Original Article

The efficacy of ischemic conditioning in the prevention of gastroesophageal anastomotic complications: a meta-analysis

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Background: The blood supply to the gastric conduit is thought to be the most crucial factor affecting the healing of the gastroesophageal anastomosis. By selective ligation or embolization of gastric vessels, ischemic conditioning (IC) could promote the hypertrophy and neovascularization of the remaining gastric vessels. So that it could help the stomach adapt to the decline of blood supply before esophagectomy. However, the safety and efficacy of the technique still needs to be proved. Several new studies on this topic have been published recently. We conduct this meta-analysis to update the evidence on this topic.

Methods: A logistic searching strategy was designed to find out related publications on four medical databases (PubMed, EMBASE, Medline, and Cochrane Central Register of controlled trials). The included studies were confirmed by reading the title, abstract, or full text. Based on these included studies, the comparison of postoperative outcomes between patients who received IC and those did not was made. After that, the safety and efficacy of IC were assessed.

Results: Fourteen studies were enrolled in the meta-analysis. The pooled analysis showed IC reduced the incidence of anastomotic leakage significantly. And both the embolization and laparoscopic ligation approach were effective. The subgroup analysis indicated the interval between IC and esophagectomy should be over two weeks before the IC worked. The IC also could decrease the anastomotic stricture rate dominantly. What's more, the IC didn't increase the mortality.

Conclusions: This meta-analysis proved that ischemic conditioning is a safe intervention that could reduce anastomotic complications effectively. Future randomized controlled clinical trials are needed to provide high-level evidence on this topic.

Keywords: Esophagectomy; ischemic conditioning (IC); anastomotic complication; meta-analysis

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Introduction

Esophageal cancer is the 6th leading cause of cancer-related deaths worldwide (1). Regardless of the development of surgical technique and perioperative management, the incidence of anastomotic leakage (AL) remains high (2,3). The blood supply to the gastric conduit is thought to be the most crucial factor affecting the healing of the anastomosis (4,5). The right gastroepiploic artery becomes the primary supplier of the conduit after esophagectomy (6). So the blood supply to the proximal end (near the gastric fundus) of the conduit, which is far away from the primary trunk of the right gastroepiploic artery, is weaker than other parts. And the condition would be even worse in patients who undergo cervical anastomosis for a higher anastomotic level. A meta-analysis shows that cervical anastomosis has a significantly higher risk of AL than intrathoracic anastomosis (7).

The evidence above makes us believe the improvement of the blood supply to the anastomotic site is the key to decreasing the incidence of AL. The simplest way to improve the blood supply is by bringing down the anastomotic level. However, it is not feasible in the upper esophageal tumors for the concern of a positive surgical margin (8). Some hospitals have started using fluorescence imaging to guide the selection of the anastomotic site (9,10). However, the technique is unable to deal with a globally poor perfusion conduit. The anastomotic site has to be placed in the proximal end of the conduit to achieve a tension-free anastomosis in some cases (11). The ischemic conditioning (IC) of the stomach was proposed over 20 years ago. By ligation or embolization of the gastric vessels, it promotes hypertrophy and neovascularization of the remaining arteries helping the stomach adapt to the decline of blood supply before esophagectomy (12). Pham and his colleagues observed IC produced a 67% increase of microvessels counts, compared to the controls (12). The animal model conducted by Perry *et al.* also showed IC could significantly increase neovascularization (13). What's more, they found the degree of inflammation at the healing anastomosis decreased dominantly. These findings indicate IC could provide a better environment supporting the healing of gastroesophageal anastomosis. The meta-analysis conducted by Heger *et al.* shows the incidence of AL is 9.6% and 11.5% for patients undergo IC, and those do not, respectively (14). The difference doesn't reach a statistical significance. However, the studies they included were published before the year of 2012. Several new studies on this topic have been published in the past few years. So we conduct this meta-analysis to update the evidence on this topic.

This study was carried out according to the Cochrane handbook for systemic reviews of intervention, and the results were reported following the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) reporting checklist. Available at http://dx.doi.org/10.21037/apm-19-569.

Methods

We performed a systematic search in the online database of PubMed, Medline, EMBASE, and Cochrane Central Register of controlled trials on 30th September 2019 to find out potentially relevant publications. The searching strategy consisted of the following terms: (esophagus OR esophageal or oesophagus OR oesophageal OR esophagectomy OR oesophagectomy) AND (gastric conditioning OR ischemic conditioning OR vascular conditioning OR ischaemic conditioning OR embolization OR devascularization OR preconditioning). This is a meta-analysis. It does not involve any ethical or informed consent problems. This article does not contain any studies with human participants performed by any of the authors.

Inclusion and exclusion criteria

Inclusion criteria: (I) studies enrolled patients undergoing esophagectomy with gastroesophageal anastomosis; (II) studies compared the outcomes between the patients who received IC, and those did not.

Exclusion criteria: (I) following publication types: review, meta-analysis, case report, study protocol, conference abstract, letter, and reply; (II) when duplicate data occurred, only the study with a larger sample size would be included.

Study screening and data extraction

The first-round screening was done by reading the titles and abstracts of the studies. Most irrelevant studies were excluded in this step. Then, the second-round screening was performed by reading the full texts of the potentially relevant studies. After that, we started to extract relevant data to finally confirm the studies which could be included in the meta-analysis. The following baseline characteristics data of the studies were collected: Name of the first author, publication year, participants, sample size, ischemic conditioning strategy, and anastomosis technique. The incidence of anastomotic complications was used to evaluate the efficacy of ischemic conditioning.

All the work above was accomplished by two authors (Zhuo and Shen) independently and then checked with each other. Disagreements were resolved by discussing it with another author (Lin).

Quality assessment

The Methodological Index for Non-Randomized Studies (MINORS) (15), which contained eight items, was used to assess the quality of included studies.

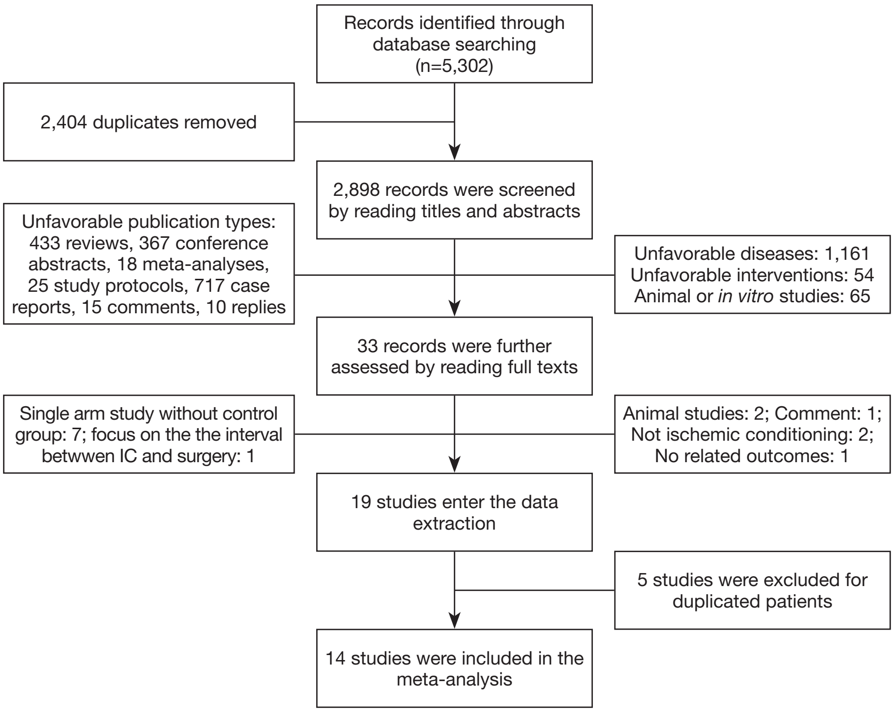


Figure 1 Flow diagram displays the screening procedures of included studies. IC, ischemic conditioning.

Statistical analysis

The Review Manager Version 5.3 and STATA Version 12.0 software (Stata Corporation, College Station, TX, USA) were used to run the data analysis. The Odds Ratio (OR) was used in the comparison of dichotomous data. The I^2 was used as the indicator of heterogeneity. I^2 <25%, 25%≤ I^2 <50% and I^2 ≥50% indicated low, moderate and high heterogeneity. When high heterogeneity was detected, subgroup analysis and meta-regression analysis would be performed to explore the source of heterogeneity. Begg's and Egger's tests were used to detect publication bias. A P value of less than 0.05 was considered to be statistically significant.

Results

Selection of included studies

The online database searching identified a total of 5,302 potentially relevant studies. The screening of the included studies was shown in *Figure 1*. Firstly, two thousand and four duplicated studies were removed. By reading the titles and abstracts, 1,575 unfavorable publication types (reviews, case reports, conference abstracts, meta-analyses, study protocols, replies, and comments), 65 animal or *in vitro* studies were excluded. Another 1,216 studies which didn't focus on the targeted disease and intervention were excluded as well. Then, 32 potentially relevant studies were carefully checked by reading the full texts. Nineteen of them met the requirements of our study and entered the data extraction step. After the removal of 5 studies with duplicated patients, 14 studies enrolling 1,705 patients were finally included in the meta-analysis.

Baseline characteristics of included studies

The baseline characteristics of the included studies were shown in *Table 1*. Four studies (16-19) achieved the IC by embolism of the gastric vessels, while the left ten studies (5,12,20-27) were through the laparoscopic approach. The interval between the IC and esophagectomy varied considerably among the 14 studies ranging from 3 to 205 days. Eleven studies showed the ischemic conditioning (IC) group had a lower incidence of anastomotic leakage (AL) than the no ischemic conditioning (NIC) group, while three studies showed the IC group had a higher rate of AL.

Table 1 The baseline characteristics of the included studies

Study	Design	Patients	Method of IC	Interval between IC and surgery	Anastomosis location (neck/thorax)	Leakage rate	MINORS score
Akiyama 1988	NA	EC	Embolization of LGA, RGA, and SA	NA	IC: 18/36; NIC: 7/18	1/54 (1.9%); 2/25 (8.0%)	11
Perry 2010	P	EC	Laparoscopic ligation of LGA and SGA	1 week or 12 weeks (neoadjuvant)	IC: 7/0; NIC: 25/0	0/7 (0%); 4/25 (8.0%)	13
Schroder 2010	R	ADC: 252; SCC: 160; other: 7	Laparoscopic ligation of gastric vessels	Range from 3 to 7 days	IC: 0/238; NIC: 0/181	18/238 (7.6%); 17/181 (9.4%)	9
Pham 2011	P	ADC: 22; SCC: 1	laparoscopic ligation of SGA	At least 7 days	Neck: 18; thorax: 5	0/4 (0%); 6/19 (31.6%)	13
Diana 2011	R	ADC: 39; SCC: 18	Embolization of LGA, SGA, and SA	Mean 17 days	IC: 2/17; NIC: 4/34	2/19 (10.5%); 8/38 (21.1%)	11
Farran 2011	R	EC: 25; other:14	Embolization of LGA, RGA, and SA	Range from 14 to 21 days	IC: 33/0; NIC: 4/0	1/33 (3.0%); 1/4 (25.0%)	9
Wajed 2012	P	EC	Laparoscopic ligation of LGA	14 days	IC: 67/0; NIC: 64/0	9/67 (13.4%); 12/64 (18.8%)	11
Nguyen 2012	R	ADC: 102; SCC: 19; other:31	Laparoscopic ligation of LGA alone or LGA and SGA	Mean 6 days	NA	9/81 (11.1%); 6/71 (8.5%)	11
Patel 2016	R	NA	laparoscopic ligation of gastric vessels	Median 7 days	NA	10/77 (13.0%); 10/41 (24.4%)	11
Ghelfi 2017	R	ADC: 32; SCC: 24; other: 3	Embolization of LGA, RGA, and SGA	Median 36 days (range 17–103)	IC: 13/33; NIC: 4/9	6/46 (13.0%); 6/13 (46.2%)	11
Pham 2017	R	ADC: 26; SCC: 4	Laparoscopic ligation of SGA alone or SGA and LGA	Mean 121 days	IC: 17/4; NIC: 2/7	2/21 (9.5%); 0/9 (0%)	11
Siegal 2018	R	ADC: 165; SCC: 23	Laparoscopic ligation of LGA and SGA	Mean 98 days (range 11–205)	IC: 34/3; NIC: 157/12	3/38 (7.9%); 9/169 (5.3%)	11
Kohler 2019	NA	ADC: 12; SCC: 9; other: 1	Laparoscopic ligation of LGA and SGA	Range from 3 to 7 days	IC: 0/14; NIC: 0/8	0/14 (0%); 1/8 (12.5%)	9
Carrott 2019	NA	NA	Laparoscopic ligation of LGA and SGA	Median 87 days (range 26–196)	NA	1/28 (3.6%); 63/311 (20.3%)	11

NA, not available; P, prospective; R, retrospective; EC, esophageal cancer; ADC, adenocarcinoma; SCC, squamous cell carcinoma; IC, ischemic conditioning; NIC, no ischemic conditioning; LGA, left gastric artery; RGA, right gastric artery; SGA, short gastric artery; SA, splenic artery; MINORS, Methodological Index for Non-Randomized Studies.

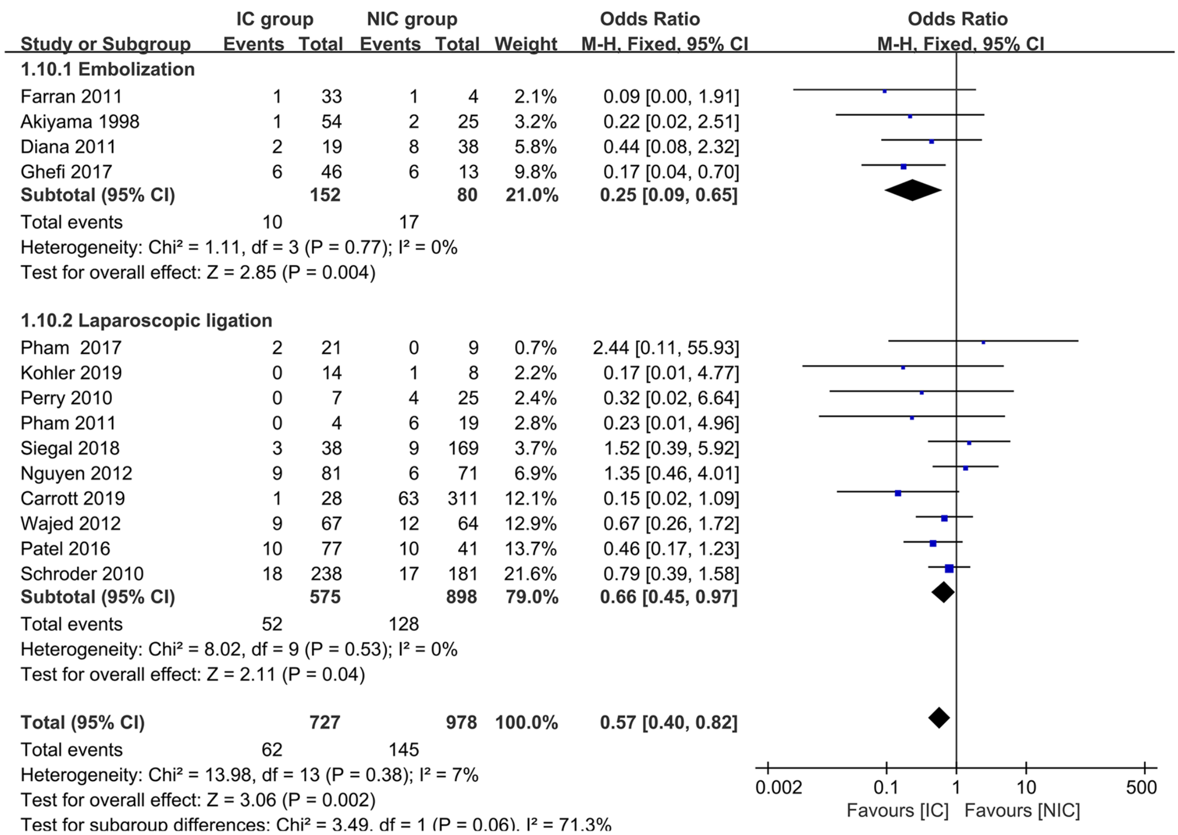


Figure 2 Comparison of anastomotic leakage (AL) rate between ischemic conditioning (IC) group and no ischemic conditioning (NIC) group. The IC group had a lower rate of AL than the NIC group (8.5% *vs.* 14.8%). The difference reached statistically significant (OR =0.57, 95% CI: 0.40–0.82, P value=0.002). Both the embolization and laparoscopic ligation approach were efficacy in the reduction of AL.

Comparison of postoperative outcomes

The data of anastomotic leakage (AL) was available in all 14 studies. The pooled analysis showed the incidence of AL was 8.5% and 14.8% for the IC group and NIC group, respectively. The difference reached statistically significant (OR =0.57, 95% CI: 0.40–0.82, P value =0.002, *Figure 2*). What's more, both of the embolization and laparoscopic ligation approach were efficacy in the reduction of AL (*Figure 2*). A subgroup analysis was performed according to the interval between IC and gastroesophageal anastomosis. It showed the IC was effective in the reduction of AL when the interval above 2 weeks (P value =0.002, *Figure 3*). The incidence of AL was comparable between the IC and NIC group in the one-week subgroup (7.1% *vs.* 9.5%, P value =0.36, *Figure 3*).

The incidence of anastomotic stricture was available in 9 studies. The overall stricture rate was 12.1% and 27.9% in the IC and NIC group, respectively. The meta-analysis showed the IC group had a significantly lower stricture rate than the NIC group (OR =0.46, 95% CI: 0.29–0.71, P value =0.0005, *Figure 4*). On the other hand, the mortality was lower in the IC group, but the difference didn't reach a statistically significant difference (3.7% *vs.* 5.1%, P value =0.19, *Figure 5*).

Heterogeneity and publication bias

All the analyses above showed low or moderate heterogeneity. The Begg's (P value =0.913, *Figure 6A*) and Egger's test (P value =0.544, *Figure 6B*) showed no publication bias.

Discussion

Anastomotic leakage (AL) and anastomotic stenosis (AS) are the two mainly anastomosis-related complications. The

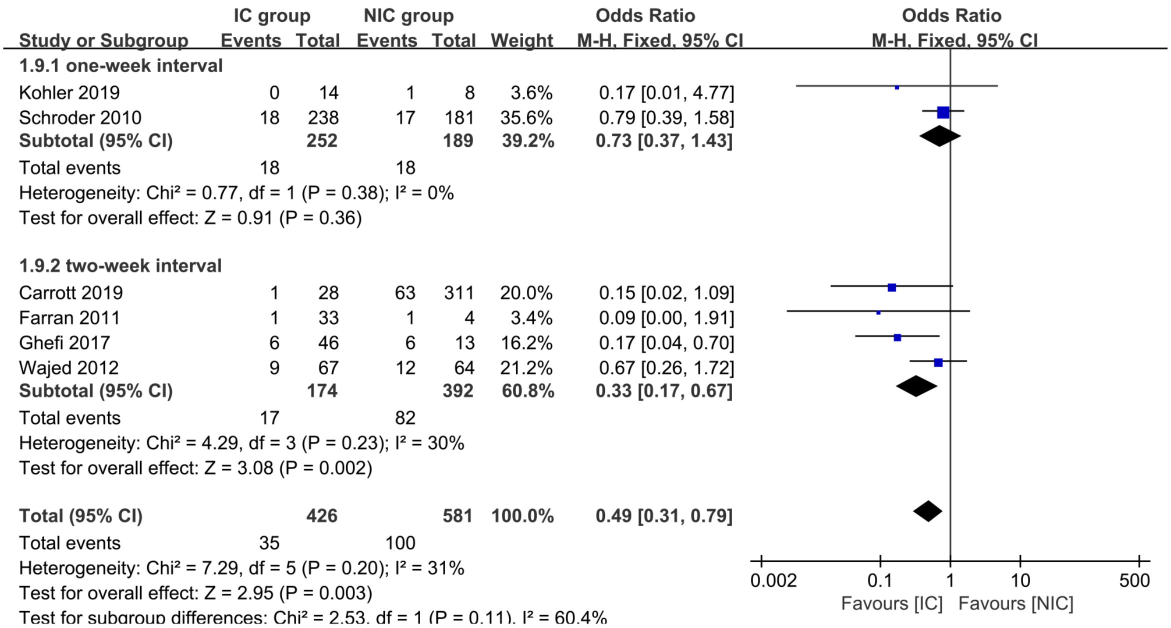


Figure 3 Subgroup analysis of the anastomotic leakage (AL) according to the interval between ischemic conditioning (IC) and gastroesophageal anastomosis. The IC was effective in the reducing of AL when the interval was above two weeks (OR =0.33, 95% CI: 0.17–0.67, P value =0.002), while the incidence of AL was comparable between one-week interval IC and NIC group (OR =0.73, 95% CI: 0.37–1.43, P value =0.36).

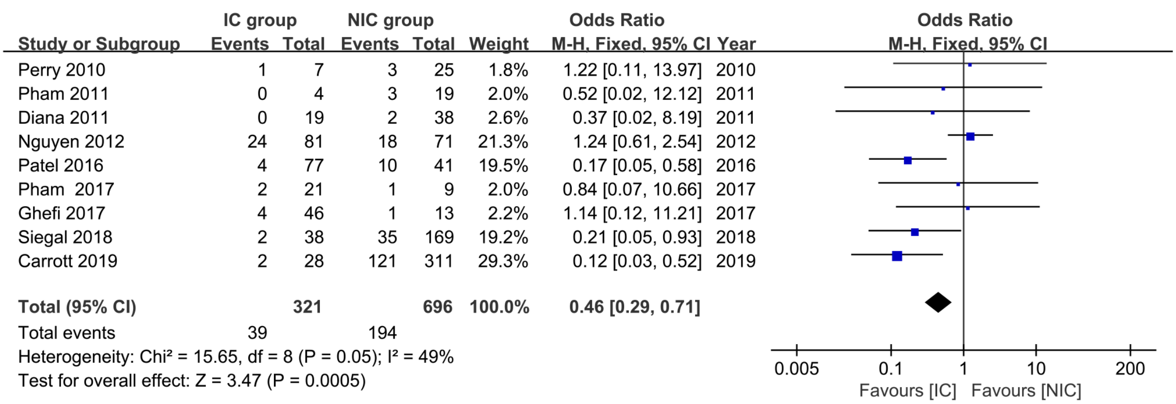


Figure 4 Comparison of anastomotic stricture rate between ischemic conditioning (IC) group and no ischemic conditioning (NIC) group. The IC group had a significantly lower stricture rate than the NIC group (12.1% *vs.* 27.9%, OR =0.46, 95% CI: 0.29–0.71, P value =0.0005).

latter often happens a long time after the surgery, and it is much less dangerous. The AS is handled by endoscopic dilation mostly. As for AL, it often happened within a short time after the surgery. It is an unpredictable and lethal complication. The early reorganization of high-risk patients, well preoperative communication, early postoperative detection, and timely treatment are the rules for the management of AL. The good drainage and adequate nutrient supply are the major weapons to deal with the AL, and most patients could recover in a few weeks. However, about 5–10% of patients who suffer from AL would die (28). So the prevention of AL is quite important.

The previously published meta-analysis showed patients who underwent IC had a lower incidence of anastomotic

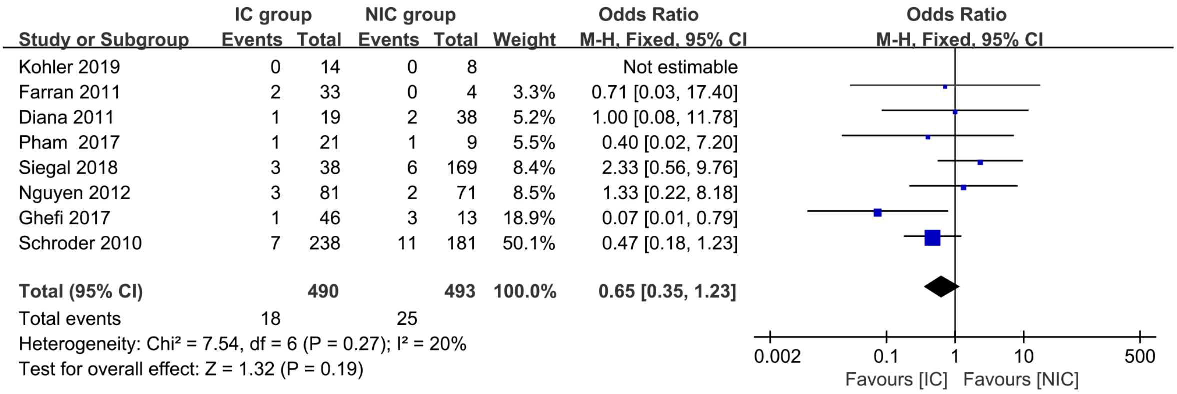


Figure 5 Comparison of mortality between ischemic conditioning (IC) group and no ischemic conditioning (NIC) group. The mortality was comparable between IC and NIC group [3.7% *vs.* 5.1%, OR=0.65, 95% CI: 0.35–1.23), P value =0.19].

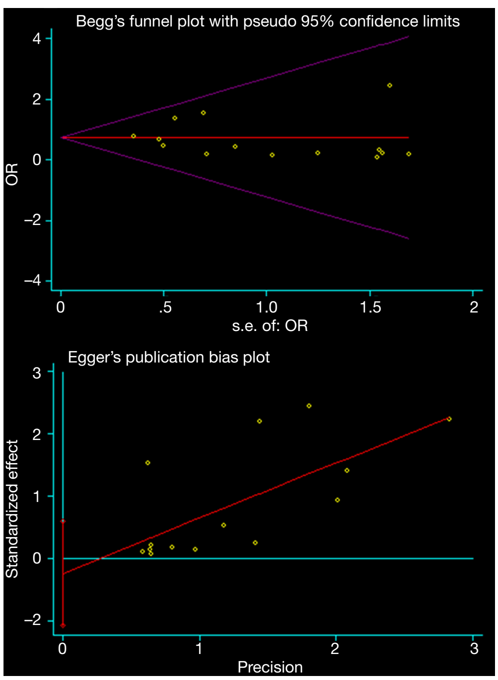
A
B


Figure 6 Begg's and Egger's test for the detection of publication bias. Both the Begg's (P value =0.913) and Egger's test (P value =0.544) detected no publication bias in the comparison of anastomotic leakage.

complications than those who did not (14). However, the difference didn't reach a statistical significance. After the inclusion of newly published studies, our study proved the efficacy of the ischemic conditioning (IC) in the reduction of anastomotic complications for the first time. The IC significantly decreased the incidence of anastomotic leakage, and it also reduced the happen of postoperative stricture.

The blood supply around the gastric fundus is weaker than other parts of the stomach, so that the top portion of the gastric conduit is especially insufficient in blood supply (29). Therefore, the cervical anastomosis, which has to put the anastomotic site closer to the top of the conduit, has a significantly higher risk of anastomotic leakage (AL) than the intrathoracic anastomosis (4). So, the efficacy of the IC should be more dominant in patients undergoing cervical anastomosis theoretically. Among the fourteen studies included in the meta-analysis, two studies (20,23) performed cervical anastomosis, and another two studies (21,26) performed intrathoracic anastomosis. In contrast, the left ten studies perform both the cervical and intrathoracic anastomosis. So the subgroup analysis, according to the anastomotic level, was unable to be performed independently. If the patients undergoing cervical anastomosis would benefit more from the ischemic conditioning needs to be further proved.

The embolization or ligation of the gastric vessels may promote the hypertrophy and neovascularization of the preserved gastric vessels (6,30). The compensation helps the stomach adapt to the decline of the blood supply gradually. It is how the ischemic conditioning works. The animal experiments conducted by Perry *et al.* showed the 7-day ischemic conditioning didn't produce increased neovascularity while the 30-day conditioning increased the microvessel counts significantly (13). So, the interval between the IC and esophagectomy is an essential factor affecting the efficacy of the IC. However, the optimal interval remains questionable, and it varies significantly among different studies (6,23,31). The subgroup analysis, according to the interval between IC and anastomosis, showed the incidence of AL was comparable between the IC group and the NIC group in the 1-week subgroup. When it came to the 2-week subgroup, the IC group had a statistically significant lower rate of AL than the NIC group. Therefore, the interval between IC and surgery should be enough to let the compensations happen. The results of our analysis recommended the interval should be over 2 weeks.

The anastomotic stricture is a complication that dramatically decreases the quality of life of the patients (32,33). The stricture rate could be as high as 18–42% after the gastroesophageal anastomosis (32). Siegal *et al.* reported the IC could significantly decrease the incidence of anastomotic stricture fourfold (5). The studies conducted by Carrott *et al.* and Patel *et al.* also supported the result (25,27). Our meta-analysis showed the overall incidence of anastomotic stricture dropped to 12.1%, which otherwise would be as high as 27.9%. The animal experiment showed the IC could increase muscularis propria preservation and decreased collagen deposition at the healing anastomosis (13). So the low stricture rate in the IC group may associate with the reduced fibrosis of the anastomotic site.

The IC is a traumatic procedure. So it also has some side effects. The side effect of the laparoscopic approach is similar to general laparoscopic gastric surgery such as wound infection, bleeding, hiatal hernia, and so on (24). As for the embolization approach, it is more complicated. The reported side effect includes partial splenic infarct, vesicular ischemia, gastric perforation, and pancreatitis, and so on (18). Thankfully, the morbidity rate is quite low, and most of them are mild.

In summary, our study proved the ischemic conditioning is a safe intervention that could reduce the anastomotic complications effectively. It could play a role in the prevention of anastomotic leakage among high-risk patients. However, the studies included in the meta-analysis were cohort or case-control study. It brought down the evidence level of our findings. Future randomized controlled clinical trials are needed to provide high-level evidence on this topic.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-19-569). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This is a meta-analysis. It does not involve any ethical or informed consent problems. This article does not contain any studies with human participants performed by any of the authors.

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