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Pure cut vs. Endocut in endoscopic biliary sphincterotomy: A systematic review and meta-analysis of Randomized Clinical Trials.

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Eduardo Guimarães Hourneaux de Moura: consultor of Boston Scientific and Olympus

The remaining authors have no conflict of interest to declare.

Abstract:
Introduction: Biliary sphincterotomy is a crucial step in endoscopic retrograde cholangiopancreatography (ERCP), a procedure known to carry a 5-10% risk of complications. The relationship between Pure cut, Endocut, post-ERCP pancreatitis (PEP) and bleeding is unclear. This systematic review and meta-analysis compares these two current types and their relationships with adverse events.
Methods: This systematic review involved searching articles in multiple databases until August 2023 comparing pure cut versus Endocut in biliary sphincterotomy. The meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).
Results: A total of 987 patients from four randomized controlled trials were included. Overall pancreatitis: a higher risk of pancreatitis was found in the Endocut group than in the pure cut group (P=0.001, RD=0,04 [0.01,0.06]; I2=29%). Overall immediate bleeding: statistical significance was found to favour Endocut, (P=0.05; RD=-0.15 [-0.29, -0.00]; I2=93%). No statistical significance between current modes was found in immediate bleeding without endoscopic intervention (P=0.10; RD=-0.13 [-0.29, 0.02]; I2=88%), immediate bleeding with endoscopic intervention (P=0.06; RD=-0.07 [-0.14,0,00]; I2=76%), delayed bleeding (P=0.40; RD=0.01 [-0.02,0.05]; I2=72%), zipper cut (P=0.58; RD= -0.03 [-0.16,0.09]; I2= 97%), perforation (P= 1.00; RD= 0.00 [-0.01,0.01]; I2= 0%) and cholangitis (P= 0.77; RD= 0.00 [-0.01,0.02]; I2= 29%).
Conclusion: The available data in the literature shows that Endocut carries an increased risk for PEP and does not prevent delayed or clinically significant bleeding, although it prevents intraprocedural bleeding. Based on such findings, pure cut should be the preferred electric current mode for biliary sphincterotomy.

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Thieme

Pure cut vs. Endocut in endoscopic biliary sphincterotomy: A systematic review and meta-analysis of Randomized Clinical Trials.

Introduction

Endoscopic biliary sphincterotomy is a crucial step in endoscopic retrograde cholangiopancreatography (ERCP), a procedure known to carry a 5-10% risk of complications, including post-ERCP pancreatitis (PEP), bleeding, cholangitis, perforation, sepsis, and even death [1, 2, 3, 4, 5]. Two commonly used current modes in sphincterotomy are pure cut and Endocut (or pulsed cut) [6, 7, 8].

Pure cut utilizes a pure sine wave with high frequency and lower voltage, with arcs that have a voltage higher than 200 volts and are generated as soon as the vaporization of liquid in the tissue creates a small gap between the cutting wire and the tissue of the duodenal papilla (ERBE Elektromedizin GmbH. Endo CUT I. Tubingen: ERBE; 2016). Endocut (types 2 or 3) uses coagulation between the cutting cycles. Coagulation presents a very short active sinus wave (6-10% of cycle) with a more extended cooling period (inactivated 90-94% of cycle, lasting 720-750 ms) [9, 10, 11, 12]. Therefore, in this text, Endocut refers to types 2 and 3.

Thermal injury from the coagulation effect of Endocut can lead to local edema in the major papilla, potentially impairing pancreatic duct drainage and predisposing post-ERCP pancreatitis (PEP), as some studies suggest [11, 12, 13, 14]. However, the most recent meta-analysis by Funari et al. did not find statistical evidence supporting this claim [15]. On the other hand, Endocut has been shown to decrease intraprocedural bleeding, likely due to its coagulation effect [11, 12]. However, previous studies did not show that Endocut is capable of reducing delayed bleeding with clinical repercussions [15, 16].

Thus, the primary objective of our study is to compare these two current modes (pure cut and Endocut) considering post-ERCP adverse events, especially PEP and bleeding. Therefore, we intend to investigate whether the available literature can provide the selection of the optimal current mode during biliary sphincterotomy, ultimately enhancing patient safety and clinical outcomes related to this procedure.

Materials and Methods

Protocol and Registration

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The research was carried out following the PRISMA flow diagram (Figure 1), guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) and registered in PROSPERO (International Prospective Register of Systematic Reviews) under the registration number CRD42023458386 [17, 18].

Figure 1 – PRISMA flow diagram

Eligibility criteria

Only randomized clinical trials (RCTs) comparing pure cut and Endocut modes for endoscopic biliary sphincterotomy were eligible for inclusion. The exclusion criteria were as follows: studies that discussed any current mode other than Endocut or pure cut, patients under 18 years old, animal studies, retrospective studies, and patients with significant anatomical alterations (e.g., Roux-en-Y and Billroth II).

Search strategy, study selection and data collection process

For this meta-analysis, a comprehensive search was conducted independently by two authors (LBO and MPF) across multiple databases, including Medline, Embase, Lilacs, Central Cochrane, and Google Scholar, spanning from inception until June 2023. The search process involved meticulously reviewing all titles within these databases, removing any duplicate entries. Subsequently, articles that did not meet the predetermined inclusion criteria were excluded. In the second phase, all abstracts of the remaining articles were thoroughly assessed. From this selection, both reviewers cross-referenced the results to ensure accuracy. In cases where there was uncertainty or disagreement between the reviewers, a third reviewer (ASTK) was consulted to reach a consensus. To facilitate data extraction, the researchers utilized standardized Excel spreadsheets to record information related to the dichotomous outcomes, including pancreatitis and its grades, intraprocedural bleeding with and without the need for endoscopic intervention, delayed bleeding, uncontrolled sphincterotomy, perforation, and cholangitis [1] .

Search strategy

The keywords for the strategy search for PubMed (Medline) were papillotomy, sphincterotomy, retrograde cholangiopancreatography, endoscopic, cut, blend and Endocut. The full strategy:

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(((((papillotomy OR Sphincterotomy OR Sphincterotomies OR Sphincterotome OR Sphincteroplasty OR Sphincteroplasties) OR ((Retrograde Cholangiopancreatography, Endoscopic OR Cholangiopancreatographies, Endoscopic Retrograde OR Endoscopic Retrograde Cholangiopancreatographies OR Retrograde Cholangiopancreatographies, Endoscopic OR Endoscopic Retrograde Cholangiopancreatography OR ERCP) AND (cut OR electrosurg* OR knife OR blend OR electric* OR blend OR electrocautery OR cautery OR coagulation OR endocut))))).

Data analysis

All outcomes were assessed by dichotomous variables using the Mantel–Haenszel test to determine risk differences. We used a confidence interval (CI) of 95% and a significant p value of <0.05. We preferred to apply confidence interval (CI) than prediction interval due to the Cochrane Handbook for Systematic Reviews of Interventions explicitly states that a minimum of ten studies is typically recommended for the application of prediction intervals, and in our meta-analysis, we had a total of four studies. Nevertheless, CI was used in others recent meta-analyses on this topic (references 15 and 16). We assessed the heterogeneity of the forest plot by the Higgins test (I^2). If I^2 is 0% to 40%, the heterogeneity might not be significant; if 30% to 60%, the results may represent substantial heterogeneity; and if 75% to 100%, they represent considerable heterogeneity [19]. A sensitivity analysis was performed utilizing a funnel plot to identify potential outliers.

If the exclusion of specific studies from the meta-analysis resulted in a homogenous dataset, those studies were considered true outliers and permanently excluded. In such cases, the fixed-effect model was employed for the final analysis. However, if no outliers were identified or if heterogeneity remained high despite excluding outliers, we opted for the random-effects model. This approach helps mitigate the impact of heterogeneity on the overall findings, ensuring a more robust and reliable conclusion.

In the case of moderate or high heterogeneity, if I^2> 50%, the random-effects model was used. Otherwise, in the case of low heterogeneity, I^2 < 50%, and the fixed-effects test was performed. All direct analyses were carried out in RevMan 5 software (Review Manager version 5.4.1—Cochrane Collaboration Copyright) [20].

Methodology quality and risk of bias in individual studies

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To comprehensively assess the overall quality of each outcome analysis and the respective RCTs, we followed the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) standards [21]. Utilizing the GRADEpro software for guideline development tools (GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime, 2022).

The biases present in the selected RCTs were carefully assessed using the Cochrane Risk of Bias Tool (Rob 2- Table 1) [22]. The evaluation of study quality encompassed patient selection, comparability of the study groups, and outcome measures. Each RCT was meticulously analyzed using Rob2, focusing on aspects such as randomization and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), handling of incomplete outcome data (attrition bias), adherence to outcome and prognostic factors, intention-to-treat analysis, sample size calculation, and selective reporting.

To ensure consistency and accuracy in the bias assessment using Rob 2 and the GRADE analysis, two independent reviewers (LBO and MPF) conducted the evaluations. In instances of disagreements, a third reviewer (ASTK) was consulted to achieve a consensus and ensure the reliability of the findings.

Outcome Definitions

- Bleeding: There is no standardized graduation for immediate (intraprocedural) bleeding, and the included studies use different definitions. To homogenize this analysis, we classified the study definitions into either self-limited bleeding or bleeding with the need for endoscopic intervention. Delayed bleeding was defined and graded according to the Cotton criteria [23].
- Perforation**:** For meta-analysis purposes, we only considered perforations related to biliary sphincterotomy, classified as Stapfer II [24].
- PEP: Was defined according to Cotton's criteria since Funari, Norton and Kida mentioned Cotton's classification. Ellahi mentioned "according to a consensus definition". However, we considered Cotton because this was an abstract of 2001 and at that time, Cotton's criteria was the only classification in this theme (created in 1991), while Atlanta's Classification was developed just in 2012 [23] .

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- Adverse events: In this review all adverse events described in the studies in question were mentioned, However, our focus will be a more in-depth exploration of procedure-related adverse events, which are notably prevalent in this context. Specifically, we will delve into issues such as pancreatitis, bleeding, perforation, zipper cut, and cholangitis—areas of particular interest to us. Consequently, when we reference adverse events in this review, we are specifically alluding to those aforementioned.

Results

Study selection and characteristics of included studies

A total of 24,588 studies were found in the systematic review. After screening, six articles were selected for full-text analysis. After applying the eligibility criteria, four studies were included in the meta-analysis (Table 2).

Two studies were randomized controlled trials, and two were congress abstracts. Most studies indicated choledocolithiasis, stenosis (benign and malignant), and dysfunction of Oddi's sphincter (SOD). Patients were on average 59 years old of both genders (basically 50% of each). More details of the included studies are summarized in Table 2.

Methodology quality and risk of bias

The quality of evidence of each outcome analysis evaluated by GRADE were demonstrated in Table 3 and the risk of bias of all the included studies were described in Table 2.

Metanalysis

Mild pancreatitis

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Four articles analyzing mild pancreatitis were included, totaling 987 patients. No statistical significance was identified with the current mode (P= 0.20; RD=0.02 [-0.01, 0.05]; I^2= 56%) as shown in Figure 2. The GRADEpro tool shows a low level of certainty.

Figure 2 - Forest plot for mild pancreatitis

Moderate pancreatitis

Four articles were included in this outcome, totaling 987 patients, with no statistical significance association with the current mode (P= 0.10; RD=0.01 [-0.00, 0.02]; I^2= 0%) as shown in Figure 3. The GRADEpro tool shows a high level of certainty.

Figure 3- Forest plot for moderate pancreatitis

Severe pancreatitis

Four articles were included in this outcome, totaling 987 patients. No statistical significant association with the current mode was observed (P= 0.70; RD= 0.00 [-0.01, 0.02]; I^2= 60%) as shown in Figure 4. The GRADEpro tool shows a low certainty level and high bias risk. It presents severe imprecision and high magnitude.

Figure 4 - Forest plot for severe pancreatitis

Overall pancreatitis

Four articles were included in the evaluation of overall pancreatitis, with a total of 987 patients. A higher risk of pancreatitis was found in the Endocut group than in the pure cut group (P=0.001, RD=0,04 [0.01, 0.06]; I^2 = 29%) as shown in Figure 5. The GRADE pro tool shows a high level of certainty. The number needed to treat (NNT) is 25.

Figure 5 - Forest plot for pancreatitis in general

Immediate bleeding (no endoscopic intervention)

Three articles were included in this outcome, totaling 901 patients. The synthesis showed no statistical significance between current modes (P= 0.10; RD= -0.13 [-0.29, 0.02];

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I^2= 88%) as shown in Figure 6. The GRADEpro tool shows a very low level of certainty and high heterogeneity (I^2= 88%). This outcome presented a high risk of bias.

Figure 6 - Forrest plot for immediate bleeding (no endoscopic intervention)

Immediate bleeding (with endoscopic intervention)

Three articles were included in this outcome, totaling 901 patients. The synthesis demonstrated no statistical significance in the risk of bleeding requiring endoscopic intervention between groups (P=0.06; RD= -0.07 [-0.14, 0,00]; I^2= 76%) as shown in Figure 7. The GRADEpro tool shows a very low level of certainty, high heterogeneity (I^2= 76%) and high risk of bias.

Figure 7 - Forrest plot for immediate bleeding (with endoscopic intervention)

Overall immediate bleeding

Four articles were included in this outcome, totaling 987 patients. The summary effect showed a statistical significance between pure cut and Endocut concerning overall immediate bleeding (P=0.05; RD= -0.15 [-0.29, -0.00]; I^2= 93%) as shown in Figure 8. The GRADEpro tool shows a very low level of certainty, high heterogeneity (i^2= 93%) and high risk of bias. The NNT is 6,66.

Figure 8 - Forest plot for overall immediate bleeding

Delayed Bleeding

Three studies were included in this outcome, totaling 903 patients. No statistical significance was found (P= 0.40; RD= 0.01 [-0.02, 0.05]; I^2= 72%) as shown in Figure 9. The GRADEpro tool presents very low certainty, high level of heterogeneity and low high bias.

Figure 9 - Forrest plot for delayed bleeding

Zipper cut sphincterotomy

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Three articles were included in this outcome, totaling 896 patients. No statistical significance was found (P=0.58; RD= -0.03 [-0.16, 0.09]; I^2= 97%). The GRADEpro tool considered very low the level of certainty, low inconsistency, and high risk of bias.

Perforation

Three studies were included in this outcome, totaling 901 patients. No statistical significance was found concerning perforation rates (P= 1.00; RD= 0.00 [-0.01, 0.01]; I^2= 0%). The GRADEpro tool presents a high level of certainty, low level of heterogeneity and high risk of bias.

Cholangitis

Two articles were included in this outcome, totaling 636 patients. No statistical significance was found (P= 0.77; RD= 0.00 [-0.01, 0.02]; I^2= 29%). The GRADEpro tool considered a low level of certainty, very serious inconsistency, and high risk of bias.

Discussion

To date, this is the fourth meta-analysis comparing Endocut and pure Cut for sphincterotomies but is the only one to include all four currently available RCTs. The three previously published meta-analyses (Hedjoudje 2021, Funari 2018, Verma 2007) demonstrated similar results: lower rates of immediate bleeding with pure cut and no difference for PEP, delayed bleeding, and other adverse events [15, 16, 25]. Based on such findings, an important recent guideline recommends using Endocut to perform sphincterotomies [12].

It is important to emphasize that the studies used different types of electrical surgery units that influence electric power and details of the type of coagulation. This is because they are performed in different countries and years, so they cannot be homogeneous. However, the most frequent and concerning post-ERCP AE is PEP. The recent publication of a large RCT has made us hypothesize that Endocut is a risk factor for PEP, which corroborates the principles of electrosurgery [12, 27, 28, 29]. Theoretically, local edema due to the pronounced thermal injury from the coagulation modes could obstruct the pancreatic duct, favoring PEP. Our results confirm this assumption. Nevertheless, it is unclear whether associated measures, such as rectal NSAIDs, could further enhance the protective effect of pure cute or if moderate and severe pancreatitis could also be reduced.

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Immediate bleeding with the need for endoscopic intervention at the index ERCP seems to have a trend in favor of Endocut. This result corroborates the above mentioned meta-analyses [7, 8, 29]. Notably, however, the reported intraprocedural bleeding had no clinical repercussions, and all cases were controlled in the same procedure.

Delayed bleeding was also not different between groups. Some studies have suggested that increased intraprocedural bleeding might be a risk factor for delayed bleeding; however, the extensive series and our results did not corroborate this finding [15, 27, 29, 30]. We speculate that pure cute allows for a cleaner cut, which increases the chance of identifying and immediately treating bleeding vessels during ERCP. Ultimately, immediate hemostatic control would prevent delayed bleeding. Therefore, Endocut should not be considered a measure to prevent bleeding with clinical repercussions.

Some authors consider Endocut to be safer in terms of uncontrolled sphincterotomy (zipper cut) and sphincterotomy-related perforation [31, 32]. However, our results did not prove such a rationale. Regardless, one should note that pure cut must be used cautiously (quick steps on the pedal activating the electrosurgical unit) to prevent endoscopists from gaining control of the cut, as the generator does not interrupt the cutting cycle automatically [12, 27, 33]. Furthermore, zipper cut and perforation are strongly influenced by other technical factors, regarding the endoscopist experience, which should be considered.

Our study is not exempt from limitations, as the inclusion of abstracts made part of our analysis. However, we decided to include those studies as they provided all the essential information to fulfill our eligibility criteria, enabling our analysis. Another limitation is the lack of definition and differentiation between types of immediate bleeding, which was mitigated. tried to mitigate this by differentiating self-limited from bleeding with the need for endoscopic intervention. As well as the delayed bleeding follow-up, which was not mentioned in one of the three articles being analyzed in this variable (Ellahi et al), we agreed to consider seven days. Additionally, more than two decades separate the first and last eligible published study, and only the latest study employed the modern electrosurgical settings and generator for the Endocut mode [12, 32]. Futhermore, although the benefits of prophylactic NSAIDs for preventing PEP are well known, none of the included studies employed it [35, 36, 37]. Only one of the included studies used hyperhydration with Lactated Ringer’s solution as a preventive measure [34, 38]. Therefore, new studies are warranted to elucidate the effect of overlapping measures in the prevention of PEP. Also, the endoscopist experience influences the precision of biliary sphincterotomy, reflecting the incidence of adverse events. However, this data is not detailed in some of the studies [39].

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It is important to emphasize that the Endocut effect does not necessarily promote the coagulation effect between the cutting cycles. This term refers specifically to an automatically controlled pure cut with predetermined interruptions [12]. Starting at effect two and above effects, this modality includes coagulation modes between cutting cycles. All included studies used the equivalent to effect two or higher, reinforcing the role of thermal injury in PEP pathophysiology. Consequently, Endocut effect one is an option to use pure cut in a more controlled and safer manner [39].

In conclusion, based on the discussion, it is possible to decrease PEP incidence with a pure cut without increased bleeding with clinical repercussions.

Supplementary Material

All figures were generated by the programs mentioned in methods such as RevMan 5 software (all forest plots), risk of bias (Rob2), PRISMA guideline (both PRIMSA flow diagram and checklist) [17, 18, 20, 22, 40] .

References

1. Thaker AM, Mosko JD, Berzin TM. Post-endoscopic retrograde cholangiopancreatography pancreatitis. Gastroenterol Rep (Oxf). 2015 Feb;3(1):32-40. DOI: 10.1093/gastro/gou053

2. de Clemente Junior CC, Bernardo WM, Franzini TP, Luz GO, Dos Santos MEL, Cohen JM, et al. Comparison between endoscopic sphincterotomy vs endoscopic sphincterotomy associated with balloon dilation for removal of bile duct stones: A systematic review and meta-analysis based on randomized controlled trial. World J Gastrointest Endosc. 2018 Aug 16;10(8):130-144. DOI: 10.4253/wjge.v10.i8.130

3. Furuya CK, Sakai P, Marinho FRT, Otoch JP, Cheng S, Prudencio LL, et al. Papillary fistulotomy vs conventional cannulation for endoscopic biliary access: A prospective randomized trial. World J Gastroenterol. 2018 Apr 28;24(16):1803-1811. DOI: 10.3748/wjg.v24.i16.1803

4. Kouanda A, Bayudan A, Hussain A, Avila P, Kamal F, Hasan MK, et al. Current state of biliary cannulation techniques during endoscopic retrograde cholangiopancreatography (ERCP): International survey study. Endosc Int Open. 2023 Jun;11(6):E588-E598. DOI: 10.1055/a-1356-4542

5. Ak Ç, Aykut H, Pala E, Sayar S, Tarikçi Kiliç E, Adali G, et al. Post-ERCP Complication Analysis of an Experienced Center. Surg Laparosc Endosc Percutan Tech. 2022 Dec 1;32(6):707-713. DOI: 10.1097/SLE.0000000000001076

This article is protected by copyright. All rights reserved.

Accepted Manuscript

6. Williams EJ, Taylor S, Fairclough P, Hamlyn A, Logan RF, Martin D, et al. Risk factors for complication following ERCP; results of a large-scale, prospective multicenter study. Endoscopy. 2007 Sep;39(9):793-801. DOI: 10.1055/s-2007-966943

7. Andriulli A, Loperfido S, Napolitano G, Niro G, Valvano MR, Spirito F, et al. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. Am J Gastroenterol. 2007 Aug;102(8):1781-1788. DOI: 10.1111/j.1572-0241.2007.01279.x

8. Güitrón-Cantú A, Adalid-Martínez R, Gutiérrez-Bermúdez JA, Nieves-Rentería A, Alvarez-Valdés G. [Complications in diagnostic and therapeutic endoscopic cholangiopancreatography. Prospective study]. Rev Gastroenterol Mex. 2007;72(3):227-235.

9. Marsano LS. Principles of Electrosurgery [Internet]. [cited 27AD Sep]. Available from: http://louisville.edu/medicine/departments/medicine/dividions/gimedicine/physician-resources/lectures/procedures/electrocautery

10. Endoscopic submucosal dissection- principles and practice. New York: Springer; 2015. Pp. 75-84.

11. Ratani RS, Mills TN, Ainley CC, Swain CP. Electrophysical factors influencing endoscopic sphincterotomy. Gastrointest Endosc. 1999 Jan;49(1):43-52. DOI: 10.1016/S0016-5107(99)70219-4

12. Rey JF, Beilenhoff U, Neumann CS, Dumonceau JM. European Society of Gastrointestinal Endoscopy (ESGE) guideline: the use of electrosurgical units. Endoscopy. 2010 Sep;42(9):764-772. DOI: 10.1055/s-0030-1255560

13. Perini RF, Sadurski R, Cotton PB, Patel RS, Hawes RH, Cunningham JT. Post-sphincterotomy bleeding after the introduction of microprocessor-controlled electrosurgery: does the new technology make the difference. Gastrointest Endosc. 2005 Jan;61(1):53-57. DOI: 10.1016/S0016-5107(04)02653-6

14. Curtiss LE. High frequency currents in endoscopy: a review of principles and precautions. Gastrointest Endosc. 1973 Aug;20(1):9-12. DOI: 10.1016/S0016-5107(73)73726-9

15. Funari MP, Ribeiro IB, de Moura DTH et al. Adverse events after biliary sphincterotomy: Does the electric current mode make a difference? A systematic review and meta-analysis of randomized controlled trials. Clin Res Hepatol Gastroenterol. 2020 Oct;44(5):739-752. DOI: 10.1016/j.clinre.2019.12.007

16. Verma D, Kapadia A, Adler DG. Pure versus mixed electrosurgical current for endoscopic biliary sphincterotomy: a meta-analysis of adverse outcomes. Gastrointest Endosc. 2007 Aug;66(2):283-290. DOI: 10.1016/j.gie.2006.12.060

This article is protected by copyright. All rights reserved.

Accepted Manuscript

17. Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71. DOI: 10.1136/bmj.n71

18. PROSPERO [Internet]. York.ac.uk. 2019. Available from: https://www.crd.york.ac.uk/PROSPERO/

19. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. Cochrane.org.2019. Available from: https://www.training.cochrane.org/handbook

20. Review Manager (RevMan). Version 5. 4. 1. The Cochrane Collaboration, 21 09. 2020. Available at revman.cochrane.org.

21. Citation [Internet]. Gradepro.org. Available from: https://www.gradepro.org/terms/cite

22. Higgins JPT, Sterne JAC, Savović J, Page MJ, Hróbjartsson A, Boutron I, Reeves B, Eldridge S. A revised tool for assessing risk of bias in randomized trials In: Chandler J, McKenzie J, Boutron I, Welch V (editors). Cochrane Methods. *Cochrane Database of Systematic Reviews* 2016, Issue 10 (Suppl 1). dx.doi.org/10.1002/14651858.CD201601.

23. Cotton PB, Lehman G, Vennes J et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. Gastrointest Endosc. 1991;37(3):383-393. DOI: 10.1016/S0016-5107(91)70706-7

24. Cirocchi R, Kelly MD, Griffiths EA et al. A systematic review of the management and outcome of ERCP related duodenal perforations using a standardized classification system. Surgeon. 2017 Dec;15(6):379-387. DOI: 10.1016/j.surge.2017.06.005

25. Li DF, Yang MF, Chang X et al. Endocut Versus Conventional Blended Electrosurgical Current for Endoscopic Biliary Sphincterotomy: A Meta-Analysis of Complications. Dig Dis Sci. 2019 Aug;64(8):2088-2094. DOI: 10.1007/s10620-019-05504-7

26. Pereira Funari M, Ottoboni Brunaldi V, Mendonça Proença I et al. Pure Cut or Endocut for Biliary Sphincterotomy? A Multicenter Randomized Clinical Trial. Am J Gastroenterol. 2023 Oct 1;118(10):1871-1879. DOI: 10.14309/ajg.0000000000001307

27. Norton ID, Petersen BT, Bosco J et al. A randomized trial of endoscopic biliary sphincterotomy using pure-cut versus combined cut and coagulation waveforms. Clin Gastroenterol Hepatol. 2005 Oct;3(10):1029-1033. DOI: 10.1016/S1542-3565(05)00756-7

28. Tsang HC, Lam CS, Chu PW et al. A randomized controlled trial of auricular transcutaneous electrical nerve stimulation for managing posthysterectomy pain. Evid Based Complement Alternat Med. 2011;2011:276769. DOI: 10.1093/ecam/nep125

This article is protected by copyright. All rights reserved.

Accepted Manuscript

29. Freeman ML, Nelson DB, Sherman S et al. Complications of endoscopic biliary sphincterotomy. N Engl J Med. 1996 Sep 26;335(13):909-918. DOI: 10.1056/NEJM199609263351301

30. Köksal AŞ, Eminler AT, Parlak E. Biliary endoscopic sphincterotomy: Techniques and complications. World J Clin Cases. 2018 Dec 26;6(16):1073-1086. DOI: 10.12998/wjcc.v6.i16.1073

31. Testoni PA, Mariani A, Aabakken L et al. Papillary cannulation and sphincterotomy techniques at ERCP: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2016 Jul;48(7):657-683. DOI: 10.1055/s-0042-108689

32. Kim HJ, Kim MH, Kim DI et al. Endoscopic hemostasis in sphincterotomy-induced hemorrhage: its efficacy and safety. Endoscopy. 1999 Aug;31(6):431-436. DOI: 10.1055/s-1999-4

33. Serrano JPR, de Moura DTH, Bernardo WM et al. Nonsteroidal anti-inflammatory drugs versus placebo for post-endoscopic retrograde cholangiopancreatography pancreatitis: a systematic review and meta-analysis. Endosc Int Open. 2019 Apr;7(4):E477-E486. DOI: 10.1055/a-0851-4574

34. Puig I, Calvet X, Baylina M et al. How and when should NSAIDs be used for preventing post-ERCP pancreatitis? A systematic review and meta-analysis. PLoS One. 2014;9(3):e92922. DOI: 10.1371/journal.pone.0092922

35. Akshintala VS, Sperna Weiland CJ, Bhullar FA et al. Non-steroidal anti-inflammatory drugs, intravenous fluids, pancreatic stents, or their combinations for the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a systematic review and network meta-analysis. Lancet Gastroenterol Hepatol. 2021 Sep;6(9):733-742. DOI: 10.1016/S2468-1253(21)00130-0

36. Thanage R, Jain S, Chandnani S et al. Is the Combination of Rectal Diclofenac and Intravenous Ringer Lactate Superior to Individual Therapy for Prophylaxis of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis: A Prospective, Open-Label, Single-Center Randomized Trial. Pancreas. 2021 Sep 1;50(8):1236-1342. DOI: 10.1097/MPA.0000000000001723

37. Marín-Gabriel JC, Romito R, Guarner-Argente C et al. Use of electrosurgical units in the endoscopic resection of gastrointestinal tumors. Gastroenterol Hepatol. 2019 Oct;42(8):512-523. DOI: 10.1016/j.gastrohep.2019.06.004

38. Chandrasekhara V, Khashab MA, Muthusamy VR et al. Adverse events associated with ERCP. Gastrointest Endosc. 2017 Jan;85(1):32-47. DOI: 10.1016/j.gie.2016.06.019

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39. Jena A, Jain S, Sundaram S, Singh AK et al. Electrosurgical unit in GI endoscopy: the proper settings for practice. Expert Rev Gastroenterol Hepatol. 2023;17(8):825-835. DOI: 10.1080/17474124.2023.2013322
40. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366: l4898.

Legends

Figure 1- PRISMA Flow Diagram
Figure 2 - Forest plot for mild pancreatitis
Figure 3- Forest plot for moderate pancreatitis
Figure 4 - Forest plot for severe pancreatitis
Figure 5 - Forest plot for pancreatitis in general
Figure 6 - Forrest plot for immediate bleeding (no endoscopic intervention)
Figure 7 - Forrest plot for immediate bleeding (with endoscopic intervention)
Figure 8 - Forest plot for overall immediate bleeding
Figure 9 - Forrest plot for delayed bleeding
Table 1- Risk of Bias (Robs2)
Table 2- Details of the included studies
Table 3 - GRADEpro Guideline Development Tool

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Study	D1	D2	D3	D4	D5	Overall
Norton et al						
Kida et al						
Ellahi et al						
Funari et al						

Table 1- Rob 2

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STUDY	N	COMPARED GROUPS	ERCP INDICATION	ELECTROSURGICAL UNIT	AGE (MEAN)	GENDER (M/F)	OUTCOMES
Funari, 2023 (fully published artcle)	550	Endocut (278)	Choledocolithiasis, stenosis (benign and malignant), fistula, others	ERBE VIO 300 and ERBE VIO 3 Endocut I, effect 2, cutting duration 3, cutting interval 3	52,84	60%	**Pancreatitis**: 9 mild; 3 moderate; 0 severe; **Immediate bleeding:** 35 (total); **Immediate bleeding (E. I.):** 12 **Immediate bleeding (N.I.):** 23 **Delayed Bleeding:** 12 **Cholangitis**: 2 (total); **Perforation:** 0 (total);
		Pure cut (272)		WEM SS-200E pure cut 30-50 W (WEM/Medtronic, Minneapolis, Minnesota, USA) and ERBE ICC 200 (ERBE Elektromedizin, Tübingen, Germany) 3, 30-50 W		39%	**Pancreatitis:** 3 mild; 1 moderate; 0 severe; **Immediate bleeding:** 66 (total); **Immediate bleeding (E. I.):** 39 **Immediate bleeding (N.I.):** 27 **Delayed Bleeding**: 4 **Cholangitis:** 0 (total); **Perforation:** 0 (total);
Norton, 2005 (fully published article)	267	Endocut (134)	Choledocolithiasis, stenosis (benign and malignant), SOD, PSC	Erbe ICC200 (Erbe, Marietta, GA) 150-W	59 (19-99)	47%	**Pancreatitis:** 1 mild; 2 moderate, 0 severe. **Immediate bleeding:** 8 **Immediate bleeding (E. I.):** 4 **Immediate bleeding (N.I.):** 8 **Delayed Bleeding**: 0 **Perforation:** 0 (total)
		Pure cut (133)		Valleylab ForceEZ 60-W on the Low Coag-3 setting		51%	**Pancreatitis**: 1 mild; 0 moderate, 0 severe. **Immediate bleeding:** 35 **Immediate bleeding (E. I.):** 6 **Immediate bleeding (N.I.):** 35 **Delayed Bleeding**: 0 **Perforation:** 0 (total)
Kida, 2004 (abstract)	84	Endocut (41)	Choledocolithiasis, malignant strictures, others	No information	66,2	53%	**Pancreatitis:** 4 (total) **Immediate bleeding**: 13 **Immediate bleeding (E. I.):** 1 **Immediate bleeding (N.I.):** 12 **Perforation:** 0 (total)
		Pure cut (43)		No information		47%	**Pancreatitis:** 1 (total) **Immediate bleeding:** 28 **Immediate bleeding (E. I.):** 6 **Immediate bleeding (N.I.):** 22 **Perforation:** 0 (total)
Ellahi, 2001 (abstract)	86	Endocut (55)	Choledocolithiasis, SOD, Obstructive jaudice and pancreatitis	No information	NR	Unclear	**Pancreatitis**: 1 mild; 3 moderate; 1 severe; **Immediate bleeding:** 0 (total) **Cholangitis:** 1 (total) **Perforation**: 1 (total)
		Pure cut (31)		No information			**Pancreatitis**: 0 mild; 0 moderate; 0 severe; **Immediate bleeding:**0 (total) **Cholangitis:** 1 (total) **Perforation:** 0 (total)

Table 2- Details of the included studies

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pure cut	Endocut	Relative (95% CI)	Absolute (95% CI)		
Pancreatitis												
4	randomised trials	serious[a]	not serious	not serious	not serious	strong association all plausible residual confounding would reduce the demonstrated effect	28/507 (5.5%)	8/480 (1.7%)	not estimable	**40 fewer per 1.000** (from 60 fewer to 10 fewer)	⨁⨁⨁⨁ High	CRITICAL
Mild Pancreatitis												
4	randomised trials	serious[a]	serious[b]	serious[c]	serious[c]	strong association all plausible residual confounding would reduce the demonstrated effect	24/507 (4.7%)	9/480 (1.9%)	not estimable	**20 fewer per 1.000** (from 50 fewer to 10 more)	⨁⨁◯◯ Low	CRITICAL
Moderate pancreatitis												
4	randomised trials	serious[a]	not serious	not serious	serious[c]	strong association all plausible residual confounding would reduce the demonstrated effect	7/507 (1.4%)	1/480 (0.2%)	not estimable	**10 fewer per 1.000** (from 20 fewer to 0 fewer)	⨁⨁⨁⨁ High	IMPORTANT
Severe pancreatitis												
4	randomised trials	serious[a]	serious[b]	not serious	very serious[d]	strong association all plausible residual confounding would reduce the demonstrated effect	7/507 (1.4%)	1/480 (0.2%)	not estimable	**0 fewer per 1.000** (from 20 fewer to 10 more)	⨁⨁◯◯ Low	IMPORTANTE
Overall Immediate bleeding												
4	randomised trials	serious	very serious[e]	not serious	not serious	none	56/507 (11.0%)	129/480 (26.9%)	not estimable	**150 more per 1.000** (from 0 fewer to 290 more)	⨁◯◯◯ Very low	CRITICAL
Immediate bleeding (no endoscopic intervention)												

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pure cut	Endocut	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious[a, f]	very serious[e]	serious[g]	not serious	strong association	43/452 (9.5%)	84/449 (18.7%)	not estimable	**130 more per 1.000** (from 20 fewer to 290 more)	⨁◯◯◯ Very low	NOT IMPORTANT
Immediate bleeding (with endoscopic intervention)												
3	randomised trials	serious[a, f]	very serious[e]	not serious	serious[c]	none	17/452 (3.8%)	51/449 (11.4%)	not estimable	**70 more per 1.000** (from 0 fewer to 140 more)	⨁◯◯◯ Very low	IMPORTANT
Delayed Bleeding												
3	randomised trials	serious[a, f]	not serious	serious[f]	very serious[d]	strong association	13/466 (2.8%)	4/437 (0.9%)	not estimable	**10 fewer per 1.000** (from 50 fewer to 20 more)	⨁◯◯◯ Very low	CRITICAL
Perforation												
3	randomised trials	not serious	not serious	not serious	not serious	strong association all plausible residual confounding would suggest spurious effect, while no effect was observed	0/452 (0.0%)	0/134 (0.0%)	not estimable	**0 fewer per 1.000** (from 10 fewer to 10 fewer)	⨁⨁⨁⨁ High	CRITICAL
Zipper cut												
3	randomised trials	serious[a]	very serious[e]	not serious	not serious	strong association	0/452 (0.0%)	12/449 (2.7%)	not estimable	**30 more per 1.000** (from 90 fewer to 160 more)	⨁⨁◯◯ Low	IMPORTANT
Cholangitis												
2	randomised trials	serious	not serious	not serious	very serious[d]	all plausible residual confounding would suggest spurious effect, while no effect was observed	2/333 (0.6%)	1/303 (0.3%)	not estimable	**0 fewer per 1.000** (from 20 fewer to 10 more)	⨁⨁◯◯ Low	NOT IMPORTANT

Table 3- GRADE

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CI: confidence interval

Explanations

a. According RoB-2

b. 50% < I^2 < 75%

c. Ratio of confidence interval by standard deviation > 2

d. Ratio of confidence interval by standard deviation >3

e. i^2 >75%

f. There is a lack of information about the definition of bleeding (grades and time it happened)

g. There is a lack of information about the definition for bleeding

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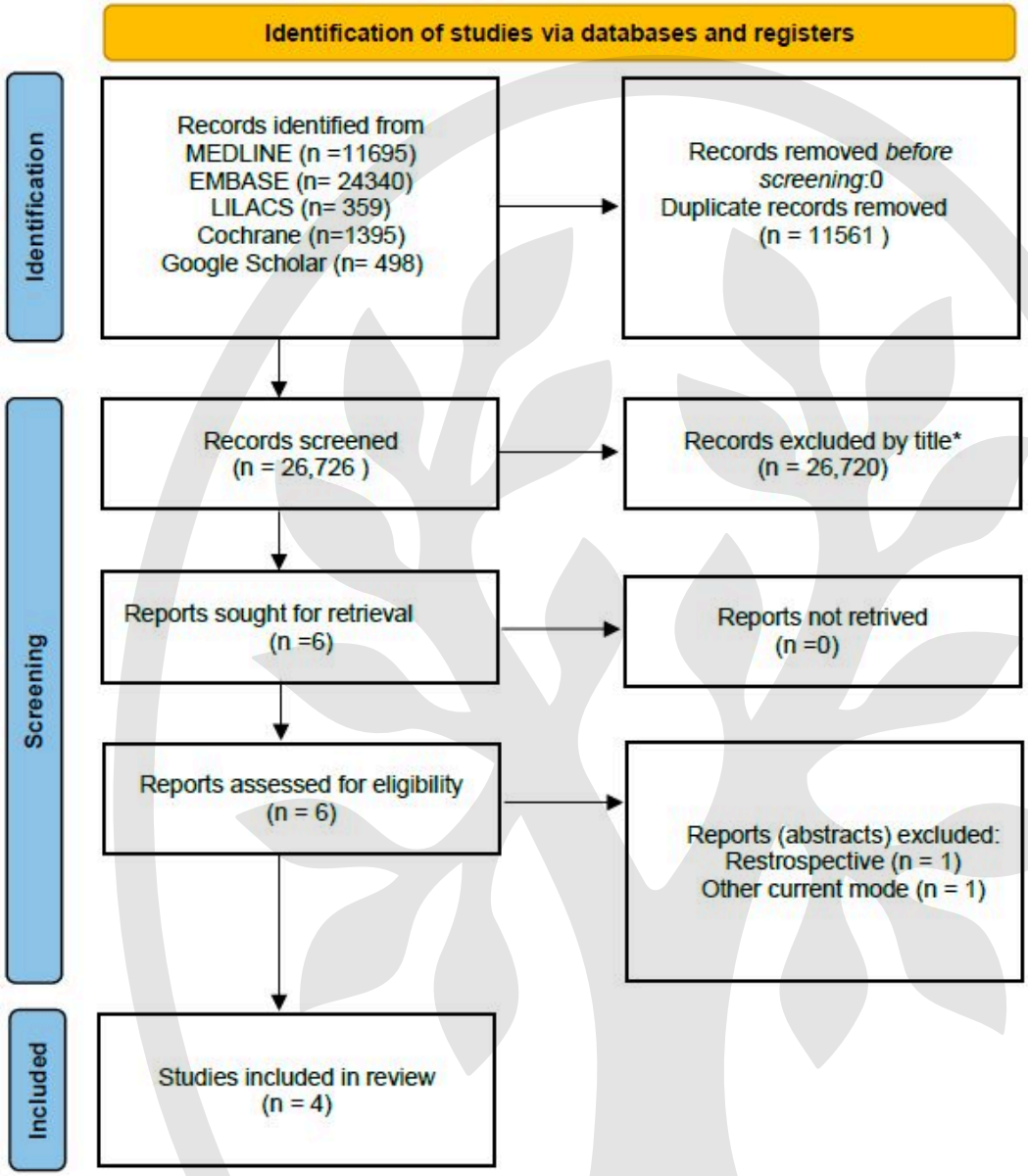
PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



*Excluded if the title didn't included the mesh terms described in Methods.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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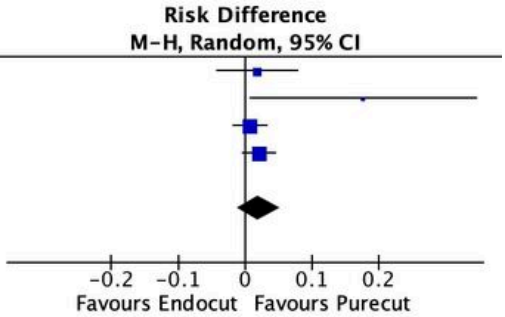
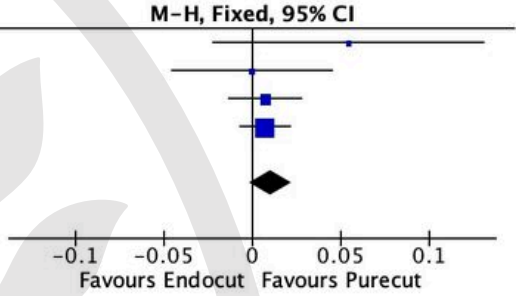
Study or Subgroup	Endocut Events	Total	Purecut Events	Total	Weight	Risk Difference M-H, Random, 95% CI	Year
Ellahi et al 2000	1	55	0	31	17.7%	0.02 [-0.04, 0.08]	2000
Kida et al 2004	12	41	5	43	3.2%	0.18 [0.01, 0.35]	2004
Norton et al 2015	2	133	1	134	39.1%	0.01 [-0.02, 0.03]	2015
Funari et al 2023	9	278	3	272	40.0%	0.02 [-0.00, 0.05]	2023
Total (95% CI)		**507**		**480**	**100.0%**	**0.02 [-0.01, 0.05]**	
Total events	24		9				

Heterogeneity: Tau² = 0.00; Chi² = 6.77, df = 3 (P = 0.08); I² = 56%
Test for overall effect: Z = 1.28 (P = 0.20)



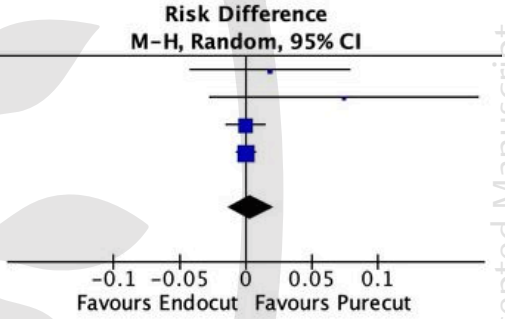
Study or Subgroup	Endocut Events	Total	Purecut Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI	Year
Ellahi et al 2000	3	55	0	31	8.1%	0.05 [-0.02, 0.13]	2000
Kida et al 2004	0	41	0	43	8.6%	0.00 [-0.05, 0.05]	2004
Norton et al 2015	1	133	0	134	27.2%	0.01 [-0.01, 0.03]	2015
Funari et al 2023	3	278	1	272	56.1%	0.01 [-0.01, 0.02]	2023
Total (95% CI)		**507**		**480**	**100.0%**	**0.01 [-0.00, 0.02]**	
Total events	7		1				

Heterogeneity: Chi² = 1.77, df = 3 (P = 0.62); I² = 0%
Test for overall effect: Z = 1.67 (P = 0.10)



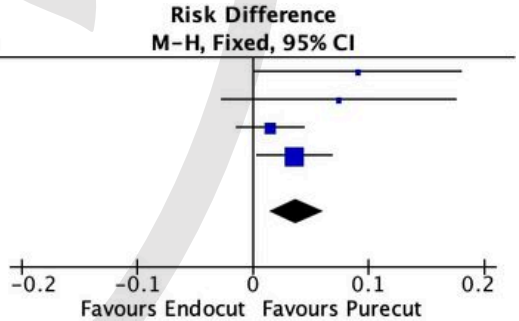
Study or Subgroup	Endocut Events	Total	Purecut Events	Total	Weight	Risk Difference M-H, Random, 95% CI	Year
Ellahi et al 2000	1	55	0	31	7.2%	0.02 [-0.04, 0.08]	2000
Kida et al 2004	4	41	1	43	2.8%	0.07 [-0.03, 0.18]	2004
Norton et al 2015	0	133	0	134	39.7%	0.00 [-0.01, 0.01]	2015
Funari et al 2023	0	278	0	272	50.3%	0.00 [-0.01, 0.01]	2023
Total (95% CI)		**507**		**480**	**100.0%**	**0.00 [-0.01, 0.02]**	
Total events	5		1				

Heterogeneity: Tau² = 0.00; Chi² = 7.56, df = 3 (P = 0.06); I² = 60%
Test for overall effect: Z = 0.38 (P = 0.70)



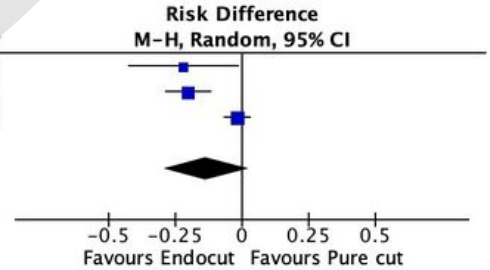
Study or Subgroup	Endocut Events	Total	Purecut Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI	Year
Ellahi et al 2000	5	55	0	31	8.1%	0.09 [0.00, 0.18]	2000
Kida et al 2004	4	41	1	43	8.6%	0.07 [-0.03, 0.18]	2004
Norton et al 2015	3	133	1	134	27.2%	0.02 [-0.01, 0.04]	2015
Funari et al 2023	16	278	6	272	56.1%	0.04 [0.00, 0.07]	2023
Total (95% CI)		**507**		**480**	**100.0%**	**0.04 [0.01, 0.06]**	
Total events	28		8				

Heterogeneity: Chi² = 4.21, df = 3 (P = 0.24); I² = 29%
Test for overall effect: Z = 3.23 (P = 0.001)



Study or Subgroup	Favour Endocut Events	Total	Favours Pure cut Events	Total	Weight	Risk Difference M-H, Random, 95% CI	Year
Kida et al 2004	12	41	22	43	24.2%	-0.22 [-0.42, -0.01]	2004
Norton et al 2015	8	133	35	134	36.5%	-0.20 [-0.29, -0.12]	2015
Funari et al 2023	23	278	27	272	39.3%	-0.02 [-0.06, 0.03]	2023
Total (95% CI)		**452**		**449**	**100.0%**	**-0.13 [-0.29, 0.02]**	
Total events	43		84				

Heterogeneity: Tau² = 0.02; Chi² = 17.12, df = 2 (P = 0.0002); I² = 88%
Test for overall effect: Z = 1.65 (P = 0.10)



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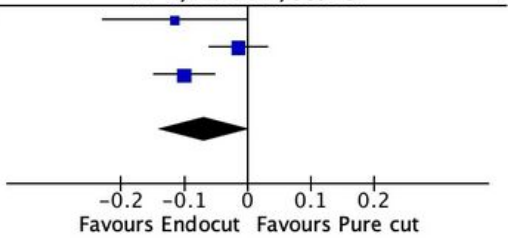
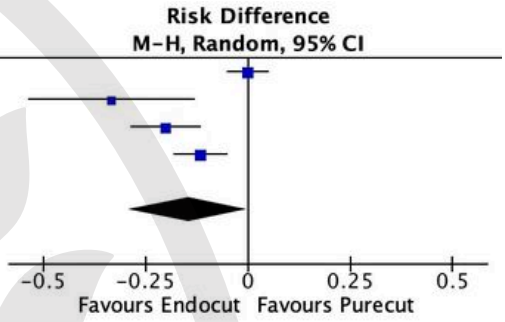
Study or Subgroup	Endocut Events	Total	Pure cut Events	Total	Weight	Risk Difference M-H, Random, 95% CI	Year
Kida et al 2004	1	41	6	43	21.8%	-0.12 [-0.23, -0.00]	2004
Norton et al 2015	4	133	6	134	39.4%	-0.01 [-0.06, 0.03]	2015
Funari et al 2023	12	278	39	272	38.8%	-0.10 [-0.15, -0.05]	2023
Total (95% CI)		**452**		**449**	**100.0%**	**-0.07 [-0.14, 0.00]**	
Total events	17		51				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.44$, df = 2 (P = 0.01); $I^2 = 76\%$
Test for overall effect: Z = 1.87 (P = 0.06)



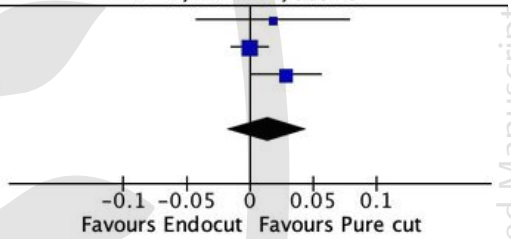
Study or Subgroup	Endocut Events	Total	Purecut Events	Total	Weight	Risk Difference M-H, Random, 95% CI	Year
Ellahi et al 2000	0	55	0	31	27.9%	0.00 [-0.05, 0.05]	2000
Kida et al 2004	13	41	28	43	18.5%	-0.33 [-0.54, -0.13]	2004
Norton et al 2015	8	133	35	134	26.3%	-0.20 [-0.29, -0.12]	2015
Funari et al 2023	35	278	66	272	27.3%	-0.12 [-0.18, -0.05]	2023
Total (95% CI)		**507**		**480**	**100.0%**	**-0.15 [-0.29, -0.00]**	
Total events	56		129				

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 40.37$, df = 3 (P < 0.00001); $I^2 = 93\%$
Test for overall effect: Z = 1.98 (P = 0.05)



Study or Subgroup	Endocut Events	Total	Pure cut Events	Total	Weight	Risk Difference M-H, Random, 95% CI	Year
Ellahi et al 2000	1	55	0	31	18.1%	0.02 [-0.04, 0.08]	2000
Norton et al 2015	0	133	0	134	45.5%	0.00 [-0.01, 0.01]	2015
Funari et al 2023	12	278	4	272	36.4%	0.03 [0.00, 0.06]	2023
Total (95% CI)		**466**		**437**	**100.0%**	**0.01 [-0.02, 0.05]**	
Total events	13		4				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.04$, df = 2 (P = 0.03); $I^2 = 72\%$
Test for overall effect: Z = 0.83 (P = 0.40)



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