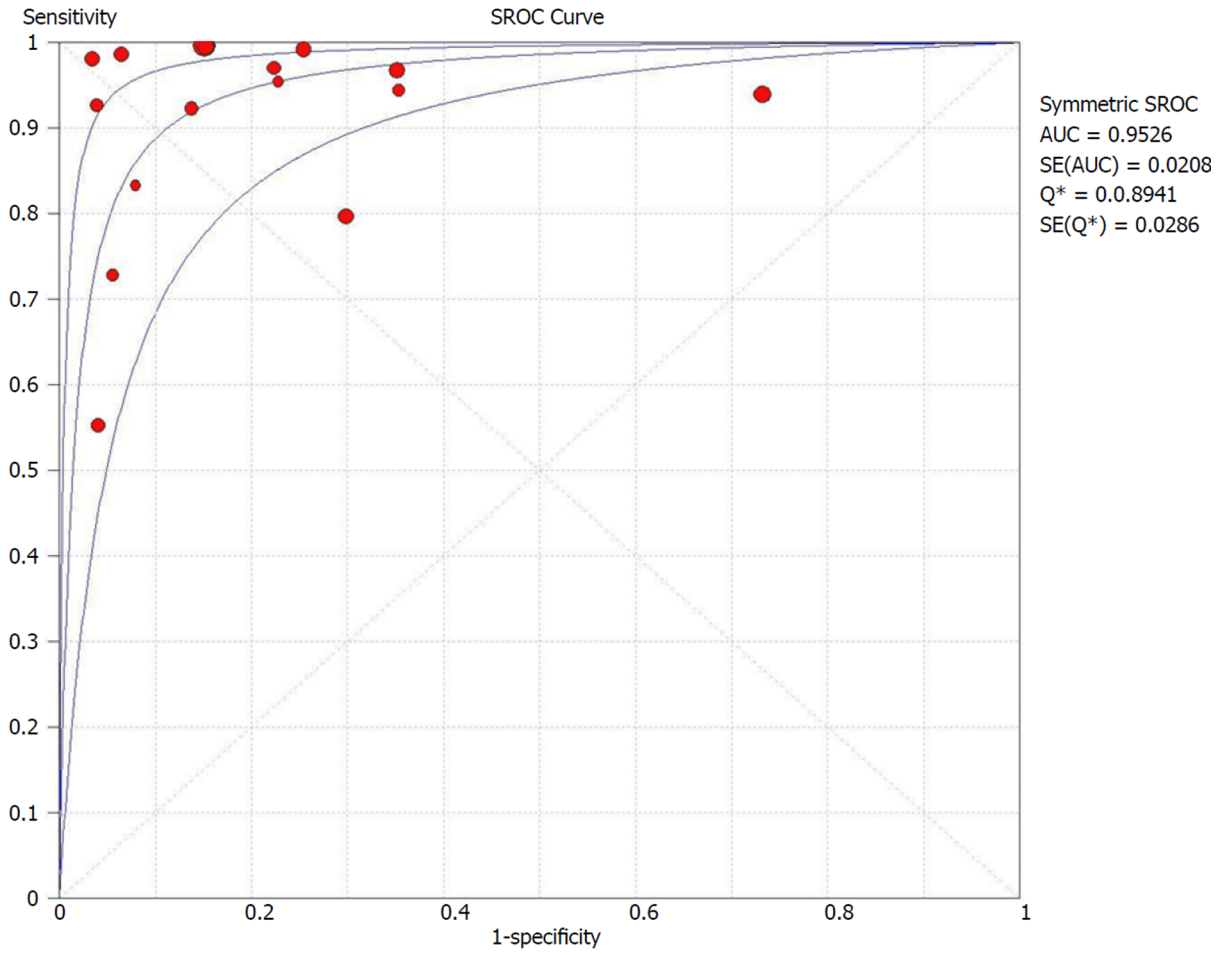

Figure 7 Summary receiver operating characteristic curve for video capsule endoscopy in per-patient analysis. sROC: Summary receiver operating characteristic.

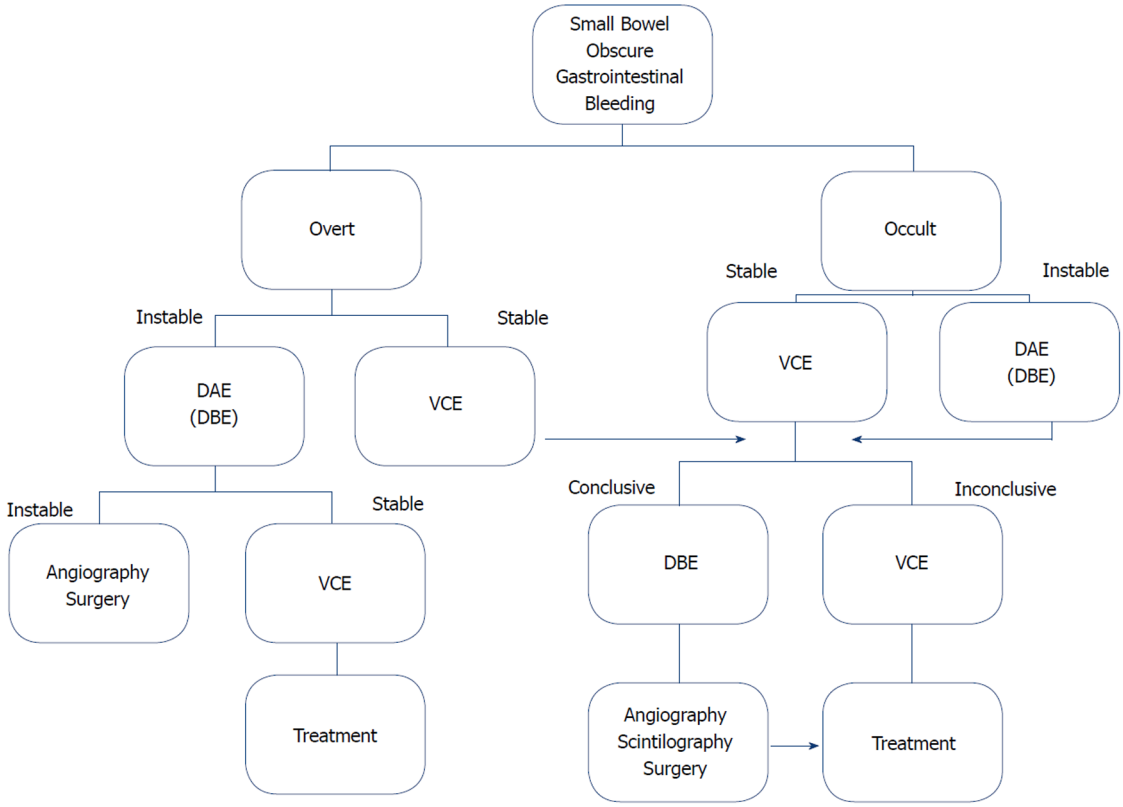

Figure 8 Suggested management approach to overt and occult small-bowel bleeding after upper endoscopy and colonoscopy did not identify vascular bleeding origin. Positive test results should direct specific therapy. When video capsule endoscopy is contraindicated or unavailable, device-assisted endoscopy may serve as the initial test for small-bowel evaluation. VCE: Video capsule endoscopy; DAE: Device-assisted endoscopy; DBE: Double-balloon enteroscopy.

ARTICLE HIGHLIGHTS

Research background

Obscure gastrointestinal bleeding (OGIB) is a challenge to the professional who faces this occurrence. Although only a small part of these bleeds occurs in the midgut, the difficulty in accessing it implies a longer interval between the onset of symptoms and diagnosis and therapy. Initially, we used enteroscopes with single balloon, including spiral and double balloon overtubes, which is the most commonly used. Subsequently, the endoscopic capsule was introduced, allowing a greater index of complete observation of the small intestine with greater comfort to the patient. A weakness includes the therapeutic impossibility present in balloon enteroscopy. Due to the particularities of each of the methods, we should seek data in the available scientific literature to support our most appropriate diagnostic decision.

Research motivation

Video capsule endoscopy (VCE) and double-balloon enteroscopy (DBE) are recognized endoscopic diagnostic approaches for OGIB, for which vascular origins represent the most common source. Our initial motivation was to determine whether there is a preferential diagnostic approach in OGIB by vascular origin that maintains high accuracy. From the literature review about the subject, we realized some characteristics that we interpreted as important limitations in the previous works. Thereafter, this study sought to remove these limitations and to follow a rigorous methodological approach in the selection and analysis to enhance knowledge about accuracy data.

Research objectives

We want to compare accuracy data between the two most widespread indicated endoscopic approach methods in OGIB: VCE and DBE. It was possible to obtain a large sample of patients submitted to both methods from the literature. We believe that future systematic reviews on this issue can be based on our selection and analysis methodology. In addition, new studies that will be published can be added to update and provide a greater dimension to the theme.

Research methods

This systematic review was conducted according to the PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and registered on PROSPERO international database. The search was performed in the electronic databases MedLine (*via* PubMed), LILACS

(*via* BVS) and Cochrane/CENTRAL virtual databases. The QUADAS-2 tool was used to evaluate the risk of bias and the applicability of primary diagnostic accuracy studies and the incorporation of recent studies on the OGIB approach. All articles were read and chosen based on common consensus among three authors, and restricted inclusion criteria provide greater magnitude and accuracy.

Research results

Seventeen studies were included with 3150 exams performed in 2043 patients, resulting in the identification of 1467 vascular lesions. The specificity found for DBE is greater than that of VCE (92% *vs* 82%) possibly because the examiner is able to examine in more detail the alterations found when performing DBE. In contrast, the sensitivity of the VCE is greater than that of the DBE (93% *vs* 84%) perhaps due to the natural increase in the capacity of the lens of the capsule and the fact that the insufflation of air in the small intestine during the examination with DBE greatly increases the pressure in the organ above the capillary pressure, which prevents the lesions from being observed in this exam. The increase in the diagnostic yield to the vascular lesion is greater when the DBE is performed after VCE.

Research conclusions

Through direct meta-analysis of the largest sample ever collected, we compared in isolation the diagnostic methods studied. The diagnostic accuracy of detecting small bowel bleeding from a vascular source is greater with VCE despite reduced specificity. This study sought to remove the bias from the lack of methodological rigor applied in the restrict inclusion criteria with the use of more than two authors for study selection and rigorous protocols accepted worldwide for the choice these studies, thus obtaining more purified results. This study also proposes that in addition to contributing to a greater specificity intrinsic to the examination, performing DBE after the use of VCE contributes to increased accuracy.

Research perspectives

The comparison between these two methods through meta-analyses always could be influenced by the technical differences applied in each study. A pertinent study design would include multicentric study with standardized protocols of care, including initial care, standard interval time between onset of symptoms and the first exam, standardized time between the exams, and standardized patient follow-up and bowel preparation.

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META-ANALYSIS

Sodium picosulphate or polyethylene glycol before elective colonoscopy in outpatients? A systematic review and meta-analysis

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Abstract

AIM

To determine the best option for bowel preparation [sodium picosulphate or polyethylene glycol (PEG)] for elective colonoscopy in adult outpatients.

METHODS

A systematic review of the literature following the PRISMA guidelines was performed using Medline, Scopus, EMBASE, Central, Cinahl and Lilacs. No restrictions were placed for country, year of publication or language. The last search in the literature was performed on November 20th, 2017. Only randomized clinical trials with full texts published were included. The subjects included were adult outpatients who underwent bowel cleansing for elective colonoscopy. The included studies compared sodium picosulphate with magnesium citrate (SPMC) and PEG for bowel preparation. Exclusion criteria were the inclusion of inpatients or groups with specific conditions, failure to mention patient status (outpatient or inpatient) or dietary restrictions, and permission to have unrestricted diet on the day prior to the exam. Primary outcomes were bowel cleaning success and/or tolerability of colon preparation. Secondary outcomes were adverse events, polyp and adenoma detection rates. Data on intention-to-treat were extracted by two independent authors and risk of bias assessed through the Jadad scale. Funnel plots, Egger's test, Higgins' test (I^2) and sensitivity analyses were used to assess reporting bias and heterogeneity. The meta-analysis was performed by computing risk difference (RD) using Mantel-Haenszel (MH) method with fixed-effects (FE) and random-effects (RE) models. Review Manager 5 (RevMan 5) version 6.1 (The Cochrane Collaboration) was the software chosen to perform the meta-analysis.

conception and design of the study, critical revision, final approval.

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RESULTS

662 records were identified but only 16 trials with 6200 subjects were included for the meta-analysis. High heterogeneity among studies was found and sensitivity analysis was needed and performed to interpret data. In the pooled analysis, SPMC was better for bowel cleaning [MH FE, RD 0.03, IC (0.01, 0.05), $P = 0.003$, $I^2 = 33\%$, NNT 34], for tolerability [MH RE, RD 0.08, IC (0.03, 0.13), $P = 0.002$, $I^2 = 88\%$, NNT 13] and for adverse events [MH RE, RD 0.13, IC (0.05, 0.22), $P = 0.002$, $I^2 = 88\%$, NNT 7]. There was no difference in regard to polyp and adenoma detection rates. Additional analyses were made by subgroups (type of regimen, volume of PEG solution and dietary recommendations). SPMC demonstrated better tolerability levels when compared to PEG in the following subgroups: "day-before preparation" [MH FE, RD 0.17, IC (0.13, 0.21), $P < 0.0001$, $I^2 = 0\%$, NNT 6], "preparation in accordance with time interval for colonoscopy" [MH RE, RD 0.08, IC (0.01, 0.15), $P = 0.02$, $I^2 = 54\%$, NNT 13], when compared to "high-volume PEG solutions" [MH RE, RD 0.08, IC (0.01, 0.14), $I^2 = 89\%$, $P = 0.02$, NNT 13] and in the subgroup "liquid diet on day before" [MH RE, RD 0.14, IC (0.06,0.22), $P = 0.0006$, $I^2 = 81\%$, NNT 8]. SPMC was also found to cause fewer adverse events than PEG in the "high-volume PEG solutions" [MH RE, RD -0.18, IC (-0.30, -0.07), $P = 0.002$, $I^2 = 79\%$, NNT 6] and PEG in the "low-residue diet" subgroup [MH RE, RD -0.17, IC (-0.27, 0.07), $P = 0.0008$, $I^2 = 86\%$, NNT 6].

CONCLUSION

SPMC seems to be better than PEG for bowel preparation, with a similar bowel cleaning success rate, better tolerability and lower prevalence of adverse events.

Key words: Sodium picosulphate; Polyethylene glycol; Bowel cleaning success; Tolerability; Colonoscopy; Randomized clinical trials; Meta-analysis

Core tip: Previous meta-analyses did not consider patient status (if inpatient or outpatient) for inclusion in the studies and grouped different types of patients. They also failed to conduct analyses by subgroups (regimen schedule, volume of polyethylene glycol solution, dietary restriction) in order to elucidate confounding factors. This is the first systematic review and meta-analysis for this specific group of patients and the first to communicate effectiveness by NNT.

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INTRODUCTION

Colonoscopy is the gold-standard method for polyp and adenoma detection and can reduce both incidence and mortality for colorectal cancer[1,2]. Different devices and tools were created to improve mucosal exposure and the detection of neoplastic lesions[3] and carbon dioxide insufflation used to increase tolerance to colonoscopy[4]. Even so, bowel cleaning is still the cornerstone for optimizing colonoscopy.

Cleaning efficacy is the most important characteristic of bowel cleansers as the quality of cleaning directly impacts on evaluation, difficulty, speed, and completeness of colonoscopy[5,6]. As inadequate bowel preparation results in missing pre-cancerous lesions and increases the costs related to repetition of colonoscopy, the choice of the product should aim to achieve high-quality bowel preparation and optimize the evaluation[7,8].

Polyethylene glycol (PEG)-based solutions are the most widely used and studied bowel cleansers. PEG is an isosmotic laxative which achieves high-quality bowel preparations through the ingestion of large volumes of the solution (approximately four liters). Their poor palatability and the volume to be ingested increase the

incidence of adverse events and decrease full intake of the medication[9-11].

Among purgatives that have been recently developed to overcome these limitations is sodium picosulphate with magnesium citrate (PICO or SPMC), a low-volume dual laxative which may cause less gastrointestinal symptoms. It promotes colon cleansing by retaining fluids in the colon and by increasing the frequency and the force of peristalsis; however, due to electrolyte exchanges it can cause dehydration and biochemical impairments[12,13].

PEG solutions trials date from 1982 and have contributed to their consolidation as the most widely used solutions[14]. Although sodium picosulphate has been used for several years in the United Kingdom and Australia, large randomized clinical trials evaluating its efficacy are recent and usually compare it to PEG solution[13,15]. Other solutions that have already been compared to SPMC are oral sulfate solution and mannitol[16,17].

The highest level of evidence for medical practice is found in meta-analyses of randomized clinical trials. Among meta-analyses that compared PEG and sodium picosulphate for bowel preparation before colonoscopy[18-20], the largest one (Jin *et al*[20]) included 21 studies and showed no difference in bowel cleaning efficacy between them. Unfortunately, inclusion criteria for population did not specify patient status (their condition of inpatient or outpatient), which impaired the quality of the results obtained to be applied in medical practice as inpatient status is an independent risk factor for inadequate bowel preparation[11,21].

As most colonoscopies are performed in outpatients and there is no established evidence comparing sodium picosulphate and PEG cleaning efficacy and tolerability in this subset of patients, we therefore conducted this meta-analysis. Regimens adopted for bowel preparation were also considered for analysis since there are studies demonstrating differences in cleaning efficacy depending on the kind of the regimen adopted[22].

MATERIALS AND METHODS

Protocol and registration

Strategies for the search, selection and analysis were pre-specified as stated in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and documented in a protocol registered in International Prospective Register of Systematic Reviews (PROSPERO) database (CRD 42016050059)[23].

Eligibility criteria

Eligibility criteria were based on PICOS (population, intervention, comparison, outcomes and study design) strategy. Only randomized clinical trials with full texts published were included irrespective of language or time of publication. The subjects included were adult outpatients who underwent bowel cleaning for elective colonoscopy. The included studies compared sodium picosulphate/magnesium citrate and PEG. Exclusion criteria were inpatient status, groups with specific comorbidities, combination of different products for the preparation of the solution, association with enema or enteroclysis and the absence of dietary restrictions on the day prior to the exam. Primary outcomes evaluated were efficacy and tolerability. Secondary outcomes were prevalence of adverse events, and polyp and adenoma detection rates.

Search strategy and study selection

Two independent authors identified records in the following electronic databases: Medline, Scopus, EMBASE, Central, Cinahl and Lilacs. No limits were applied for country, year of publication or language. The last search in the literature was performed on November 20th, 2017. Search keywords were "colonoscopy", "colonosc*", "sodium picosulphate", "sodium picosulfate", "polyethylene glycol", "polyethylene glycols" and "random*". Full search strategy for each database is shown in Supplementary material (Appendix 1). Medline was the main database for the development of the search strategy, as follows: "(colonoscopy OR colonoscopies OR bowel preparation OR bowel prep* OR bowel cleansing OR bowel clean* OR colon preparation OR colon prep* OR colon cleansing OR colon clean' AND (sodium picosuffate OR sodium picosulphate OR picosulfate OR picosulphate) AND (polyethylene OR polyethylene glycol OR polyethylene glycols OR polyethylene glicol OR polyethylene glicols)".

Two independent authors performed eligibility assessment and studies selection. Duplicated references were excluded and the remaining ones were screened by title and abstract. Those that met any of the exclusion criteria were disregarded. The full

texts of the remaining records were assessed and the studies that met the eligibility criteria were included for the meta-analysis. The gray literature search was made in the references of the included studies and a third author solved disagreements between the other two.

Data collection process

Data available in texts, charts or tables were extracted by two independent authors using a previously devised form. Data presented in percentage were converted into frequency and rounded up if the number obtained was not an integer.

Data items: The following data were collected for each trial: (1) characteristics of participants; (2) type of intervention; (3) outcomes; and (4) type of outcome measurement (including definition, score adopted, bowel cleansing success, tolerability, adverse events prevalence, polyp and adenoma detection rate).

The following definitions standardizations were previously established for outcomes: (1) bowel cleaning success, defined as the number of patients with successful cleaning by either the study or by the assessment score as "excellent, adequate, good or clean"; (2) tolerability, defined as the number of patients who ingested the entire bowel cleaning preparation or the minimum established by the study as acceptable; (3) adverse events prevalence, defined as the number of patients affected by at least one adverse event; (4) polyp detection rate (PDR), defined as the number of patients with at least one polyp detected during colonoscopy; (5) adenoma detection rate (ADR), defined as the number of patients with at least one adenoma detected during colonoscopy.

Risk of bias in individual studies

As treatment effect size may differ due to selection, performance, detection and attrition bias, the methodological evaluation of the studies was performed. Two authors working independently determined the adequacy of randomization, adequacy of blinding, and the description of withdrawals and dropouts using the Jadad scale[24] for the evaluation of the randomized clinical trials.

Summary measures

Meta-analysis was preferably performed using intention-to-treat (ITT) data. Per-protocol (PP) data were only used when ITT data were not available. Outcomes evaluated were dichotomous (bowel cleansing success, tolerability, adverse events prevalence, polyp and adenoma detection rate). Risk difference (RD) with 95% confidence intervals (CI) was calculated for each outcome.

Synthesis of results

Meta-analyses were performed by computing RD for dichotomous outcomes using Mantel-Haenszel method (MH) with fixed-effects (FE) and random-effects (RE) models. Heterogeneity was assessed by Cochran's Q test (*P* value), which examines the null hypothesis that all studies are evaluating the same effect, and by Higgins' test (I^2), which quantifies inconsistency across studies and describes the percentage of the variability in effect estimates that is due to heterogeneity[25]. FE model was used in the presence of null or low heterogeneity ($I^2 < 50\%$) assuming the true effect size did not differ across studies. However, an I^2 value equal to or greater than 50% was considered substantial heterogeneity and RE model was preferred to FE as true effect size varied from one study to another and a more conservative approach for statistical significance was needed. The number needed to treat (NNT) for each outcome with statistical difference was also calculated. Review Manager 5 (RevMan 5) Version 6.1 (by the Cochrane Collaboration, 2015) was the software chosen to run the meta-analysis.

Risk of bias across studies

Reporting bias across studies was evaluated by a graphic diagnostic tool named funnel plot. For each trial, the treatment effect was plotted against the measure of study precision (represented by the inverse of its standard error) and the symmetry of scatter plot assessed by Egger's test[26]. Asymmetrical funnel plot suggests the presence of reporting bias (absence of low-precision studies that have negative or non-significant results), methodological bias or true heterogeneity between smaller and larger studies.

Additional analysis

In the presence of an asymmetrical funnel plot or high heterogeneity, ($I^2 \geq 50\%$) a sensitivity analysis was conducted to explore how the results of the meta-analysis change under different assumptions[27]. Heterogeneity and funnel plot before and after the removal of each study from the meta-analysis was assessed to identify the study

accounting for the inconsistency among trials (usually due to a markedly different intervention effect or an undue influence on the summary results). If heterogeneity was reduced to below 50% after the removal of the outlier, the corrected intervention effect estimate was applied and the interpretation of results made with caution. If inconsistency did not decrease, it was considered true heterogeneity.

Subgroup analyses were performed for variables that could knowingly influence the effect sizes: (1) types of regimen [(A) full intake on the day prior the exam; (B) intake split into the day prior and the same day of the exam; and (C) intake only on the same day of the exam); (2) volume of PEG-based solution [(A) low-volume group - 2L or less; and (B) high-volume group - more than 2L]; (3) dietary restrictions on day before [(A) low fiber or low residue diet; and (B) liquid diet].

RESULTS

Search and study selection

A total of 662 records were identified through a search in the databases (57 in MEDLINE, 128 in EMBASE, 384 in Scopus, 85 in CENTRAL, 8 in CINAHL and none in LILACS) (Figure 1). After adjusting for duplicates, 457 records remained and were evaluated by title and abstract. 390 records were excluded because they met one or more exclusion criteria. Of the 67 remaining, 28 were then excluded (2 were short communications and 26 were congress abstracts). The full texts of the remaining 39 records were examined and 23 were rejected. Reasons are presented in Supplementary material (Appendix 2). At the end, 16 studies were included in the meta-analysis[9,11,23-36].

Studies characteristics

All 16 studies selected were RCTs, with full text available, published in English between 1996 and 2017. Included studies involved 6200 participants, from 18 to 86 years of age. Main patient exclusion criteria were age, renal insufficiency, congestive heart failure, recent myocardial infarction, constipation, gastrointestinal or colon disorders, and previous colorectal surgery (Table 1).

Thirteen of 16 studies were multicenter. Six studies were conducted in South Korea, two in the United States and eight in different countries. Brand names of sodium picosulphate based products were CitraFleet®, Pico®, Pico-Salax®, Picolax®, Picoprep®, Picolight powder® and Prepopik®, while polyethylene glycol-based products were Colyte®, ColonLytely®, Coolprep powder®, Endofalk®, Half-Lytely®, Kleanprep®, Moviprep®, New Meroken® and Fortrans™.

Seven studies compared split dose regimens[28-30,32,33,38,40] and 4 studies compared day-before dose[13,33,34,41]. None of the included studies compared same-day dose. Four studies compared different regimens of bowel cleaning between the two products[15,31,39,40] and three others[35-37] according to the interval time to colonoscopy.

Two different adjuvants were used in 5 studies. Four studies[13,15,36,41] used Bisacodyl with PEG and 2 studies used it with SPMC[29,41]. Magnesium citrate was also used separated from sodium picosulphate in one study[36].

Dietary restrictions on the day prior to the procedure were considered in all studies. In four studies, patients were given liquid diet[13,15,34,36] and in twelve studies a low-fiber or low-residue diet[23-26,28,30,32-36] was allowed.

Outcomes

Sixteen studies evaluated bowel cleaning success. Efficacy was measured by five different bowel preparation scales: a 4-point scale[42], Boston bowel preparation scale[29,30,32,37,38], Aronchick scale[13,15,32,33,40,41], Harefield scale[32] and Ottawa bowel preparation scale[15,35,36,39,40]. Tolerability was evaluated in 12 studies[9,11,23,24,28-30,32-36], adverse events prevalence in 13 studies[13,15,28,29,31,34,37-39,41], PDR in seven[28,31,37-41] and ADR in five studies[31,32,38,39,41].

Risk of bias within studies

The maximum Jadad score obtained was three, since patient blinding was not possible due to the different characteristics of cleaning protocols (Table 2). Eleven studies scored three points[9,11,26-28,30-34,36], four studies scored two points[28-30,34] and one study scored just one point[40]. All of them were randomized, but Kim *et al*[40] did not describe the randomization method and Regev *et al*[34] randomized patients inappropriately. Kim *et al*[40], Leitao *et al*[28], Kim *et al*[29] and Munsterman *et al*[30] also failed to describe losses.

Results of individual studies

Raw data of included studies are presented in Supplementary material (appendix 3).

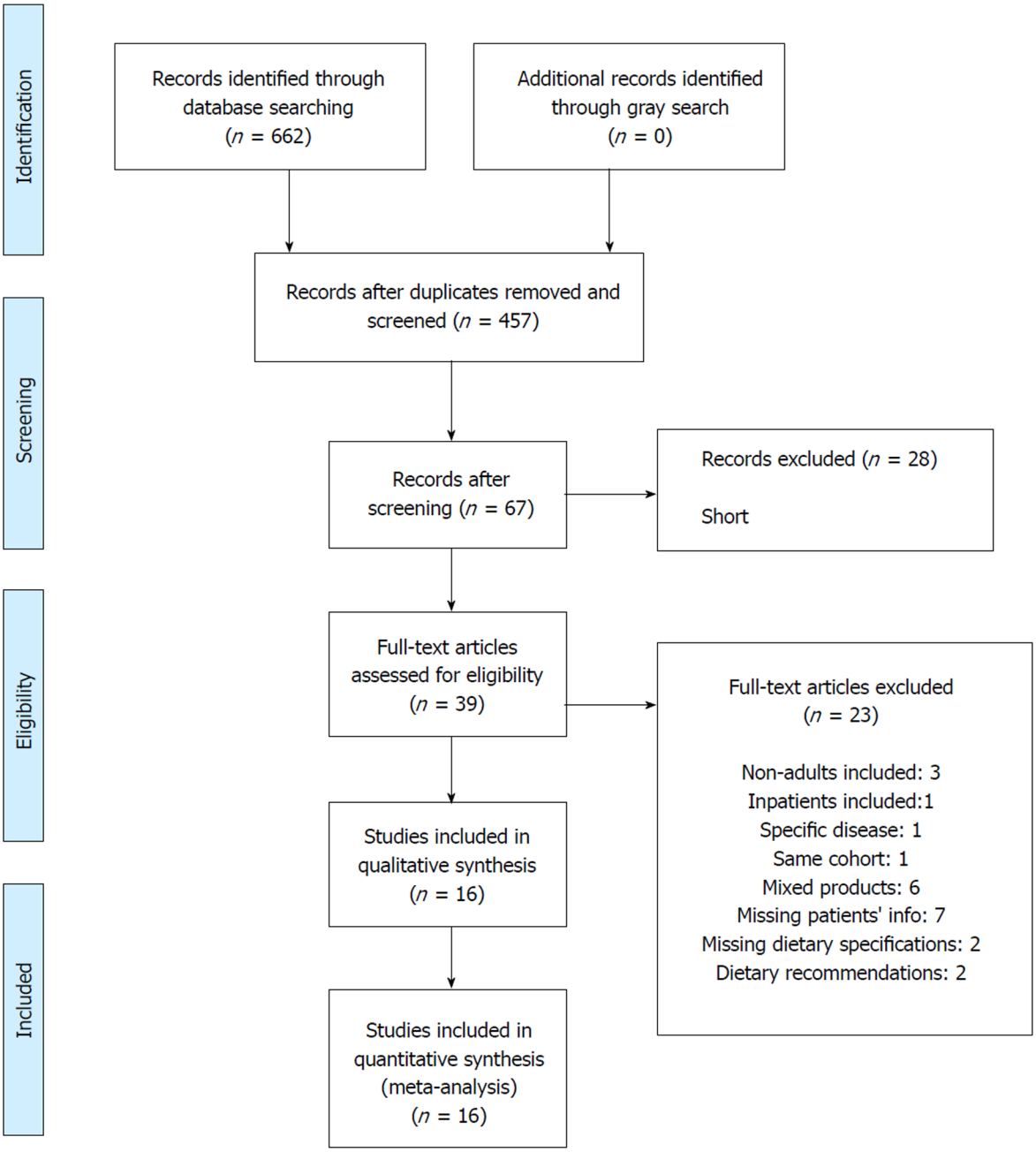

Figure 1 Flow diagram of included studies.

One study (Kim *et al*[40]) presented four different treatment arms, two of which were SPMC arms (with 2 or 3 sachets in split dose regimen) and two others of PEG arms (4 L of solution in a split or in a same-day dose regimen). For the analysis, the study was dismembered into two based on treatment regimens (Kim *et al*[40], SPMC split dose arms *vs* PEG split dose; and Kim *et al*[40], SPMC split dose *vs* PEG same-day dose).

Another study (Kojecky *et al*[33]) presented three different treatment arms (PEG, PEG plus ascorbic acid and SPMC) with two subgroups each (day-before dose and split dose). PEG and PEG-A treatment arms were grouped and the study dismembered into two according to the regimen (Kojecky *et al*[33], day-before dose; and Kojecky *et al*[33], split dose).

Bowel cleansing success: Twelve studies (corresponding to fourteen comparisons) demonstrated that sodium picosulphate and PEG had the same efficacy in bowel cleaning[13,29,33-40], two studies demonstrated that sodium picosulphate was better[15,41] and one study demonstrated that PEG was better[31].

Tolerability: Three studies (four comparisons) demonstrated that both obtained the same tolerability level[37,39,40], seven demonstrated that SPMC was better

Table 1 Studies characteristics

STUDY	SITE	POPULATION	INTERVENTION (ITT/PP)	COMPARISON (ITT/PP)	OUTCOMES
Regev *et al*[34]	1	29 to 86 y	Pico-Salax (1+1+1)/0 sachets	New-Meroken® 3/0 L	Bowel cleansing quality
	Israel		+ (200/h for 16h)/0 mL of water		Cecal intubation
		ITT: 68	+ clear liquid diet	+ clear liquid diet	General discomfort
		PP: 68	39/39	29/29	Medication Intake
					Adverse events
Lawrance *et al*[35]	1	18 to 75 y	Pico® (1+1)/0 sachets for morning procedure or	ColonLytely® 4/0 L for morning procedure or	Bowel cleansing quality
	Australia		Pico 1/1 sachets for afternoon procedure	ColonLytely® 4/0 L for afternoon procedure	
			+ liquid	+ clear liquid 2/0	
		ITT: 634	+ low residue diet	284/279	Medication Intake
		PP: 625	171/169		
			CB fleet® (45+45)/0 mL		
			+ (750+750)/0 mL of water for morning procedure or		Mucosal inflammation
			CB fleet® 45/45 mL		
			+ 750/750 mL of water for afternoon procedure		
			+ low residue diet		
			179/177		
Kao *et al*[36]	1	18 to 75 y	SPMC (1+1+MC)/0 sachets for morning procedure or	PEG 4/0 L for morning procedure or	Bowel cleansing quality
	Canada		SPMC (1+1)/MC sachets for afternoon procedure	PEG 2/2 L for afternoon procedure	Bowel cleansing quality according to the procedure time
		ITT: 834	+ liquid	+ liquid	Tolerability
		PP: 790	+ clear liquid diet	+ clear liquid diet	
			194/194	218/210	Adherence
			NaP 45/45/0 mL for morning procedure or	PEG 2/0 L + bisacodyl 20/0 mg for morning procedure or	Sleeping hours
			NaP 0/45/45 mL for afternoon procedure	PEG 0/2 L + bisacodyl 20/0 mg for afternoon procedure	Willingness to reuse
			+ liquid	+ liquid	Safety
			+ clear liquid diet	+ clear liquid diet	
			164/164	214/210	Ischemic colitis
Katz *et al*[15]	12	18 to 80 y	Prepopik® (1+1)/0 sachets	Half-Lytely e bisacodyl Tablets® 2/0 L	Bowel cleansing quality
	USA		+ (1200+720)/0 mL of liquid	+ 10/0 mg bisacodyl	Acceptability
					Tolerability
		ITT: 603	+ clear liquid diet	+ clear liquid diet	Medication Intake
		PP: 598			Ease to use medication
			300/296	303/302	General experience
					Taste
					Willingness to reuse
					Adverse events
Manes *et al*[37]	3	18 to 85 y	CitraFleet® (1+1)/0 sachets	Moviprep® 2/0 L	Bowel cleansing quality
	Italy		+ 3/0 L of liquid for morning procedure or	+ 1/0 L of liquid for morning procedure or	Bowel cleansing quality of right colon
		ITT: 293	CitraFleet® 1/1 sachets	Moviprep® 1/1 L	Polyps detected

		PP: 285	+ 1.5/1.5 L of liquid for afternoon procedure	+ 500/500 mL of liquid for afternoon procedure	Acceptance
			+ low-fiber diet	+ low-fiber diet	Tolerability
			145/140	148/145	Adherence
					Adverse events
Rex *et al*[15]	10	18 to 80 y	Prepopik® 1/1 sachets	Half-Lytely e bisacodyl Tablets® 2/0 L	Bowel cleansing quality
	USA		+ 1200/720 mL of liquid	+ bisacodyl 10/0 mg	Acceptability
				+ clear liquid diet	Tolerability
		ITT: 608	+ clear liquid diet		Ease to use medication
		PP: 601			Medication Intake
					Taste
			NA/305	NA/298	Willingness to reuse medication
					Adverse events
					Colonoscopy before
Jeon *et al*[38]	1	20 to 80 y	Picolight powder® (1+1)/1 sachet	Coolprep powder® 1/1 L	Bowel cleansing quality
	South Korea		+ (1+1)/1 L of water	+ 500/500 mL of water	Cecal intubation
			+ low-fiber diet	+ low-fiber diet	Withdrawal time
		ITT: 430			ADR
		PP: 388			PDR
					Tolerability
			215/195	215/193	Satisfaction
					Adverse events
Kang *et al*[39]	1	18 to ou mais	Picolight® 0/(1+1)	Colyte® 2/2 L	Bowel cleansing quality
	South Korea		+ 0/≥ 1 L of water	+ low-fiber diet	Tolerability
		ITT: 197	+ low-fiber diet	99/99	Adverse events
		PP: 197	98/98		Sleep time quantity
					PDR
					ADR
Kim *et al*[40]	1	18 to 75 y	SPMC 1/1 sachets	PEG 0/4 L	Bowel cleansing quality
	South Korea		+ 1/1 L of liquid		Adherence
			+ low-fiber diet	+ low-fiber diet	Medication Intake
		ITT: 200	50/50	50/50	
		PP: 200	SPMC (1+1)/1 sachets	PEG 2/2 L	Tolerability
			+ (1+1)/1 L of liquid		Taste
			+ low-fiber diet	+ low-fiber diet	Biochemical changes
			50/50	50/50	Adverse events
Kim *et al*[41]	1	18 to 80 y	Picolight (1+1)/0 sachets	Standard PEG 4/0 L	Acceptability
	South Korea		+ 2L of water		Adherence to instructions
		ITT: 194	+ bisacodyl 10/0 mg	+ bisacodyl 10/0 mg	Bowel cleansing quality
		PP: 184	+ low-fiber diet (ZeroCol)	+ semi-fluid diet	Adverse events
			97/94	97/90	Willingness to reuse medication
Leitao *et al*[28]	3	18 to 80 y	CitraFleet® 1/1 sachets	Enddealk® 2/1L	Bowel cleansing quality
	Norway		+ 2/2 L of water	+ 0/1 L of liquid	Tolerability
		ITT: 368	+ no-grains diet	+ diet without crops	Adherence
		PP: 368			PDR
			179/179	189/189	Cecal intubation time
					Cecal intubation
Kim *et al*[29]	13	20 to 75 y	sachets	Standard PEG 2/2 L	Bowel cleansing quality
	South Korea		+ 2/2 L of water	no bisacodyl	Satisfaction
			+ bisacodyl 10/0 mg	+ low-fiber diet	Tolerability
			+ low-fiber diet		Medication Intake

		ITT: 387	193/181	194 / 184	Ease to use
		PP: 365			Taste
					Willingness to reuse
					Adverse events
Munsterman *et al*[30]	1	18 to 80 y	Picoprep® 1/1 sachets for morning procedure or	Kleanprep® 3/1 L for morning procedure or	Bowel cleansing quality
	Netherlands	ITT: 173	Picoprep® 1/1 sachets for afternoon procedure	Kleanprep® 2/2 L for afternoon procedure	
		PP: 172	+ 2/2 L of water	+ additional liquid	Tolerability
			+ low-fiber diet	+ low-fiber diet	
			88/87	85/85	
Pohl *et al*[31]	17	40 to 80 y	CitraFleet® (1+1)/0 sachets	Moviprep® 1/1 L	Patients with at least one polyp or flat lesion
	Germany	ITT: 399	+ 250mL/h of water after sachet	+ 500/500 mL of liquid	Patients with at least one adenoma
		PP: 398			Cancer detection rate
			+ fibers restriction diet	+ fibers restriction diet	Flat lesion detection rate
			NA/197	NA/201	Advanced lesions detection rate
Yoo *et al*[32]	1	18 to 80 y	Picolight® 1/1 sachets	Coolprep® 1/1 L	Bowel cleansing quality
	South Korea		+ 1/1 L of water	+ 500/500 mL of water	Bubble score
		ITT: 200	+ low-fiber diet	+ low-fiber diet	Tolerability
		PP: 200			
			100/100	100/100	Satisfaction
Kojecky *et al*[33]	3	18 to 99 y	Picoprep® 2/0 sachets	Fortrans™ 4/0 L	Length of preparation
	Czech Republic		+ 2L of water	94/102	
		ITT: 612	92/102	Fortrans™ 3/1 L	Time to colonoscopy
				87/102	
		PP: 584	OR	Moviprep™ 2/0 L	
				+ 1/0 L of fluids	
			Picoprep® 1/1 sachets	96/102	Bowel cleansing quality
			+ 1/1 L of water		
			86/102	Moviprep™ 1/1	
				+ 0.5/0.5 L of fluids	
				93/102	Tolerability score
			+ low residue diet	+ low residue diet	

* In intervention and control columns, slash separates different days and plus sign separates different doses on the same day; * ITT: number of randomized patients (intention to treat); * PP: number of treated patients (per protocol); * NR: not reported in full-text; * PDR: polyp detection rate; * ADR: adenoma detection rate.

tolerated[13,15,28,34,35,40,41] and one that PEG was better than SPMC[39].

Adverse events prevalence: Eight studies reported adverse events prevalence as a dichotomous outcome. Five of them showed that both products regimens presented the same adverse events prevalence[13,15,28,34,38] and three of them that SPMC regimens achieved fewer adverse events[29,31,41].

PDR: Five studies (corresponding to six comparisons) demonstrated that PDR was the same with both products regimens[31,37,38,40,41]. In one study there was statistical difference in favor of SPMC[28].

ADR: Only five studies assessed ADR and none of them showed difference between SPMC and PEG[31,32,38,39,41].

Syntheses of results

The overall meta-analysis for each outcome was performed with heterogeneity assessment and cumulative treatment effect.

Bowel cleaning success: An asymmetrical funnel plot and high heterogeneity (I^2 = 91%, P < 0.00001) were observed among the 15 studies included. An outlier study

Table 2 Assessment of risk of bias by JADAD scale

#	STUDY	Randomized? (1 pt)	Randomization method	Adequate randomization? (1 pt)	Double blind? (1 pt)	Masking method	Adequate masking? (1 pt)	Loss description? (1 pt)	Jadad (0-5 pts)	GENERAL QUALITY
1	Regev *et al*[34]	Yes	Randomization per patients' ID (odd or even numbers)	No	No	Endoscopist blind for the preparation regimen	No	Yes	2	Intermidiate
2	Lawrance *et al*[35]	Yes	Randomized using Generator Pro 1.69 (Segobit software) in ratio 2:1:1 (PEG:NaP:Pi-co)	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
3	Kao *et al*[36]	Yes	Randomization in blocks of 8 and stratified per AM/PM using a computer-generated table	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
4	Katz *et al*[15]	Yes	Randomization numbers allocated sequentially by voice system	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
5	Manes *et al*[37]	Yes	Randomization by computer-generated sequence	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
6	Rex *et al*[15]	Yes	Randomization numbers allocated sequentially by voice system	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
7	Jeon *et al*[38]	Yes	Randomization by computer-generated table	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
8	Kang *et al*[39]	Yes	Randomization in blocks using website randomization.com	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
9	Kim *et al*[40]	Yes	Not described	No	No	Endoscopist blind for the preparation regimen	No	No	1	Low
10	Kim *et al*[41]	Yes	Randomization by computer-generated sequence	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
11	Leitao *et al*[28]	Yes	Randomization 1:1 with blocks of 10 by endoscopy-unit secretary	Yes	No	Endoscopist blind for the preparation regimen	No	No	2	Intermidiate

12	Kim *et al*[29]	Yes	Randomization by computer-generated table	Yes	No	Not described	No	No	2	Intermidiate
13	Munsterman *et al*[30]	Yes	Randomization by computer-generated 1:1 stratified by age (18-64) or (65-80)	Yes	No	Endoscopist blind for the preparation regimen	No	No	2	Intermidiate
14	Pohl *et al*[31]	Yes	Randomization 1:1 in blocks of 4 by statistician list-generated	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
15	Yoo *et al*[32]	Yes	Randomization 1:1 in blocks of 4 by a a computer-generated list	Yes	No	Endoscopist blind for the preparation regimen	No	Yes	3	High
16	Kojecky *et al*[33]	Yes	Randomization 1:1 using a software generated random table	Yes	No	Endoscopist blind for the preparation regiment	No	Yes	3	High

responsible for reporting bias was identified through sensitivity analysis (Pohl *et al*[31]). After its exclusion (I^2 = 35%, P = 0.09) and through the use of FE model, there was statistical difference in favor of SPMC. More cases of success were obtained with SPMC compared to PEG [MH FE, RD 0.03, IC (0.01, 0.05), P = 0.003, I^2 = 33%] with a NNT of 34 (34 people need to be treated with SPMC to obtain 1 additional benefit over PEG) (Figures 2 and 3).

Patient tolerability: Sensitivity analysis of the eleven included studies revealed true heterogeneity (I^2 = 88%, P < 0.00001) and RE model was adopted. SPMC was better tolerated than PEG [MH RE, RD 0.08, IC (0.03, 0.13), P = 0.002, I^2 = 88%], with a NNT of 13 (Figure 4). As Manes *et al*[37] and Jeon *et al*[38] criteria for completion of intake were different from other studies (failure was defined as lower than 70% and 50% of ingestion of the solutions, respectively), additional analysis was performed without them. The result still favored SPMC [MH RE, RD 0.09, IC (0.03, 0.15), P = 0.002, I^2 = 91%] and lower NNT (NNT of 11).

Adverse events prevalence: A RE model analysis was conducted due to the high heterogeneity among the ten included studies (I^2 = 88%, P < 0.00001). Fewer adverse events occurred using SPMC [MH RE, RD 0.13, IC (0.05, 0.22), P = 0.002, I^2 = 88%], and the NNT obtained was 7 (7 people need to be treated with SPMC to avoid 1 adverse event over PEG) (Figure 5).

PDR: An asymmetric funnel and inconsistency in the upper limit (I^2 = 50%, P = 0.06) were observed among the seven included studies. Sensitivity analysis identified the study responsible for the heterogeneity (Leitao *et al*[28]). The study was not excluded due to the small number of studies included (fewer than 10) and a RE model analysis was conducted. There was no difference between SPMC and PEG for polyp detection [MH RE, RD -0.03, IC (-0.09, 0.02), P = 0.30, I^2 = 50%] (Figure 6).

ADR: Heterogeneity was null among the five studies included and a FE model analysis showed no statistical difference between SPMC and PEG, but a trend in favor of PEG was present [MH FE, RD -0.05, IC (-0.11, -0.00), P = 0.05, I^2 = 0%] (Figure 7).

Subgroups analyses

Additional analyses were performed by subgroups based on type of regimen, volume of PEG solution and dietary recommendations for the day prior to colonoscopy.

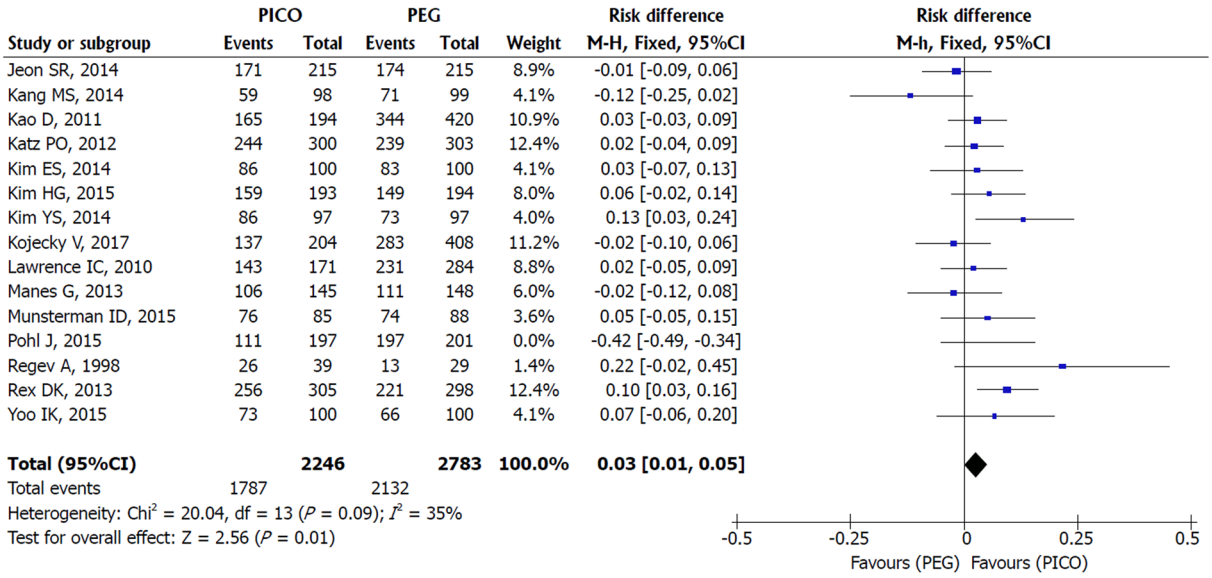

Figure 2 Metanalysis forest plot of bowel cleaning success.

Per type of regimen: Studies were divided into four subgroups according to regimens compared: day-before dose[13,33,34,41]; split dose[28-30,32,33,38,40]; according to interval time for colonoscopy[35-37]; and comparison of different regimens[15,31,39].

Bowel cleansing success: SPMC was better than PEG for bowel cleaning in day-before dose comparison [MH RE, RD 0.06, IC (0.01, 0.11), P = 0.02, I^2 = 38%], with an NNT of 17. No difference was observed in the split dose regimen [MH FE, RD 0.01, IC (-0.03, 0.05), P = 0.56, I^2 = 29%], in the according-to-interval-time regimens [MH FE, RD 0.02, IC (-0.03, 0.06), P = 0.45, I^2 = 0%] and in the different regimens subgroup [MH RE, RD -0.14, IC (-0.50, 0.21), P = 0.42, I^2 = 98%].

Additional sensitivity analysis by subgroups showed that inconsistency among all studies included in the overall meta-analysis decreased from 91% to 19% after the removal of different regimens subgroup, in which the previous outlier study for the outcome was identified (Pohl *et al*[31]). Without this subgroup, the statistical difference disappeared and there was only a trend in favor of SPMC [MH FE, RD 0.03, IC (0.00, 0.05), P = 0.03, I^2 = 19%] (Appendix 4 - Figure 1).

Patient tolerability: No difference was observed in tolerability in the split dose regimen (MH RE, RD 0.04, IC [-0.05, 0.14], P = 0.38, I^2 = 86%) and in the different regimens subgroup [MH RE, RD 0.04, IC (-0.09, 0.17), P = 0.54, I^2 = 97%]. In the day-before dose regimen [MH FE, RD 0.17, IC (0.13, 0.21), P < 0.0001, I^2 = 0%] and in the according-to-interval-time subgroups [MH RE, RD 0.08, IC (0.01, 0.15), P = 0.02, I^2 = 54%], SPMC was better tolerated than PEG, with an NNT of 6 and 13, respectively. Sensitivity analysis by subgroups did not change the overall meta-analysis results either (Appendix 4 - Figure 2).

Adverse events: Three subgroups were available (day-before dose, split dose and different regimens). No difference was found in day-before dose [MH RE, RD -0.18, IC (-0.50, 0.14), P = 0.26, I^2 = 96%] and in split dose subgroups [MH RE, RD -0.07, IC (-0.16, 0.02), P = 0.15, I^2 = 62%], but there were fewer adverse events with SPMC in the different regimens subgroup [MH RE, RD -0.10, IC (-0.19, -0.02), P = 0.01, I^2 = 60%], with a NNT of 10(Appendix 4 - Figure 3).

PDR: The analysis showed no difference in PDR in the split dose subgroup [MH FE, RD 0.04, IC (-0.03, 0.10), P = 0.28, I^2 = 43%] and superiority of PEG over SPMC in the different regimens subgroup [MH FE, RD -0.09, IC (-0.17, -0.01), P = 0.02, I^2 = 0%], with a NNT of 12 (Appendix 4 - Figure 4).

ADR: Only two subgroups (split dose and different regimens) with 2 studies each were available. There was no statistical difference in ADR between them [split dose: MH FE, RD -0.02, IC (-0.11, 0.07), P = 0.70, I^2 = 0%; different regimens: MH FE, RD -0.06, IC (-0.14, 0.01), P = 0.09, I^2 = 0%] (Appendix 4 - Figure 5).

Per volume of PEG solution: Eight studies were included in low-volume subgroup[13,15,31-33,36-38] and nine in high-volume subgroup[29,30,33-36,39-41].

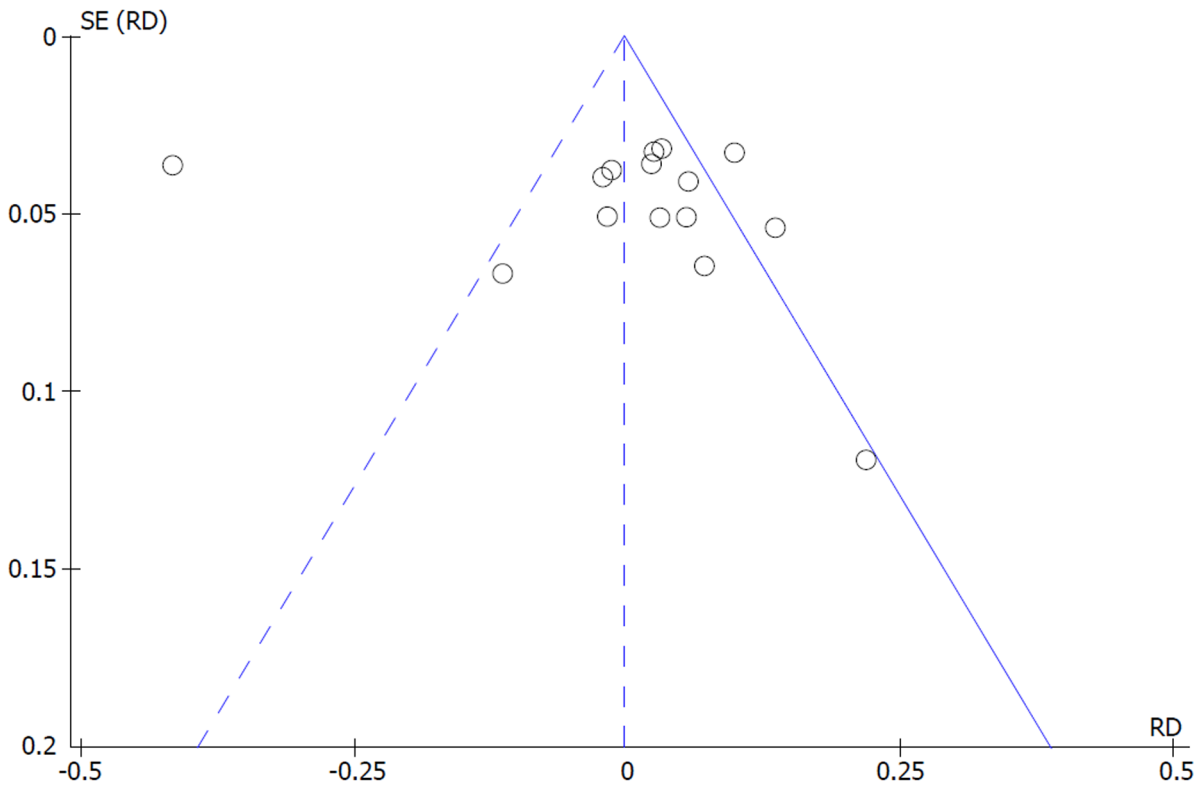

Figure 3 Metanalysis funnel plot of bowel cleaning success.

Bowel cleansing success: Low-volume PEG subgroup presented high heterogeneity (I^2 = 96%, P < 0.00001) and sensitivity analysis identified one study (Pohl *et al*[31]) as the responsible for funnel asymmetry and high heterogeneity. Considering the small number of studies, it was maintained for the analysis and RE model was adopted. No difference was observed in bowel cleaning between SPMC and low-volume PEG [MH RE, RD -0.03, IC (-0.16, 0.09), P = 0.61, I^2 = 95%]. High-volume subgroup analysis also showed no difference between them [MH FE, RD 0.03, IC (-0.01, 0.06), P = 0.09, I^2 = 42%] (Appendix 4 - Figure 6).

Patient tolerability: SPMC was better tolerated than high-volume PEG solution [MH RE, RD 0.08, IC (0.01, 0.14), I^2 = 89%, P = 0.02], with a NNT of 13, and a trend in favor of SPMC was observed in the low-volume PEG subgroup [MH RE, RD 0.08, IC (0.00, 0.16), I^2 = 87%, P = 0.05]. (Appendix 4 - Figure 7).

Adverse events: After the performance of a sensitivity analysis, a study responsible for the heterogeneity in the high-volume subgroup was identified (Kim *et al*[41]), but was not excluded due to the small number of studies (fewer than 10 studies). RE model analysis showed SPMC caused fewer adverse events than PEG in the high-volume subgroup [MH RE, RD -0.18, IC (-0.30, -0.07), P = 0.002, I^2 = 79%], with a NNT of 6. There was no difference in adverse events prevalence in the low-volume subgroup [MH RE, RD 0.09, IC (-0.02, 0.20), P = 0.12, I^2 = 91%] (Appendix 4 - Figure 8).

PDR: Sensitivity analysis was carried out for high-volume subgroup and the study responsible for the inconsistency was identified (Leitao *et al*[28]). It was not removed due to the small number of included studies. There was no difference in PDR in the low-volume subgroup [MH FE -0.05, IC (-0.11, 0.01), P = 0.11, I^2 = 0] or in the high-volume subgroup [MH RE, RD -0.03, IC (-0.14, 0.09), P = 0.65, I^2 = 71%] (Appendix 4 - Figure 9).

ADR: No difference was observed between SPMC and PEG in both subgroups [low-volume: MH FE, RD -0.04, IC (-0.11, 0.02), P = 0.17, I^2 = 0%; high-volume: MH FE, RD -0.07, IC (-0.17, 0.02), P = 0.12, I^2 = 0%] (Appendix 4 - Figure 10).

Per dietary recommendations: Four studies were included in liquid diet subgroup[13,15,34,36] and twelve studies[23-28,30,32-36] in the low residue diet subgroup.

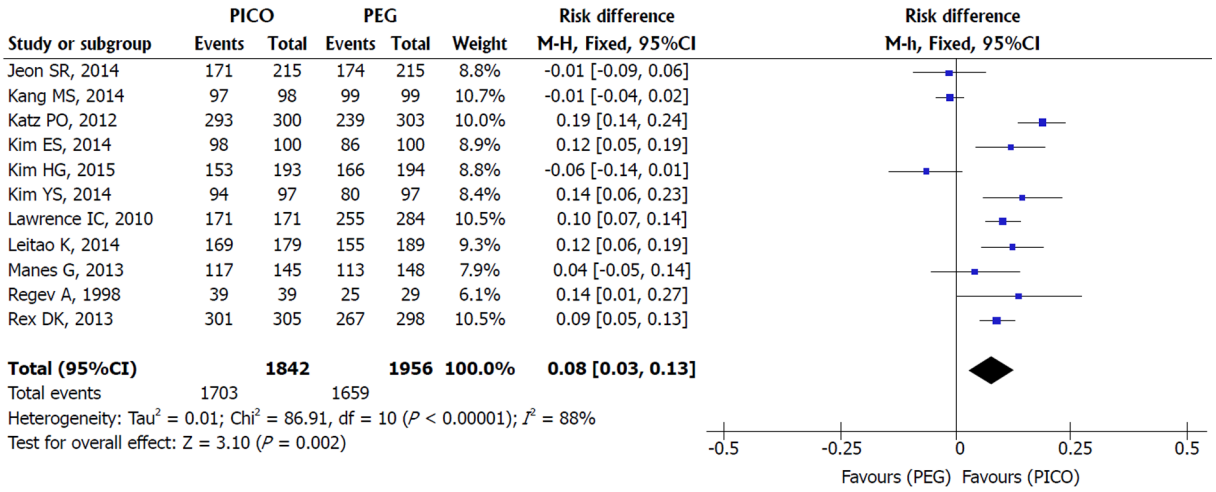

Figure 4 Metanalysis forest plot of tolerability.

Bowel cleansing success: The analysis showed that SPMC was better than PEG for bowel cleaning in the liquid diet subgroup [MH FE, RD 0.06, IC (0.02, 0.09), $P = 0.002$, $I^2 = 40\%$], with a NNT of 17. In the low residue diet subgroup, high heterogeneity and an asymmetrical funnel plot were initially observed ($I^2 = 93\%$, $P < 0.00001$). After sensitivity analysis, one study (Pohl *et al*[31]) was identified as the responsible for reporting bias. After its exclusion, heterogeneity decreased to an acceptable level ($I^2 = 31\%$) and analysis using FE model showed that SPMC and PEG were similar in the low residue subgroup [MH FE, RD 0.01, IC (-0.02, 0.04), $I^2 = 30\%$, $P = 0.38$] (Appendix 4 – Figure 11).

Patient tolerability: SPMC was better tolerated than PEG in the liquid diet group [MH RE, RD 0.14, IC (0.06, 0.22), $I^2 = 81\%$, $P = 0.0006$], with an NNT of 8, and a trend in favor of SPMC was identified in the low residue subgroup [MH RE, RD 0.06, IC (0.00, 0.11), $I^2 = 86\%$, $P = 0.05$] (Appendix 4 - Figure 12).

Adverse events: There was low heterogeneity ($I^2 = 43\%$, $P = 0.17$) among the three studies included in the liquid diet subgroup and high heterogeneity ($I^2 = 86\%$, $P < 0.00001$) among the seven studies included in the low residue subgroup. FE and RE models were used for liquid diet and low residue subgroups, respectively. There was no difference between SPMC and PEG in the liquid diet subgroup [MH FE, RD -0.02, IC (-0.08, 0.05), $P = 0.59$, $I^2 = 43\%$], but the low residue subgroup SPMC presented fewer adverse events than PEG [MH RE, RD -0.17, IC (-0.27, -0.07), $P = 0.0008$, $I^2 = 86\%$], with a NNT of 6 (Appendix 4 - Figure 13).

Polyp and adenoma detection rates: PDR and ADR subgroups were the same for SPMC *vs* PEG comparison because all the included trials in this comparison recommended only low residue diet on the day before.

DISCUSSION

Summary of evidence

Results from the meta-analysis of the 16 included studies (with 6200 subjects from ten different countries) indicate that for adult outpatients before elective colonoscopy, SPMC is at least similar to PEG in bowel cleaning efficacy, better in tolerability and in adverse events prevalence and similar in polyp and adenoma detection rate.

As high inconsistency and true heterogeneity were present among the included studies despite the strict inclusion criteria adopted, caution for interpretation of data is recommended. Populations of different countries with different dietary patterns, different options of dosage and schedule for bowel preparation and different scales and different instruments to measure outcomes may have contributed to increase heterogeneity. As bowel cleaning protocols vary between different institutions worldwide, variations across trials are inherent and expected.

As this meta-analysis provided an overall impression by grouping different bowel cleaning protocols and did not consider confounding factors, such as type of regimen, volume of solution ingested and dietary restrictions, additional analyses by subgroups were conducted to elucidate these aspects and to help decision-making in

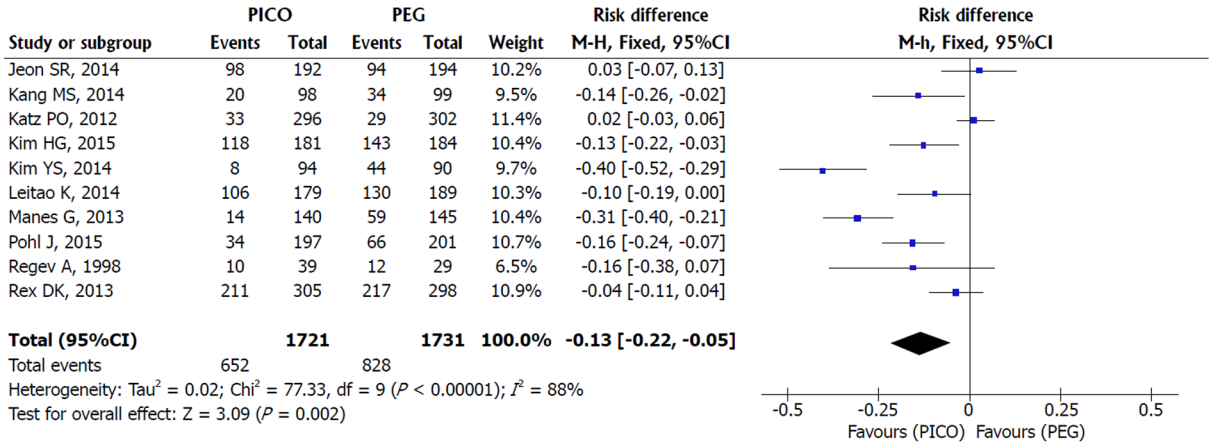

Figure 5 Metanalysis forest plot of adverse events.

daily clinical practice.

Sensitivity analyses provided additional information on the influence of the studies in the meta-analysis, helping with the confounding factors. Pohl *et al*[31] was identified as the main outlier study for bowel cleaning due to its methodological bias of treatment: the comparison of different regimens of bowel preparation.

As previously known in a meta-analysis by Bucci *et al*[43], the interval time between the last drink of bowel preparation and the beginning of colonoscopy (also known as "runway time") is a key factor for cleaning quality. When Pohl *et al*[31] compared different regimens (a split regimen of PEG and a day-before regimen of SPMC), the difference between treatment effects was increased and favored that one with the shorter "runway time" (PEG).

The sensitivity analysis by subgroups of regimen confirmed the impact of including trials comparing different regimens. Through the exclusion of this subgroup (Rex *et al*[15], Kang *et al*[39], Kim *et al*[40] and Pohl *et al*[31]), a more reliable analysis with less heterogeneity was obtained and the difference in bowel cleaning and the trend in favor of PEG for adenoma detection disappeared. Hence, the more rational approach was to assume SPMC and PEG were similar for both outcomes.

Statistical difference in favor of SPMC was also identified in the sub-analysis in the following situations: (1) bowel preparation was made on the day before (better bowel cleaning success and better tolerability); (2) bowel preparation was made based on the interval time to colonoscopy (also better tolerability); (3) when compared to high-volume solution of PEG (better tolerability and fewer adverse events); (4) liquid diet was the option on the day before (with better bowel cleaning success and better tolerability); and (5) low residue diet was the option on the day before (fewer adverse events).

Although there was statistical difference in these outcomes, it is also important to observe the number needed to treat to evaluate treatment effectiveness properly and to help deciding about changes in daily clinical practice. If the NNT is high, there is low chance of benefits for the patient with the alternative treatment, which might not justify its adoption.

The high NNTs of SPMC for bowel cleaning (NNT of 34) and for tolerability (NNT of 13) result in a small chance of benefit for the patient (2.9% and 7.6%, respectively). However, the small NNT for adverse events (NNT of 7) reveals a significant reduction of 14.2% when SPMC is used, this being its main advantage and the reason for its adoption over PEG.

Benefits of using SPMC are also obtained in day-before preparations (16.6% more chance of tolerability), against high-volume solutions of PEG (reduction of 16.6% in chance of adverse events) and with prior-day dietary restrictions (a 12.5% greater chance of tolerability with the use of liquid diet and a 16.6% reduction in the chance of adverse events with low residue diet).

Despite the potential benefits of SPMC demonstrated in this meta-analysis, care should be taken in regard to some of the product faults. Because of the potential electrolyte shifts, SPMC is not recommended in patients with renal insufficiency, end-stage liver disease, heart failure and electrolyte abnormalities[44,45]. PEG is the product of choice for those patients as it is an inert molecule and isosmotic solution, which also induces less mucosal damage (inflammation or ulceration) by ten times when compared to SPMC[35].

The main disadvantage of PEG consists in the amount of solution to be ingested as

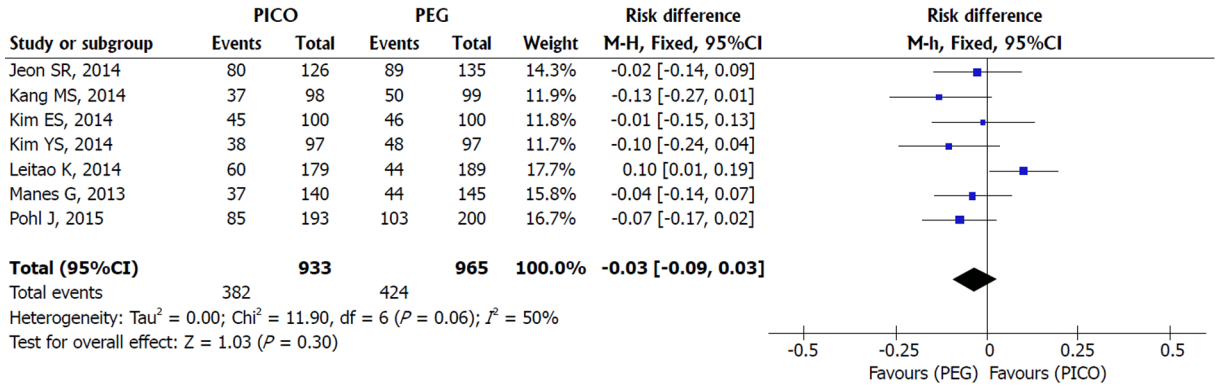

Figure 6 Metanalysis forest plot of polyp detection rate.

observed in the meta-analysis by Xie *et al*[46]. Further sub-analyses by volume of PEG solution presented in this meta-analysis reinforce this drawback. High-volume PEG presented less tolerability and more adverse events than SPMC whereas no difference was found between low-volume PEG and SPMC. As tolerability and adverse events are correlated factors that can affect bowel cleaning, SPMC appears as an interesting alternative.

An extensive search strategy, well-defined eligibility criteria, careful inclusion of the studies and analyses based on "intention-to-treat" data are the strength of this study. Results obtained by additional analyses focusing on subgroups based on regimen schedule, volume of PEG solution and dietary restriction bring new information and complement two recent meta-analyses.

Jin *et al*[20] and van Lieshout *et al*[47] showed that SPMC was equally effective or slightly superior to PEG in terms of bowel cleaning efficacy and that it was better tolerated than PEG. However, they did not consider patient status (if inpatient or outpatient) for studies selection and grouped different types of patients. This is the first meta-analysis for this specific group of patients and the first communicating effectiveness of bowel preparation using NNT.

Limitations

Nine full-text trials identified in the search were not included in this meta-analysis due to the lack of essential information concerning eligibility criteria[48-56]. Their absence may have contributed to borderline results in some sub-analyses with few included studies, but it assured the assertiveness of the results for this specific population.

Quality of bowel cleaning measured by different cleanliness scores and patients' preferences and impressions of the products are other important outcomes that were not evaluated. Due to the different instruments to collect data used by trials, matching these data is prejudiced.

The type and severity of adverse events were also not explored. Owing to the methodological feature of RCTs and the characteristics of those products, the events are generally mild to moderate gastrointestinal symptoms (nausea, vomiting, abdominal pain, bloating and dizziness). Serious adverse events after bowel preparation are rare[57].

In addition, results obtained by this meta-analysis should be only inferred to healthy patients or those with mild disease as the included trials excluded other types of patients. This is especially important for the use of SPMC, as it is known for the occurrence of electrolyte disturbances which could have a repercussion in moderately or severely diseased patients.

Finally, although all the included studies were randomized clinical trials, five of them presented problems regarding randomization and masking, the description of losses and failure in reporting the outcomes, which compromised the quality of the evidence. Therefore, the quality of the evidence obtained was moderate for bowel cleaning efficacy, tolerability and adverse events prevalence, and low for polyp and adenoma detection rates[58]. Future studies might influence some outcomes and sub-analyses, especially those with borderline differences, with high NNTs or few studies included.

Conclusion

According to data published until now, SPMC seems to be a better product than PEG for bowel preparation in healthy or mildly diseased adult outpatients before

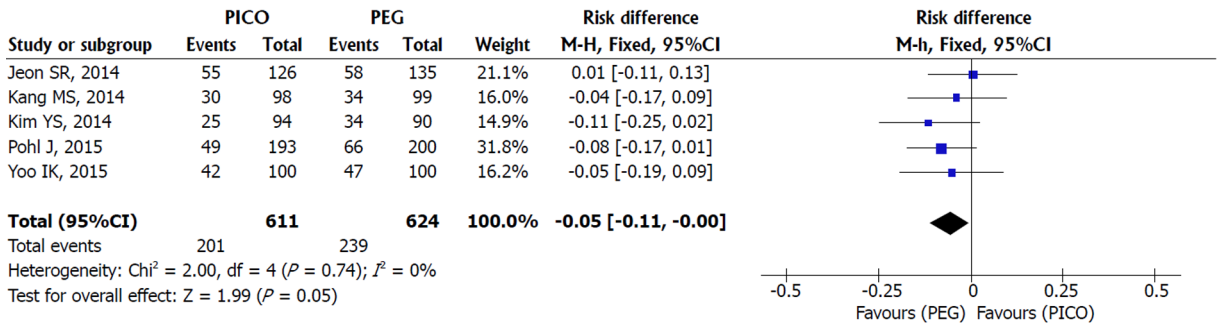

Figure 7 Metanalysis forest plot of adenoma detection rate.

colonoscopy as its bowel cleaning efficacy is at least equal to that of PEG, its tolerability is better and adverse events prevalence is lower. The latter corresponds to the main advantage of using SPMC instead of PEG. Both SPMC and PEG can be used for split preparations as there are no difference in bowel cleaning success, tolerability and adverse events prevalence, but SPMC should be the choice for day-before preparations because of its better tolerability.

ARTICLE HIGHLIGHTS

Research background

Colonoscopy reduces the incidence and mortality for colorectal cancer. Bowel preparation is the cornerstone for colonoscopy as the quality of bowel cleaning directly affects the effectiveness for detecting neoplastic lesions. Different options of purgatives exist as a result of the search for the ideal product and none of them have all the ideal features. PEG solutions are the most widely used and studied bowel cleanser, while SPMC is a recently developed one to overcome PEG's poor palatability and large volume of solution to be ingested. Meta-analyses of RCTs are the best evidence for medical practice, but none of them compared SPMC and PEG for outpatients before colonoscopy, leaving a gap in the literature.

Research motivation

Most of elective colonoscopies are performed in outpatients and inpatient status is an independent risk factor for inadequate bowel preparation. As previous meta-analyses comparing SPMC and PEG before elective colonoscopy did not consider patient status for inclusion criteria, there is no established evidence for this subset of patients.

Research objectives

To determine the best option for bowel preparation in adult outpatients before elective colonoscopy by comparing cleaning efficacy, tolerability, AE prevalence, PDR and ADR between SPMC and PEG. This is the first meta-analysis to include only outpatients and to communicate effectiveness using NNT.

Research methods

Systematic review and meta-analysis followed PRISMA Statement. Eligibility criteria were based on PICOS strategy. Search was performed in MEDLINE, Scopus, EMBASE, CENTRAL/Cochrane, CINAHL and LILACS. Jadad scale was the tool adopted to evaluate the methodological quality of included RCTs and heterogeneity among studies was assessed by Higgins' test (I^2). Meta-analysis was preferably performed using intention-to-treat data by computing risk difference (RD) for dichotomous outcomes using Mantel-Haenszel (MH) method and NNT calculated for each outcome with statistical difference.

Research results

Sixteen RCTs with 6200 subjects were included for the meta-analysis and high heterogeneity was found among them. Sensitivity analysis and sub analysis by type of regime, volume of PEG solution and dietary recommendations were performed to interpret data. In the overall analysis, SPMC was better for bowel cleaning [RD 0.03, IC (0.01, 0.05), NNT 34], for tolerability [RD 0.08, IC (0.03, 0.13), NNT 13] and for adverse events [RD 0.13, IC (0.05, 0.22), NNT 7]. The small NNT for adverse events (NNT of 7) reveals a reduction of 14.2% when SPMC is used. Better tolerability for SPMC was also found in "Day-before preparations" [RD 0.17, IC (0.13, 0.21), NNT 6], "According to interval time" [RD 0.08, IC (0.01, 0.15), NNT 13], "Against high-volume of PEG" [RD 0.08, IC (0.01, 0.14), NNT 13] and "Liquid diet subgroup" [RD 0.14, IC (0.06,0.22), NNT 8].

Research conclusions

Data from published RCTs suggests SPMC is a better bowel cleanser than PEG before elective colonoscopy for healthy and mildly diseased adult outpatients because of its better tolerability,

lower AE prevalence and cleaning efficacy at least equal to that of PEG. For split preparations, SPMC and PEG can be equally use, but for day-before preparations SPMC should be the standard choice.

Research perspectives

Future RCTs might influence the outcomes of this meta-analysis with few studies included and/or with borderline differences obtained (*e.g.*, PDR, ADR, per type of regimen and per dietary recommendations) since Meta-analyzes are limited by the number of studies available and by the quality of the studies included. More homogeneous and definitive results should be obtained through a large intercontinental multi-center RCT, with the same bowel preparation protocol and tools for evaluating results. Although expensive and hard-working, it would be the best study format to compare purgatives and determine the best conditions for each of the available purgatives.

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