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ORIGINAL ARTICLE

Adverse events after biliary sphincterotomy: Does the electric current mode make a difference? A systematic review and meta-analysis of randomized controlled trials

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KEYWORDS
Adverse events;
Electric current;
Sphincterotomy;
Endoscopic retrograde cholangiopancreatography;
ERCP;
Systematic review

Summary
Background: Biliary sphincterotomy is an invasive method that allows access to the bile ducts, however, this procedure is not exempt of complications. Studies in the literature indicate that the mode of electric current used for sphincterotomy may carry different incidences of adverse events such as pancreatitis, hemorrhage, perforation, and cholangitis.
Aim: To evaluate the safety of different modes of electrical current during biliary sphincterotomy based on incidence of adverse events.
Methods: We searched articles for this systematic review in Medline, EMBASE, Central Cochrane, Lilacs, and gray literature from inception to September 2019. Data from studies describing different types of electric current were meta-analyzed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The following electric current modalities were evaluated: endocut, blend, pure cut, pure cut followed by blend, monopolar, and bipolar.

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Results: A total of 1791 patients from 11 randomized clinical trials evaluating the following comparisons: 1. Endocut vs Blend: No statistical difference in the incidence of bleeding (7% vs 13.4%; RD: −0.11 [−0.31, 0.08], $P = 0.27$, $I^2 = 86\%$), pancreatitis (4.4% vs 3.5%; RD: 0.01 [−0.03, 0.04], $P = 0.62$, $I^2 = 48\%$) and perforation (absence of cases in both arms). 2. Endocut vs Pure cut: Higher incidence of mild bleeding (without drop in hemoglobin levels, clinical repercussion or need for endoscopic intervention) in the pure cut group (9.2% vs 28.8%; RD: −0.19 [−0.27, −0.12], $P < 0.00001$, $I^2 = 0\%$). No statistical difference regarding pancreatitis (5.2% vs 0.9%; RD: 0.05 [−0.01, 0.11], $P = 0.12$, $I^2 = 57\%$), perforation (0.4% vs 0%; RD: 0.00 [−0.01, 0.02], $P = 0.7$, $I^2 = 0\%$) or cholangitis (1.8% vs 3.2%; RD: −0.01 [−0.09, 0.06], $P = 0,7$). 3. Pure cut vs blend: higher incidence of mild bleeding in the pure cut group (40.4% vs 16.7%; RD: 0.24 [0.15, 0.33], $P < 0.00001$, $I^2 = 0\%$). No statistical difference concerning incidence of pancreatitis or cholangitis. 4. Pure cut vs Pure cut followed by Blend: No statistical difference regarding incidence of bleeding (22.5% vs 11.7%; RD: −0.10 [−0.24, 0.04], $P = 0.18$, $I^2 = 61\%$) and pancreatitis (8.9% vs 14.8%; RD 0.06 [−0.02, 0.13], $P = 0.12$, $I^2 = 0\%$). 5. Blend vs pure cut followed by blend: no statistical difference regarding incidence of bleeding and pancreatitis (11.3% vs 10.4%; RD −0.01 [−0.11, 0.09], $P = 0.82$, $I^2 = 0\%$). 6. Monopolar vs bipolar: higher incidence of pancreatitis in the monopolar mode group (12% vs 0%; RD 0.12 [0.02, 0.22], $P = 0.01$).

Conclusion: Pure cut carries higher incidences of mild bleeding compared to endocut and blend. However, this modality might present a lower incidence of pancreatitis. The monopolar mode elicits higher rates of pancreatitis in comparison with the bipolar mode. There is no difference in incidence of cholangitis or perforation between different types of electric current. There is a lack of evidence in the literature to recommend one method over the others, therefore new studies are warranted. As there is no perfect electric current mode, the choice in clinical practice must be based on the patient risk factors.

Introduction

As minimally invasive medicine advances, ERCP associated with biliary sphincterotomy has been increasingly used in medical practice. However, this procedure is associated with significant complications (4 to 5% of cases) such as pancreatitis, bleeding, perforation, cholangitis, and even death (0.02 to 0.4%) [1—8]. Thus, many studies have aimed to better understand these adverse events and to characterize their risk factors, providing measures to avoid them.

Sherman et al. [9] were among the pioneers to correlate incidence of complications with electric current mode used during sphincterotomy. Since then, several studies have been conducted to better understand the subject [7,10—13].

The main modes of electric current are coagulation and pure cut. The coagulation mode has a low frequency of intermittent high voltage waves, reaching temperatures between 60 and 100 °C, so that the energy is dissipated by the tissues, causing cellular dehydration, tissue contraction, and consequently, more adjacent tissue injury. For these reasons, this modality would be associated with a higher incidence of pancreatitis, but with less bleeding. The pure cut mode works with high frequency continuous waves and lower voltage, causing intense and abrupt heating (temperatures above 100 °C). The energy is dissipated as steam (smoke) without propagating through the tissues: the cells vaporize and lose contact with the electrode, which results in cellular lysis and less adjacent tissue damage. Thus, pure cut would be associated with a lower incidence of pancreatitis, but with less coagulation power [10,11,13—17].

In order to conciliate the benefits of the two modes of current, mixed current modalities were developed: endocut and blend. The endocut mode automatically switches between the two types of electric current (pure cut and coagulation). The ratio of time between current modes is controllable through the different modes of the endocut (endocut 1, 2, and 3). On the other hand, the blend mode uses an intermediate wave frequency between cut and coagulation (blends) during millisecond intervals between the cutting waves (time for the energy to dissipate as heat through the tissue, causing the coagulation effect). In this mode there is also the possibility to control each type of proportion effect (the higher the number of the blend, the greater the coagulation power) [10,11,13—17].

The most widely used modes to perform sphincterotomy are endocut and pure cut; however, there is no concrete evidence to evaluate which mode would be the safest and most effective modality. Thus, the present study critically evaluates the studies on this subject, aiming to help the endoscopist's decision to reduce the incidence of adverse events.

Materials and Methods

Protocol and registration

This study was performed according to PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) and registered in PROSPERO (International Prospective Register of Systematic Reviews) under the register CRD42018109713 [18].

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Eligibility criteria

Types of studies: Only randomized clinical trials (RCT) with the necessary data available from the results and methods and that, compared different modes of electric current used during endoscopic biliary sphincterotomy were included irrespective of language or date of publication.

Types of participants: patients older than 18 years who underwent biliary sphincterotomy randomized to different modes of electrical current.

Exclusion criteria: patients with alterations in endoscopic access to the biliary tract, such as postoperative gastrectomy with reconstruction in Billroth II or Roux-en-Y. Studies that evaluated pancreatic sphincterotomy.

Search strategy, study selection and data collection process

Two independent authors identified records in the following electronic databases: Medline, Scopus, Embase, Central, Cinahl and Lilacs. Search strategies were performed from inception through September 2019. All relevant articles irrespective of language, year of publication, type of publication, or publication status were included. Titles and abstracts of all potentially relevant studies were screened for eligibility. Duplicates were removed. If necessary, we accessed complementary and supplemental information in the research protocols of the studies available on the online registration platforms (for example, Clinical Trials or PROSPERO).

Reference lists of studies of interest were manually reviewed for additional articles by cross checking bibliographies. Two reviewers (MPF and IBR) independently screened titles and abstracts of all articles according to predefined inclusion and exclusion criteria as described above. Any differences were resolved by mutual agreement and in consultation with a third reviewer (DTHM). The researchers used Excel spreadsheets to extract the data of the following dichotomous outcomes: pancreatitis, bleeding, perforation, cholangitis, and hyperamylasemia.

Search

The search strategy for Medline (Pubmed) was: (((((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 current OR electric* OR Thermocoagulation OR Galvanocautery OR Diathermy OR Fulguration OR vio 200 OR vio 300 OR ERBE OR valley lab OR valleylab OR WEM OR blend OR current OR electrocautery OR cautery OR insulation OR insulated OR coagulation OR endocut OR waves)))))).

We used simplified strategies derived from the one above for the remaining databases as follows: Embase: (papillotomy OR sphincterotomy OR cholangiopancreatography OR ercp) AND (electrosurg* OR knife OR electric* OR thermocoagulation OR galvanocautery OR diathermy OR fulguration OR cut OR ''vio 200'' OR ''vio 300'' OR erbe OR ''valley lab'' OR valleylab OR wem OR blend OR current OR electrocautery OR cautery OR insulation OR insulated OR coagulation OR endocut OR waves); Central Cochrane: (papillotomy OR sphincterotomy OR cholangiopancreatography OR ercp) AND (electrosurg* OR knife OR electric* OR thermocoagulation OR galvanocautery OR diathermy OR fulguration OR cut OR ''vio 200'' OR ''vio 300'' OR erbe OR ''valley lab'' OR valleylab OR wem OR blend OR current OR electrocautery OR cautery OR insulation OR insulated OR coagulation OR endocut OR waves) and Lilacs/Bireme: (papillotomy OR sphincterotomy OR cholangiopancreatography OR ercp) AND (electrosurg$ OR knife OR electric$ OR thermocoagulation OR galvanocautery OR diathermy OR fulguration OR cut OR ''vio 200'' OR ''vio 300'' OR erbe OR ''valley lab'' OR valleylab OR wem OR blend OR current OR electrocautery OR cautery OR insulation OR insulated OR coagulation OR endocut OR waves).

Data analysis

We used RevMan 5 software (Review Manager version 5.3.5 — Cochrane Collaboration Copyright © 2014) for the meta-analysis and calculation of absolute risk difference.

For dichotomous variables, the risk difference was determined by calculating the number of events and sample size of each group using the Mantel—Haenszel test. Statistically we considered results with a 95% confidence interval (CI) and $P < 0.05$. Results of the meta-analysis were expressed as a forest plot.

Heterogeneity among studies was quantified using the Higgins test (I^2). We used the fixed effect for $I^2 < 50\%$ (low heterogeneity). If $I^2 > 50\%$ (high heterogeneity), we performed sensitivity analysis through a funnel plot to identify possible outliers. If after exclusion the sample became homogeneous, the studies were permanently excluded (considered true outliers) and the fixed model was used. In cases where there was no outlier or heterogeneity remained high after the outliers were excluded, we used random effect to reduce the impact of heterogeneity on the final result.

Methodology quality and risk of bias in individual studies

The biases of selected RCTs were assessed by the Cochrane Risk of Bias Tool (CRBT) [19]. Study quality was assessed for patient selection, comparability of the two study groups, and outcome measures used. We applied the CRBT, assessing each RCT for method of randomization and allocation concealment (selection bias), blinding participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), outcome, prognostic factors, intention to treat analysis, sample size calculation and selective reporting.

Overall quality of each outcome analysis and its respective RCTs was assessed comprehensively using GRADE standards, through GRADEpro software for guideline development tools (McMaster University, 2015, Evidence Prime, Inc., Ontario, Canada) [20]. The quality of a body of evidence considers five factors regarding study limitations: risk

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of bias, inconsistency, indirectness, imprecision and publication bias. Other considerations as a sixth limitation factor could be included if present. Overall quality of the evidence for each outcome (certainty) was a pooled result of the assessments in the above domains and was graded as very low, low, moderate or high.

Bias assessment using CRBT and the GRADE analysis were applied by two independent reviewers. In cases of disagreement, a third reviewer was consulted.

Heterogeneity of the bleeding definitions

Since the definitions regarding bleeding stratification were heterogeneous amongst the studies, we made an effort to standardize them. For this, we considered mild bleeding: more than expected bleeding during sphincterotomy, however, without need for endoscopic intervention or clinical repercussion. Moderate bleeding: need for endoscopic intervention at the time of sphincterotomy or late manifestation with fall of hematimetric levels and melena. Severe bleeding: clinical repercussion requiring blood transfusion and/or subsequent therapeutic procedures.

Risk of bias

Table S2 summarizes the bias assessment using the Cochrane Risk of Bias Tool (CRBT).

Results

We found 9812 records from Medline, 5074 from Embase, 315 from Central Cochrane and 53 from Lilacs/Bireme, totalling 15,254 records from all databases. After duplicates removal, 12,282 records remained and were evaluated by title and abstract (Fig. 1).

The full texts of the remaining 15 records were examined and four were rejected because they were retrospective: one for not being randomized, and two because they were animal studies [11,12,21–24]. Thus, we included 11 articles for the final analysis [13,14,25–33]. Table S1 exposes the selected studies, their respective features, such as the electric current modes involved, and outcomes.

Results by outcomes

Endocut vs blend

Pancreatitis

Two articles [13,27] were included, totaling 460 patients. There was no difference regarding the incidence of pancreatitis in general (RD: 0.01 [−0.03, 0.04], $P = 0.62$, $I^2 = 48\%$) (Fig. 2) and its subgroups (Fig. 2). We used random effect for mild pancreatitis due to high heterogeneity ($I^2 = 57\%$).

The GRADEpro tool shows moderate level of certainty determined by imprecision (power < 80%) (Table S3).

Bleeding

Two RCTs [13,27] totaling 460 patients were included. Individually, in both studies, the incidence of mild bleeding (without clinical repercussion, need for endoscopic intervention, or blood transfusion) was higher in the blend group. However, after grouping in the meta-analysis, this difference had no statistical significance (RD: −0.11 [−0.31, 0.08], $P = 0.27$, $I^2 = 86\%$) (Fig. 3), denoting absence of difference between the methods. The random effect in the subgroup of mild bleeding and total bleeding was used because of the high heterogeneity ($I^2 = 86\%$ in both).

There were no cases of moderate or severe bleeding in this analysis.

GRADEpro tool revealed a very low level of evidence from imprecision (power < 80%) and inconsistency ($I^2 > 75\%$) (Table S3).

Perforation

There was no case of perforation in any of the groups (total of 460 patients) [13,27].

The GRADEpro tool revealed a moderate level of evidence due to imprecision (power < 80%) (Table S3).

Endocut vs pure cut

Pancreatitis

A total of 437 patients from 3 RCTs [28,29,32] were included. The 3 studies individually presented a higher incidence of pancreatitis in the endocut group. However, synthesis of the results showed no significant difference (RD: 0.05 [−0.01, 0.11], $P = 0.12$, $I^2 = 57\%$) (Fig. 4). Due to the high heterogeneity and absence of outlier studies, we used random effect.

From the 3 previous articles [28,29,32], two (total of 353 patients) stratified by severity of pancreatitis, allowing subgroup analysis. There was no statistical difference for the subgroups mild (RD: 0.01 [−0.01, 0.03], $P = 0.42$, $I^2 = 0\%$), moderate (RD: 0.02 [−0.01, 0.04], $P = 0.14$, $I^2 = 48\%$), or severe pancreatitis (RD: 0.00 [−0.01, 0.02], $P = 0.65$, $I^2 = 0\%$).

The GRADEpro tool revealed a very low level of evidence from imprecision (power < 80%), high risk of bias individually by the CRBT, and high heterogeneity ($I^2 = 57\%$) (Table S4).

Bleeding

The initial analysis included 3 studies [28,29,32] (437 patients) revealing less bleeding with the endocut mode (RD: −0.19 [−0.25, −0.12], $P < 0.00001$, $I^2 = 96\%$). The funnel plot revealed an outlier [32], which was excluded, allowing an analysis with low heterogeneity ($I^2 = 34\%$). Therefore, 2 articles totaling 351 patients were analyzed [28,29]. The analysis remained favorable to the endocut (RD: −0.23 [−0.31, −0.15], $P < 0.00001$, $I^2 = 34\%$).

There was a higher incidence of bleeding in the pure cut group. Two studies described the severity of bleeding, allowing subgroup analysis. There was a higher incidence of only mild bleeding in the pure cut group in both studies (RD: −0.19 [−0.27, −0.12], $P < 0.00001$, $I^2 = 0\%$) (Fig. 5) and absence of difference for moderate (RD: −0.05 [−0.15, 0.05], $P = 0.3$, $I^2 = 64\%$) or severe bleeding (RD: 0.00 [−0.02, 0.02], $P = 1$, $I^2 = 0\%$). We used random effect for moderate bleeding due to high heterogeneity.

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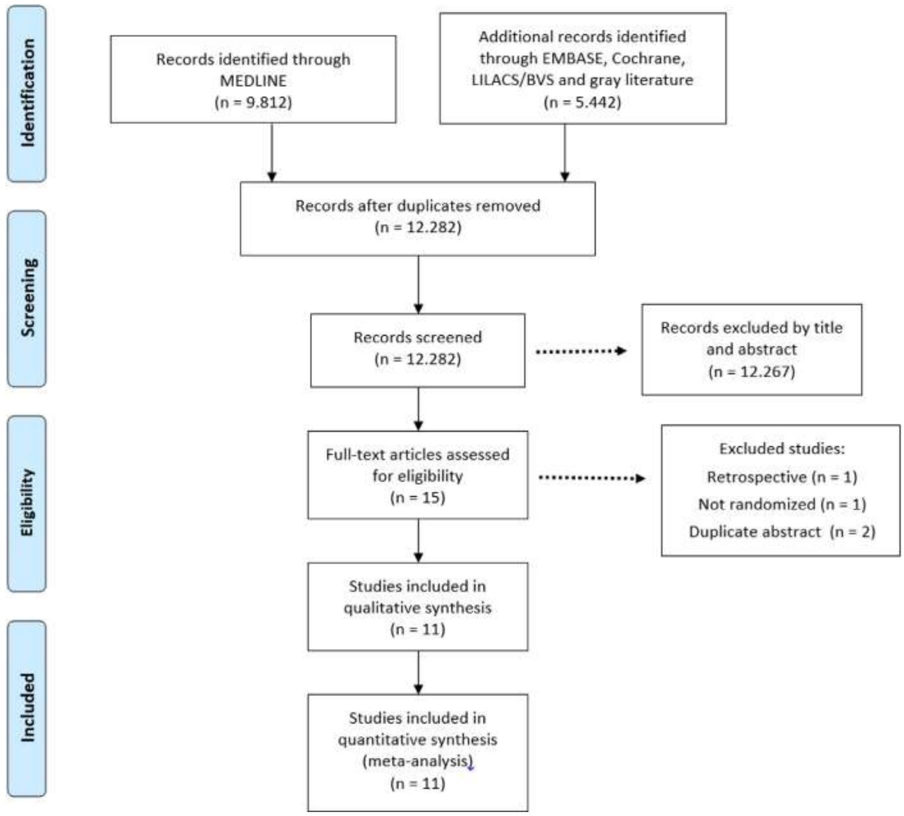

Figure 1 PRISMA Flow diagram of included and excluded clinical trials.

The GRADEpro tool revealed moderate level of evidence due to the high risk of individual study bias at the CRBT (Table S4).

Hyperamylasemia:

Only 1 study [29] (84 patients) described this outcome. There were more cases of hyperamylasemia in the endo-cut group (12/41= 29.3%) than in the pure cut group (5/43= 11.6%) with statistical difference in this individual study (RD: 0.18 [0.01, 0.35], $P = 0.04$).

Cholangitis

Analysis of only one article [32], with a total of 86 patients, revealed one event in each group (RD: −0.01 [−0.09, 0.06], $P = 0.7$).

Perforation

Analysis of 437 patients from 3 RCTs [28,29,32] demonstrated absence of difference between groups (RD: 0.00 [−0.01, 0.02], $P = 0.7$, $I^2 = 0\%$).

The GRADEpro tool revealed a low level of evidence for hyperamylasemia, cholangitis, and perforation from imprecision (power < 80%) and high risk of individual work bias by CRBT (Table S4).

Pure cut vs blend

Pancreatitis

Four articles were analyzed totaling 572 patients [14,25,30,31]. There were more episodes of mild and moderate pancreatitis in the blend group. However, the meta-analysis synthesis showed no significant difference between groups (RD: −0.03 [−0.07, 0.01], $P = 0.17$, $I^2 = 32\%$) (Fig. 6).

A trend was observed for higher incidence of mild pancreatitis in the blend group (RD: −0.03 [−0.07, 0.00], $P = 0.08$, $I^2 = 33\%$;), but without statistical difference. There was no difference for moderate (RD: −0.01 [−0.03, 0.01], $P = 0.38$, $I^2 = 0\%$) and severe pancreatitis (RD: −0.00 [−0.01, 0.02], $P = 0.68$, $I^2 = 0\%$) (Fig. 7).

The GRADEpro tool revealed a low level of evidence from imprecision (power < 80%) and high risk of individual work bias by the CRBT (Table S5).

Bleeding

The initial bleeding analysis involved 3 studies [14,30,31] with 540 patients, which showed fewer adverse events with

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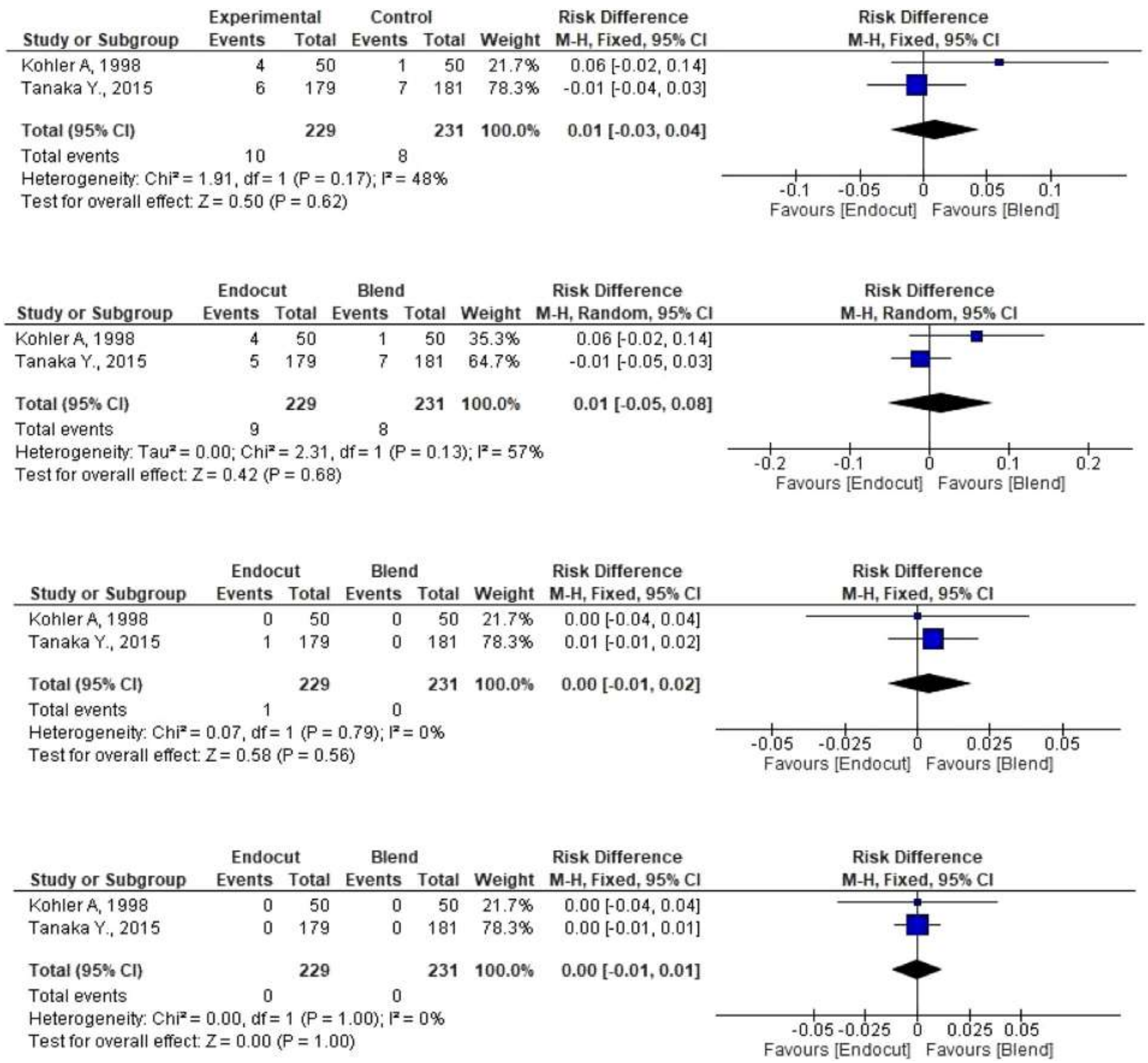

Figure 2 Pancreatitis in general, mild, moderate and severe pancreatitis (Endocut vs Blend).

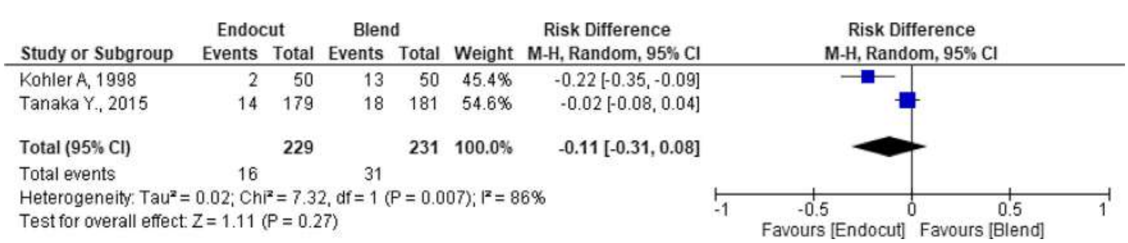

Figure 3 Bleeding in general (Endocut vs Blend).

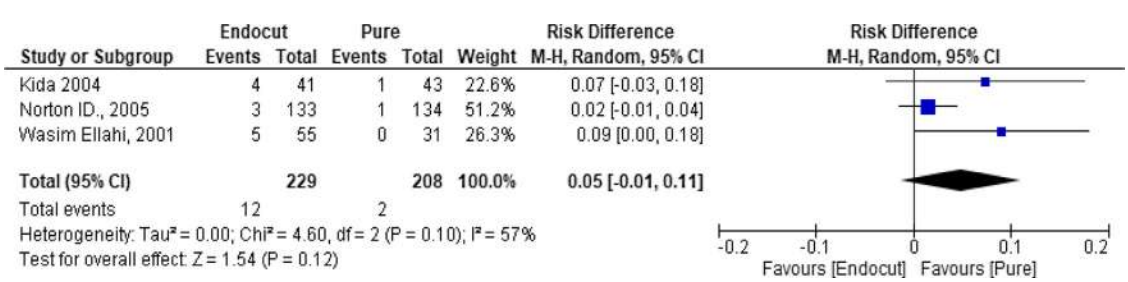

Figure 4 Pancreatitis in general (Endocut vs Pure cut).

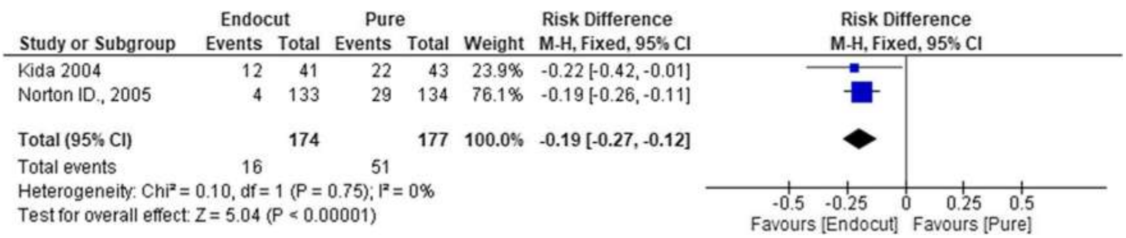

Figure 5 Mild bleeding (Endocut vs Pure cut).

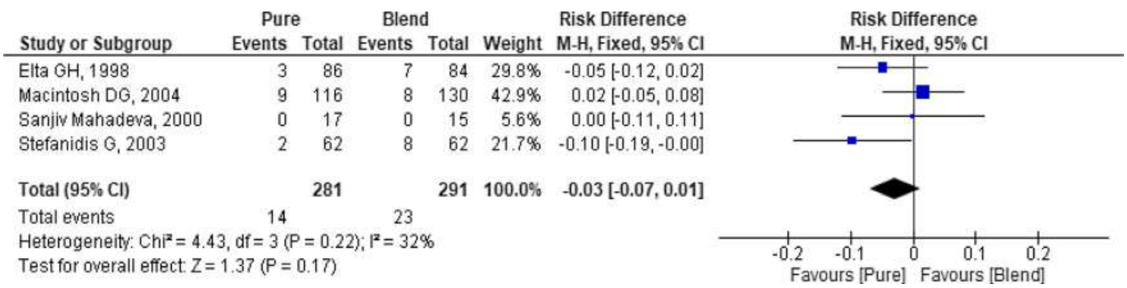

Figure 6 Pancreatitis in general (Pure cut vs Blend).

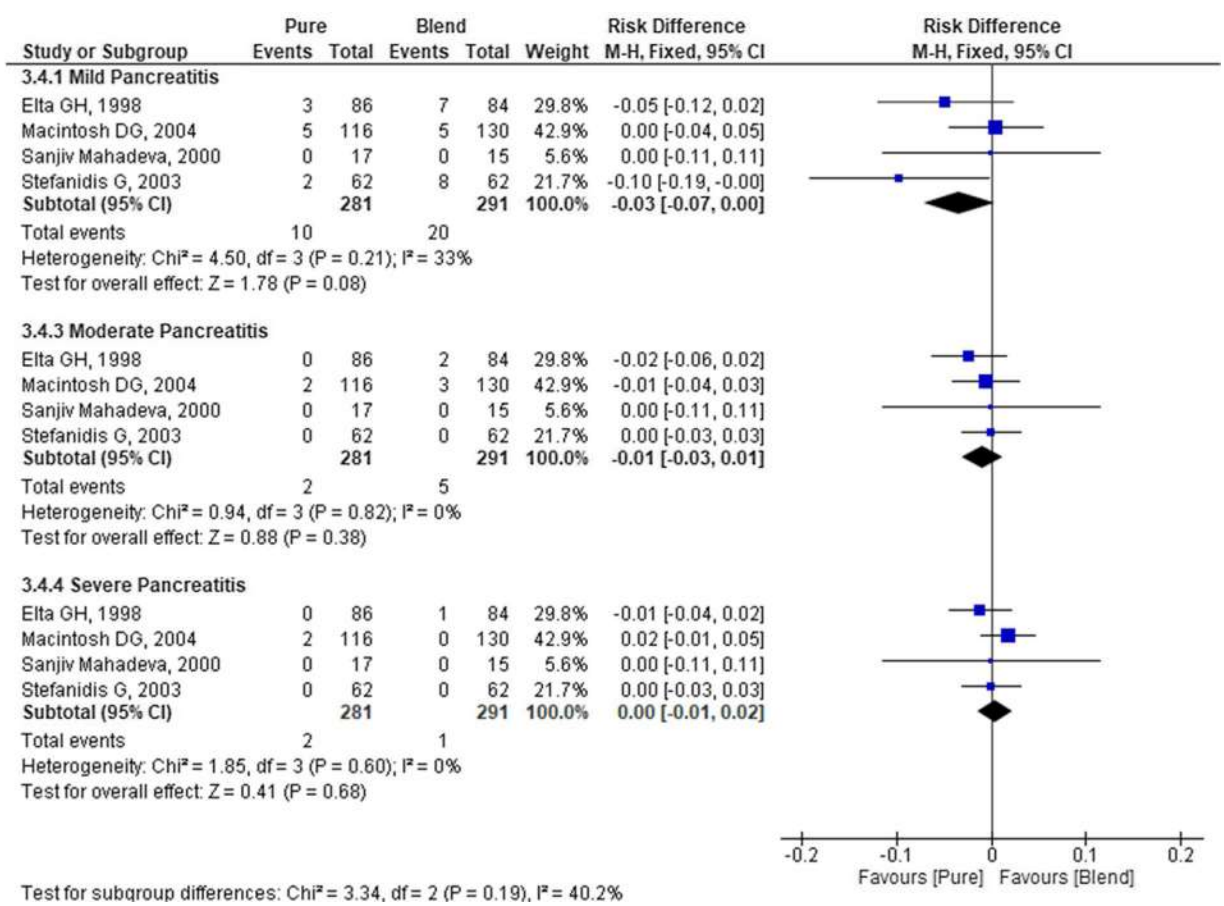

Figure 7 Mild, moderate and severe pancreatitis (Pure cut vs Blend).

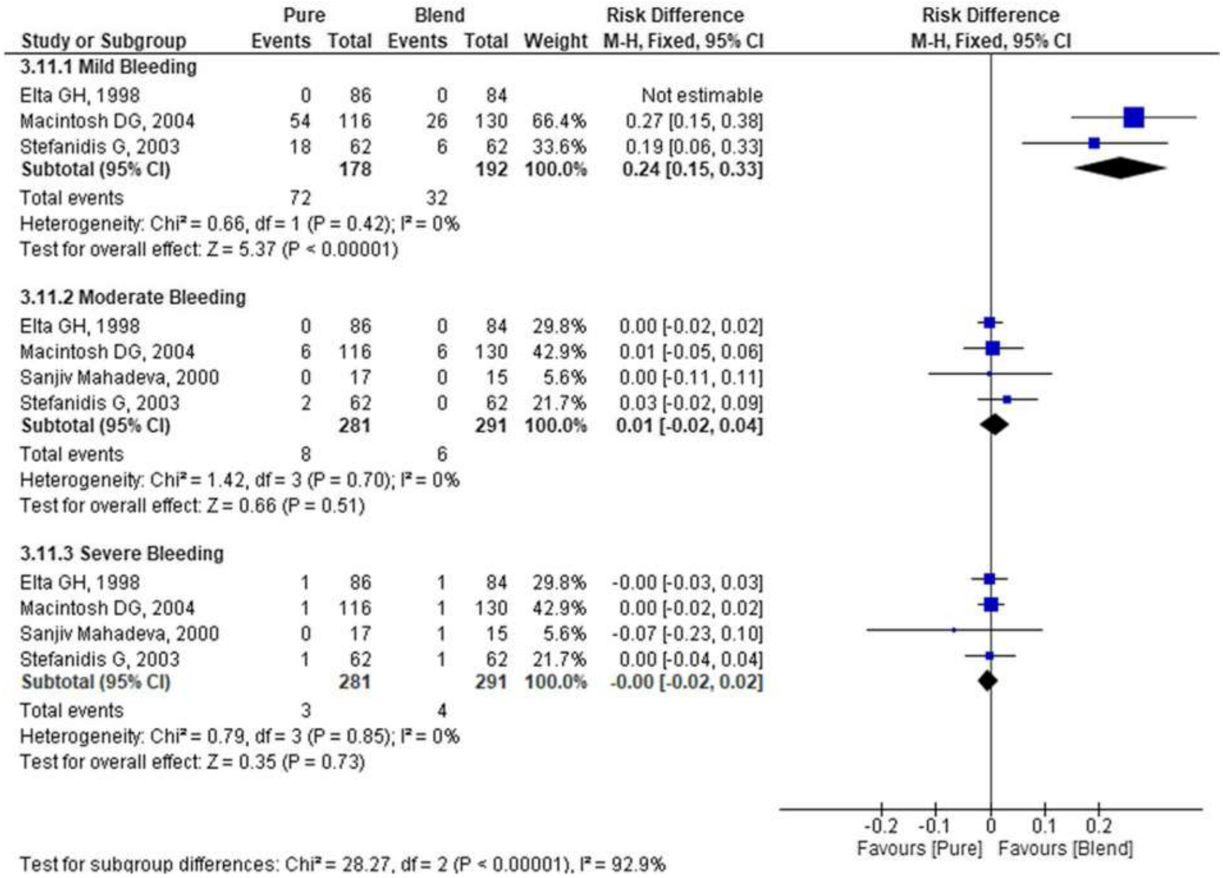

Figure 8 Mild, moderate and severe bleeding (Pure cut vs Blend).

blend mode (RD: 0.18 [0.11, 0.24], $P < 0.00001$, $I^2 = 98\%$). The funnel plot revealed an outlier [14], which was excluded, allowing an analysis with low heterogeneity ($I^2 = 0\%$). Thus, the analysis of the remainder two articles[30,31] (370 patients) was favorable to the blend modality (RD: 0.26 [0.61, 0.35], $P < 0.00001$, $I^2 = 0\%$). This difference occurs due to the subgroup of mild bleeds (RD: 0.24 [0.15, 0.33], $P < 0.00001$, $I^2 = 0\%$) (Fig. 8).

A third study [25] described moderate and severe bleeding, allowing its inclusion in the analysis of these subgroups. Therefore, in the analysis of 3 articles (572 patients), there was no difference for moderate (RD: 0.01 [−0.02, 0.04], $P = 0.51$, $I^2 = 0\%$) or severe bleeding (RD: −0.00 [−0.02, 0.02], $P = 0.73$, $I^2 = 0\%$) (Fig. 8).

The GRADEpro tool revealed a high level of evidence (Table S5).

Hyperamylasemia

Two studies evaluated hyperamylasemia, totaling 156 patients [25,31]. However, one study [31] only describes the mean values after 12 and 24 h of the procedure. This study revealed 150 (12 h) — 100U/L (24 h) using pure cut, and 475 (12 h) — 150U/L (24 h) in the blend group. Only Sanjiv et al. [25] reports individual dichotomous results, showing a similar incidence of hyperamylasemia between groups (pure cut: 1/17 vs blend 1/15).

Cholangitis

Only Elta et al. [14] assessed this complication (170 patients). There was only one event in the group that used the blend mode (no statistical significance: $p = 0.47$).

The GRADEpro tool revealed a low level of evidence due to the imprecision (power < 80%) and high risk of labor bias by the CRBT (Table S5).

Pure cut followed by blend vs pure cut

Pancreatitis

A total of 3 articles [25,31,33] were analyzed, totaling 301 patients. The 3 studies individually, showed more episodes of pancreatitis in the blend mode group. However, the meta-analysis synthesis showed no significant difference (RD: 0.06 [−0.02, 0.13], $p = 0.12$, $I^2 = 0\%$) (Fig. 9).

There was no statistically significant difference for mild (RD: 0.04 [−0.02, 0.10], $P = 0.15$, $I^2 = 23\%$), moderate (RD: 0.00 [−0.04, 0.05], $P = 0.91$, $I^2 = 0\%$), or severe pancreatitis (RD: 0.01 [−0.02, 0.04], $P = 0.45$, $I^2 = 0\%$).

The GRADEpro tool revealed a low level of evidence from imprecision (power < 80%) and high risk of individual work bias by the CRBT (Table S5).

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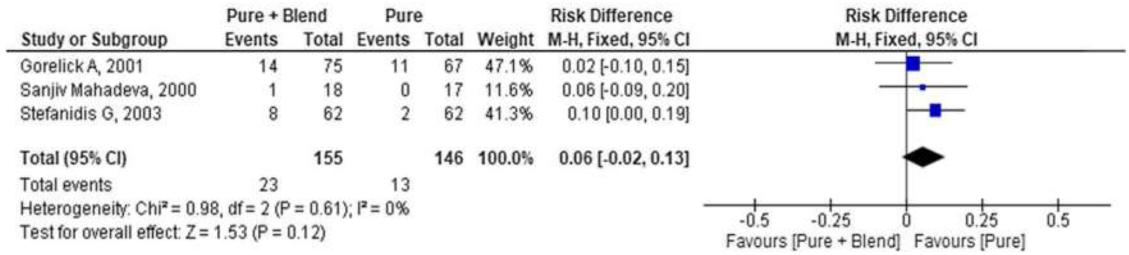

Figure 9 Pancreatitis in general (Pure cut followed by blend vs Pure cut).

Bleeding

Two studies [31,33] totaling 266 patients were analyzed. Both articles individually showed a higher incidence of bleeding in the pure cut group. However, the meta-analysis synthesis showed no significant difference between groups (RD: −0.10 [−0.24, 0.04], $P = 0.18$, $I^2 = 61\%$) (Fig. 10). Due to high heterogeneity, we used the random effect.

There was no statistically significant difference for mild bleeds (RD: −0.06 [−0.23, 0.11], $P = 0.49$, $I^2 = 77\%$). We used random effect due to high heterogeneity.

A third study [25] described moderate and severe bleeding, allowing its inclusion in the analysis of these subgroups (3 articles totalling 301 patients). There was no difference in incidence of moderate (RD: −0.03 [−0.06, 0.01], $P = 0.13$, $I^2 = 0\%$) or severe bleeds (RD: −0.01 [−0.04, 0.02], $P = 0.64$, $I^2 = 0\%$).

The GRADEpro tool revealed a low level of evidence from imprecision (power < 80%) and high risk of individual work bias by the CRBT (Table S5).

Hyperamylasemia

Two studies evaluated hyperamylasemia (159 patients). Stefanidis et al. [31], however, only describes the mean values after 12 and 24 h of the procedure. Pure cut group: 150 (12 h) — 100U/L (24 h) vs Pure cut + Blend: 600 (12 h)—150U/L (24 h).

Sanjiv et al. [25] presents dichotomous results with a similar incidence of hyperamylasemia between groups (pure cut: 1/17 vs Pure + blend 0/18).

Pure cut followed by blend vs blend

Pancreatitis

We analyzed 2 articles [25,31] totalling 157 patients. There was no statistically significant difference in incidence of pancreatitis in general (RD: −0.01 [−0.11, 0.09], $P = 0.82$, $I^2 = 0\%$), nor in the subgroups of mild (RD: 0.00 [−0.10,0.10], $P = 1.0$, $I^2 = 0\%$), moderate (RD: −0.01 [−0.04, 0.04], $P = 1{,}0$, $I^2 = 0\%$), and severe pancreatitis (RD −0.01 [−0.05, 0.03], $P = 0{,}58$, $I^2 = 0\%$).

The GRADEpro tool revealed a low level of evidence due to the imprecision (power < 80%) and the high risk of individual work bias by the CRBT (Table S5).

Bleeding

Analysis of 2 studies [25,31] totalling 157 patients. Sanjiv 2000 mentions only moderate and severe bleeding, so this article was not used in mild bleeding analysis. There was no statistically significant difference for mild (RD: −0.05 [−0.16, 0.07], $P = 0.41$), moderate (RD: 0.00 [−0.04, 0.04], $p = 1.0$, $I^2 = 0\%$), or severe bleeding (RD: 0.01 [−0.04, 0.06], $P = 0.58$, $I^2 = 0\%$).

The GRADEpro tool revealed a moderate level of evidence due to imprecision (power < 80%) (Table S5).

Hyperamylasemia

Two studies evaluated hyperamylasemia, totaling 157 patients. Stefanidis et al. [31] describes the mean values after 12 and 24 h of the procedure. Blend: 475 (12 h) — 150U/L (24 h) vs Pure cut followed by blend: 600 (12 h) — 150U/L (24 h). Sanjiv et al. [25] presents individual dichotomous results with a similar incidence of hyperamylasemia between groups (pure cut followed by blend: 0/18 vs Blend 1/15).

Monopolar vs bipolar

Pancreatitis

One article [26] analysis (100 patients). There was a lower incidence of pancreatitis in general with statistical significance using bipolar mode (RD: 0.12 [0.02, 0.22], $p = 0.01$).

The GRADEpro tool revealed a low level of evidence due to the imprecision (power < 80%) and high risk of individual work bias by the CRBT.

Discussion

Several studies suggest that the effect of electric current mode on adjacent tissue influences incidence of adverse events, which makes it essential to enhance knowledge on the subject [10,14,16,17,24,34–37]. To this end, the present study was based on an extensive search (systematic review of the literature), involving MEDLINE, Embase, Cochrane, Bireme/LILACS, and gray literature until September 2019, evaluating data from 11 RCTs (1791 patients), totaling 6 comparisons between electric current strategies used in sphincterotomy.

The previous systematic review and meta-analysis [38] was performed with data from only 4 articles [14,28,30,31]

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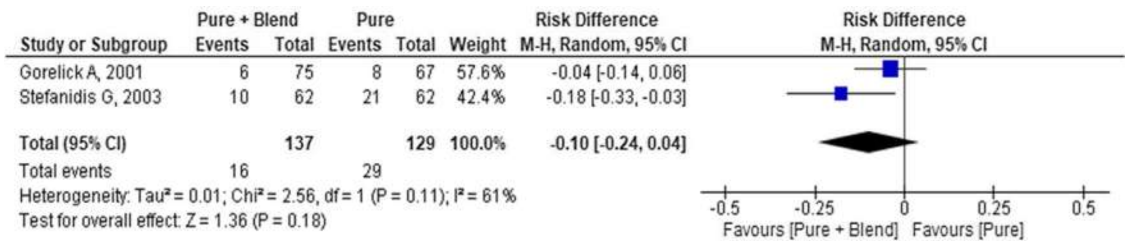

Figure 10 Bleeding in general (Pure cut followed by blend vs Pure cut).

searched exclusively in the MEDLINE database by 2005 (804 patients). Another important limitation of the Verma et al. [38] review was the incorporation of endocut and blend in the same group (mixed current), which we avoided in our analysis since they perform differently. For the final analysis, we selected articles with highest level of evidence (Evidence 1A).

A more recent meta-analysis was published in August 2019, by De-feng Li [40]. However, this study used a more limited search strategy and was restricted to fewer databases. This systematic review is focused on only two electric current modes, which restricts their conclusions among other comparisons that are important in clinical practice. The most important limitation of this paper, however, is that it includes a non-randomized study by Akiho, 2006 in the same analysis as randomized clinical trials [12]. In our search strategy, this paper was found and excluded, given the important bias generated in the comparison of randomized and non-randomized studies.

Among complications, the most feared (for its severity and frequency) is post-ERCP pancreatitis (PEP). It presents variable incidence in the literature with most estimates around 2—7%, but with varying reports from 0—40%. The mortality rate of PEP is about 0.11%[4—7,39,40—46].

Electric current used during sphincterotomy causes thermal damage of adjacent tissue (more intense in the mixed modalities: endocut and blend), which results in local edema that may obstruct the pancreatic duct and trigger the enzyme cascade inside the pancreas. This is an important element in the pathophysiology of PEP, but it is a multifactorial process, involving other factors such as mechanical trauma, hydrostatic, microbiological, enzymatic, allergic, etc.[39,40,47—49].

The comparison between pure cut and endocut has great clinical relevance, since they are among the most frequently used electric current modes. Individually, the three included studies in this analysis presented with a higher incidence of pancreatitis in the endocut group, as well as in the meta-analysis (total pancreatitis: 5.2 vs. 0.9%, $P = 0.01$). However, in the absence of outliers, high heterogeneity among studies ($I^2 = 57\%$) required use of the random effect, which increased the summary measure, making this difference not significant ($P = 0.12$).

In this analysis, Norton et al. [28] reported pancreatitis rates below the literature rate (only 1.6% vs 2—7%), which may be related to the inclusion of few cases that were at high risk of PEP, such as young patients or patients with diagnosed Oddi sphincter dysfunction (SOD) [4—7,28,39—46]. These numbers influenced the results because of their difference from the literature data and from the other studies included in this comparison (endocut vs pure cut). The risk of bias in this analysis using GRADE revealed very low certainty. It is possible that further studies may show a significant difference in incidence of pancreatitis between these current modalities.

Pure cut mode showed no advantage concerning pancreatitis when compared to blend (14/281 = 5% vs 23/291 = 7.9%, $P = 0.17$). The different proportions of coagulation and cut in the blend mode not reported by the authors may influence these results.

A strategy to avoid the main complications (pancreatitis and bleeding) is to use pure cut at the beginning of the sphincterotomy, followed by a mixed current at the end of the incision. The rationale for this technique lies in the fact that the initial part of the sphincterotomy is closer to the pancreatic ostium where thermal tissue injury and edema are at increased risk for causing pancreatitis. On the other hand, the final region of the incision presents with a greater risk of bleeding due to its proximity to important vessels (suprapapillary artery, retroduodenal branch) [25,31,33]. However, the studies that used this strategy (pure cut followed by blend), revealed no reduction in pancreatitis compared to the use of only pure cut throughout the incision (total: 23/155 = 14.8% vs 13/146 = 8.9%, $P = 0.12$).

The most frequently used circuit is the monopolar, in which the sphincterotome releases the current. It passes through the patient to the plate, and returns to the generator to close the circuit. In the bipolar circuit, the current crosses only a few millimeters of tissue between the two electrodes (lower voltage demand), closing the circuit without systemic dissemination of the current [10]. Siegel et al. [26], showed a lower incidence of pancreatitis with the bipolar circuit ($P < 0.05$). However, it is an article with a substantial risk of bias that employed a modality not commonly used for sphincterotomy — a fact that is supported by the absence of more recent studies that employ this modality. Studies from the 1990s point to negative points of the bipolar circuit such as manipulation difficulty and low durability that are factors that may have influenced reduction of its use in subsequent years.

Another important complication is bleeding, with incidence up to 30% (higher in studies that consider bleeding evident during the procedure, even if there is no clinical repercussion) and 1—2% when there is clinical repercussion [6,7,39,40,50—52]. Increased bleeding during the procedure is valued because it is a risk factor for post-operative bleeding [5,40].

There was no statistically significant difference in incidence of bleeding in the comparison between endocut and blend. Pure cut is associated with more mild bleeding (no clinical repercussion nor need for intervention) than endocut and blend. It is important to reinforce that, in our analysis, pure cut is associated with a higher risk of a self-limited bleeding of the papilla tissue during ERCP. It is not associated with a higher risk of bleeding that may have clinical repercussion or need for endoscopic intervention. This analysis carries low risk of bias (GRADE: moderate and high certainty, respectively).

Pure cut followed by blend strategy did not demonstrate an advantage when compared to isolated pure and blend currents. These data support the hypothesis that relevant bleeding (considered moderate or severe in the present study) may be related to vascular anatomical variation. The incidence of major bleeding is similar to the frequency that the retroduodenal artery is in the papillary region (about 4% of the population), favoring this hypothesis.

Mild bleeding increased with pure cut; this finding is explained by the lower coagulation effect of this current modality on adjacent tissue. On the other hand, in incisions that affect the artery in its anatomical variation, the blend and endocut modes would not be enough to prevent bleeding [5]. Currently, we have effective options for endoscopic treatment of these bleeds, reducing their morbi-mortality and impact on clinical management [50,53–58].

Based on these data, we observe that strong evidence in favor of a specific electric current mode is lacking. New studies might show a lower risk for pancreatitis and higher risk of bleeding using the pure cut mode, although, based on the current literature analysis, this is still hypothetical. It might be interesting to use pure current in patients who are at high risk to develop pancreatitis, such as young woman with normal CBD diameter and history of acute pancreatitis. On the other hand, endocut (or blend) is a valid option for patients with an increased risk for bleeding, such as low platelets level and coagulopathy. In cases without so evident risk factors, doubt still remains. Thus, it is very important to identify predictors of pancreatitis and bleeding and to take measures regarding the electric current mode and others such as rectal indomethacin or pancreatic stent in order to avoid such complications [5,24,50,53,55].

Since perforation (1 case in 897 patients) and cholangitis (3 cases in 256 patients) are extremely rare adverse events, it seems unlikely that they are related to electric current mode.

Among the limitations of this study, we have heterogeneity in bleeding definitions. We handled this problem by using a standard definition of easy understanding and clinical application. In the case of pancreatitis, not all articles specify stratification into mild, moderate and severe (some studies use the Cotton criteria, others use Atlanta and some studies do not mention the criteria used), which can also result in heterogeneity. Another limitation is different inclusion criteria between articles. Nevertheless, once the articles used random allocation, individually they have homogeneous groups. It is known that endocut and blend have different proportions of coagulation in their settings. As not all analyzed articles specify such settings, based on the current literature data, we do not know if such specifications have significant influence in the incidence of complications.

Cannulation difficulties, excessive or lack of tension in the sphincterotome, endoscopist experience, pressure on contrast injection, unknown coagulopathy, etc. are non-reportable variables that can influence adverse events [13,24,31,57,59,60]. However, when we include only RCTs, the factors have a random distribution, which mitigates their influence on the outcomes.

In summary, the present study is the only one in the literature that has evaluated, in an extensive, critical, and systematic way, the best level of evidence on this subject. The available data allow us to recommend use of pure cut mode routinely, with the possibility of using endocut or blend in cases with increased risk of bleeding or as a rescue strategy when bleeding is greater than expected. Our results have daily clinical application and offer essential data for the safety of patients undergoing ERCP.

Conclusion

Pure cut mode carries a higher risk of mild bleeding (without clinical repercussion or need for endoscopic intervention) during biliary sphincterotomy when compared to endocut and blend. However, this modality might carry a lower incidence of pancreatitis. Pancreatitis is more frequent in the monopolar circuit than in the bipolar circuit. There is no difference in incidence of cholangitis or perforation between different types of electric current and there is no statistical difference in the evaluation of adverse events between the comparisons: Endocut versus Blend, Pure versus Pure cut followed by Blend, and Blend versus Pure cut followed by Blend. There is a lack of evidence in the literature to recommend one method over the others, therefore new studies are warranted. We conclude that there is no perfect electric current mode to prevent all complications, but it is crucial to understand their respective mechanisms in order to choose the best option in clinical practice.

Author contributions

Funari, M.P.: acquisition of data, analysis, interpretation of data, drafting the article, revising the article, final approval; Ribeiro, I.B.: acquisition of data, drafting the article, revising the article, final approval; Moura, D.T.H.: analysis and interpretation of data, revising the article; Bernardo, W.M.: acquisition of data, analysis, interpretation of data, drafting the article, revising the article, final approval; Brunaldi, V.O.: analysis and interpretation of data, revising the article; Rezende, D.T.: analysis and interpretation of data, drafting the article, final approval; Resende, R.H.: drafting the article, final approval; de Marco, M.O.: drafting the article, final approval; Franzini, T.A.P.: analysis and interpretation of data, drafting the article, final approval; de Moura, E.G.H. analysis and interpretation of data, drafting the article, revising the article, final approval.

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PRISMA Checklist

The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.clinre.2019.12.009.

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