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Intracorporeal versus extracorporeal anastomosis in minimally invasive right hemicolectomy: systematic review and meta-analysis of randomized controlled trials

Chinock Cheong[1], Na Won Kim[2], Hye Sun Lee[3], Jeonghyun Kang[4]

[1]*Department of Surgery, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea*
[2]*Yonsei University Medical Library, Seoul, Korea*
[3]*Biostatistics Collaboration Unit, Yonsei University College of Medicine, Seoul, Korea*
[4]*Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea*

Purpose: Compared with extracorporeal anastomosis (ECA), intracorporeal anastomosis (ICA) is expected to provide some benefits, including a shorter operation time and less intraoperative bleeding. Nevertheless, the benefits of ICA have mainly been evaluated in nonrandomized studies. Owing to the recent update of randomized controlled trials (RCTs) for minimally invasive surgery (MIS) of right hemicolectomy (RHC), the need to measure the actual effect by synthesizing the outcomes of these studies has emerged.
Methods: We performed a comprehensive search of the PubMed, Embase, and Cochrane databases (from inception to January 30, 2023) for studies that applied ICA and ECA for RHC with MIS. We included 7 RCTs. The operation time, intraoperative blood loss, conversion rate, length of incision, and postoperative outcomes such as ileus, anastomosis leakage, length of hospitalization, and postoperative pain were compared between ICA and ECA.
Results: A total of 740 patients were included in the study. Among them, 377 and 373 underwent ICA and ECA, respectively. There were significant differences in age ($P = 0.003$) and incision type ($P < 0.001$) between ICA and ECA. ICA was associated with a significantly longer operation time ($P = 0.033$). Although the postoperative pain associated with ICA was significantly lower than that associated with ECA on postoperative day 2 (POD 2) ($P = 0.003$), it was not different on POD 3 between the groups. Other perioperative outcomes were similar between the 2 groups.
Conclusion: In this meta-analysis, ICA did not significantly improve short-term outcomes compared to ECA; other advantages to overcome ICA's longer operation time are not clear.
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Key Words: Anastomosis, Ascending colon, Colectomy, Minimally invasive surgical procedures

INTRODUCTION

Minimally invasive surgeries (MIS), such as laparoscopic or robotic surgeries, are commonly performed for various diseases. After laparoscopic surgery was introduced in 1987 [1], it was adopted for colorectal surgery in 1991 [2]. The robotic platform was adopted for colorectal surgery in 2002 [3]. These minimally invasive surgical platforms have provided several benefits for patients compared to laparotomy, including smaller scars, less postoperative pain, rapid recovery of bowel movement, and return to normal activities after hospitalization.

In the operation of colorectal diseases, detachment of the

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Corresponding Author: Jeonghyun Kang
Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 06273, Korea
Tel: +82-2-2019-3372, **Fax:** +82-2-3462-5994
E-mail: ravic@naver.com
ORCID: https://orcid.org/0000-0001-7311-6053

visceral peritoneum from the parietal peritoneum is essential, and extensive detachment of the colonic mesentery is needed for extracorporeal anastomosis (ECA). During ECA, surgeons usually pull the dissected colon through the abdominal cavity. If the length of dissection is insufficient, serious complications can occur, such as massive bleeding from the torn vessels during the extraction procedure. In addition, obese patients require a longer colon dissection because of their thick subcutaneous fat layer, which makes their surgery more difficult. Intracorporeal anastomosis (ICA) is currently being used with the expectation that it will overcome these disadvantages.

It has been reported that the ICA procedure in MIS for colorectal diseases can provide enhanced recovery after surgery and fewer perioperative complications [4-6]. Although several meta-analyses have already compared ICA and ECA in laparoscopic right hemicolectomy (RHC), most studies included nonrandomized controlled trials (RCTs), and only 1 study included RCTs of laparoscopic RHC.

Consideration should be given to the fact that robotic surgery is being performed more frequently. In addition, there are already well-established results demonstrating that robotic surgery is much more convenient for intraperitoneal suturing than laparoscopic surgery. Considering recent randomized controlled trial (RCT) results using robotic systems, it is necessary to update the results of ICA and ECA within the scope of the overall MIS approach.

Thus, this study aimed to compare the perioperative outcomes between ICA and ECA for MIS using recently published RCTs.

METHODS

This systematic review and meta-analysis was conducted using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines [7]. Furthermore, the protocol was prospectively registered with the International Prospective Register of Systematic Reviews (registration No. CRD42023399188).

Search strategy and selection criteria

We searched PubMed, Embase, and Cochrane electronic research databases for all full-text articles related to ICA *vs.* ECA for RHC in MIS published between January 1, 2015, and January 30, 2023. Only the articles published in English were included. Studies were identified using terms such as "intracorporeal anastomosis," "extracorporeal anastomosis," "right colon cancer," "ascending colon cancer," "cecal cancer," "transverse colon cancer," "right colon adenocarcinoma," "right colon neoplasm," "cecal adenocarcinoma," "transverse colon adenocarcinoma," "ascending colon adenocarcinoma," "ascending colon neoplasm," "transverse colon neoplasm," "laparoscopic surgery," "robotic surgery," and "minimally invasive surgery." The detailed search strategy and results are provided in Supplementary Information (Supplementary Table 1).

The inclusion criteria were as follows: (a) RCTs, (b) patients who underwent MIS for right colon neoplasm, and (c) the reference standard was an ECA for MIS. The exclusion criteria were as follows: (a) patients who underwent open surgery for right colon neoplasm, (b) systemic metastasis in malignant colon neoplasm, or (c) missing data.

After removing duplicate studies, the titles and abstracts were reviewed for eligibility by 2 authors (CC and JK). Any disagreements were resolved through discussion between the 2 authors to reach a consensus. Finally, 7 studies were collected for the comparison of ICA and ECA for right colon neoplasms in minimally invasive RHC.

Data extraction and quality assessment

Data were extracted from full-text articles. We assessed the risk of bias in RCTs by using the Risk of Bias 2.0 (RoB 2) tool (Cochrane Collaboration), for the effect of the assignment to the intervention (the intention-to-treat) effect [8]. Discrepancies in the risk of bias between the studies were discussed and resolved by 2 authors (CC and KJ). We assessed the following types of bias as outlined in chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions*; bias arising from the randomization process, bias due to deviations from the intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. We used the algorithms proposed by RoB2 to assign each domain one of the following levels of bias: low risk, some concerns, and high risk of bias. We estimated an overall risk of bias rating from each domain. The risk of bias assessment of RCTs is summarized in Supplementary Fig. 1.

Statistical analysis

For each study, the data were summarized in 2 × 2 contingency tables. In the basic characteristics, continuous variables were analyzed using the Student t-test and categorical variables were compared using the chi-square test and Fisher exact test. The paired t-test was used to compare postoperative pain between groups. The standardized mean difference (SMD) was used as a continuous variable, and the odds ratio (OR) was selected as a binary variable. A common- or random-effects model was used to calculate the effect sizes of the studies. When significant heterogeneity was present (inconsistency index [I^2] >50 or $P < 0.05$), a random-effects model was adopted [9]. The I^2 was used to assess the heterogeneity between studies. Heterogeneity was quantified as low, moderate, or high, with upper limits of 25%, 50%, and 75%, respectively, for I^2 [10].

All statistical analyses were performed using RevMan ver.

5.4. (Nordic Cochrane Center) and R ver. 4.1.2. (R Foundation for Statistical Computing). Differences were considered statistically significant at the P-values of <0.05.

RESULTS

Study selection

Fifty studies were extracted from the databases, and 34 remained after duplicates were removed. After reviewing titles and abstracts, 11 studies were eligible for full-text review. Finally, 7 studies were included in the systematic review and meta-analysis (Fig. 1) [11-17].

Quality assessment and publication bias

The results of the quality assessment are shown in Supplementary Fig. 1. All studies showed a low risk of missing outcome data and measurement of the outcome. Two studies showed a high risk of selection of the reported result. After all, 2 studies were assessed as having a high overall risk. Other studies demonstrated a low and some concerns in the overall assessment.

Characteristics of included studies

All the included studies were prospective RCTs. The selected studies were published between 2015 and 2023. All patients underwent RHC for benign or malignant right-sided colon tumors with MIS. In total, 750 patients were included in this meta-analysis, of whom 661 underwent laparoscopic surgery and 89 underwent robotic surgery. Among them, 377 patients underwent RHC with ICA and 373 patients underwent RHC with ECA.

The attributes used in this study are listed in Table 1. The basic characteristics of the study population between ICA and ECA are shown in Table 2. There were significant differences in age (67.67 ± 6.08 *vs.* 65.79 ± 10.45, P = 0.003) and incision type (right upper quadrant [RUQ]: 5.3% *vs.* 44.0%, midline: 28.1% *vs.* 42.1%, and Pfannenstiel incision: 54.1% *vs.* 0.5%; P < 0.001) between ICA and ECA.

Intraoperative outcomes

ICA was associated with a longer operation time (SMD, 0.455 [95% CI, 0.036–0.873]; P = 0.033, I^2 = 84.7%; 6 studies, n = 690). Intraoperative blood loss was not different between groups in 4 studies (n = 391; SMD, –0.555 [95% CI, –1.369 to 0.258]; P = 0.181, I^2 = 92.0%). There was no difference in the conversion to open surgery between ICA and ECA (ICA, 4.3% [n = 11] *vs.* ECA, 0.8% [n = 2]; OR, 0.242 [95% CI, 0.057–1.029]; P = 0.055, I^2 = 0%; 5 studies, n = 522). There was no significant difference in the length of incision between the groups (SMD, –1.463 [95% CI, –2.971 to 0.045]; P = 0.057, I^2 = 96.0%; 6 studies, n = 690) (Fig. 2).

Postoperative outcomes and recovery

The rate of Clavien-Dindo classification of ≥III was compared

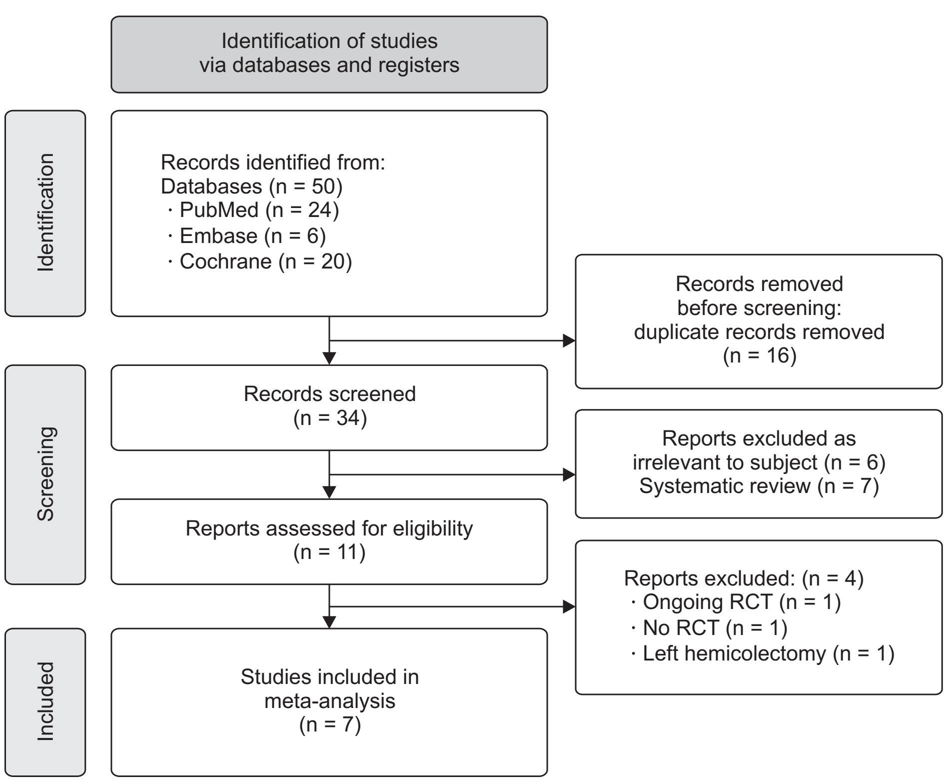

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flowchart describing the selection pipeline for studies included in our study. RCT, randomized controlled trial.

Table 1. Characteristics of included studies

Study	Year	Study design	Study period	No. of patients		Subject	Method of operation	Comparison
				ICA	ECA			
Vignali et al. [11]	2016	RCT	2001–2016	30	30	RHC	Laparoscopic	ICA *vs.* ECA
Mari et al. [12]	2018	RCT	2005–2012	30	30	RHC	Laparoscopic	ICA *vs.* ECA
Bollo et al. [14]	2020	RCT	1997–2017	69	70	RHC	Laparoscopic	ICA *vs.* ECA
Allaix et al. [13]	2019	RCT	2004–2016	70	70	RHC	Laparoscopic	ICA *vs.* ECA
Ferrer-Márquez et al. [15]	2021	RCT	2004–2011	82	78	RHC	Laparoscopic	ICA *vs.* ECA
Dohrn et al. [16]	2022	RCT	2005–2015	44	45	RHC	Robotic	ICA *vs.* ECA
Małczak et al. [17]	2022	RCT	2001–2011	52	50	RHC	Laparoscopic	ICA *vs.* ECA

ICA, intracorporeal anastomosis; ECA, extracorporeal anastomosis; RCT, randomized controlled trial; RHC, right hemicolectomy.

Table 2. Patients' characteristics between ICA and ECA

Characteristic	ICA	ECA	P-value
No. of patients	377	373	
Age (yr)	67.67 ± 6.09	65.79 ± 10.45	0.003
Sex			0.303
Male	190 (50.4)	202 (54.2)	
Female	187 (49.6)	171 (45.8)	
Body mass index (kg/m^2)	25.91 ± 5.29	25.78 ± 4.14	0.708
ASA grade			0.795
I, II	190 (50.4)	201 (53.9)	
≥III	135 (35.8)	122 (32.7)	
Missing	52 (13.8)	50 (13.4)	
Previous abdominal surgery			0.534
Yes	82	96	
No	169	152	
Missing	126	125	
Location of tumor			0.818
Cecum	145 (38.5)	160 (42.9)	
Ascending colon	113 (30.0)	94 (25.2)	
Hepatic flexure	75 (19.9)	74 (19.8)	
Missing	44 (11.7)	45 (12.1)	
Method of MIS			0.868
Laparoscopic	333 (88.3)	328 (87.9)	
Robot	44 (11.7)	45 (12.1)	
Method of incision			<0.001
Right upper quadrant	20 (5.3)	164 (44.0)	
Midline	106 (28.1)	157 (42.1)	
Pfannenstiel	204 (54.1)	2 (0.5)	
Others (off-mid/McBurney)	17 (4.5)	20 (5.4)	
Missing	30 (8.0)	30 (8.0)	

Values are presented as number only, mean ± standard deviation, or number (%).
ICA, intracorporeal anastomosis; ECA, extracorporeal anastomosis; ASA, American Society of Anesthesiologists; MIS, minimally invasive surgery.

and found to be similar between groups (ICA, 6.2% *vs.* ECA, 5.3%; OR, 1.342 [95% CI, 0.536–3.358], P = 0.530, I^2 = 42.0%; 5 studies, n = 450). The rate of pulmonary complication was not different (ICA, 5.6% *vs.* ECA, 4.5%; OR, 1.266 [95% CI, 0.546–2.934]; P = 0.583, I^2=0%; 4 studies, n = 491). In the surgical site infection, there was no difference between groups (OR, 0.482 [95% CI, 0.221–1.051]; P = 0.067, I^2 = 23.0%; 5 studies, n = 559). Postoperative bleeding was 2.3% in the ICA group and 5% in the ECA group (OR, 0.388 [95% CI, 0.123–1.229; P = 0.108; I^2 = 32.0%; 4 studies, n = 441). Postoperative ileus was 10.5% in the ICA group and 14.9% in the ECA group (OR, 0.646 [95% CI, 0.388–1.078]; P = 0.094, I^2 = 53.2%; 6 studies, n = 661). The rate of anastomosis leakage was not significantly different between the ICA and ECA groups (ICA, 4.2% *vs.* ECA, 4.3%; OR, 0.949 [95% CI, 0.453–1.989]; P = 0.889, I^2 = 3.0%; 7 studies, n = 750). The rate of reoperation due to postoperative complications was 3.6% in the ICA group and 6.9% in the ECA group (OR, 0.534 [95% CI, 0.245–1.164]; P = 0.114, I^2 = 0%; 6 studies, n = 610). The length of hospitalization was not significantly different (SMD, –0.154 [95% CI, –0.618 to 0.309]; P = 0.514, I^2 = 70.0%; 3 studies, n = 280). Readmission was 4.0% in the ICA group and 5.5% in the ECA group (OR, 0.949 [95% CI, 0.429–2.097]; P = 0.896, I^2 = 37.0%; 6 studies, n = 690) (Fig. 3).

Postoperative pain

When we compared postoperative pain between both ICA and ECA groups (4 studies, n = 428), there was no difference on postoperative day (POD) 1 (SMD, –0.004 [95% CI, –0.193 to 0.186]; P = 0.971, I^2 = 0%). Postoperative pain on POD 2 became significant and decreased in the ICA group compared to the ECA group (SMD, –0.288 [95% CI, –0.479 to –0.097]; P = 0.003, I^2 = 34.0%). However, there was no difference between the groups on POD 3 (SMD, –0.813 [95% CI, –1.926 to 0.300]; P = 0.152, I^2 = 96.0%) (Fig. 4).

Sensitivity analysis

We conducted a sensitivity analysis using a one-on-one exclusion because of heterogeneity in the time of operation, intraoperative blood loss, and length of incision (Supplementary Fig. 2). Regarding time of operation, we excluded 3 studies by Allaix et al. [13], Ferrer-Márquez et al. [15], and Małczak et al. [17] After exclusion, the heterogeneity decreased from 85% to 57%,

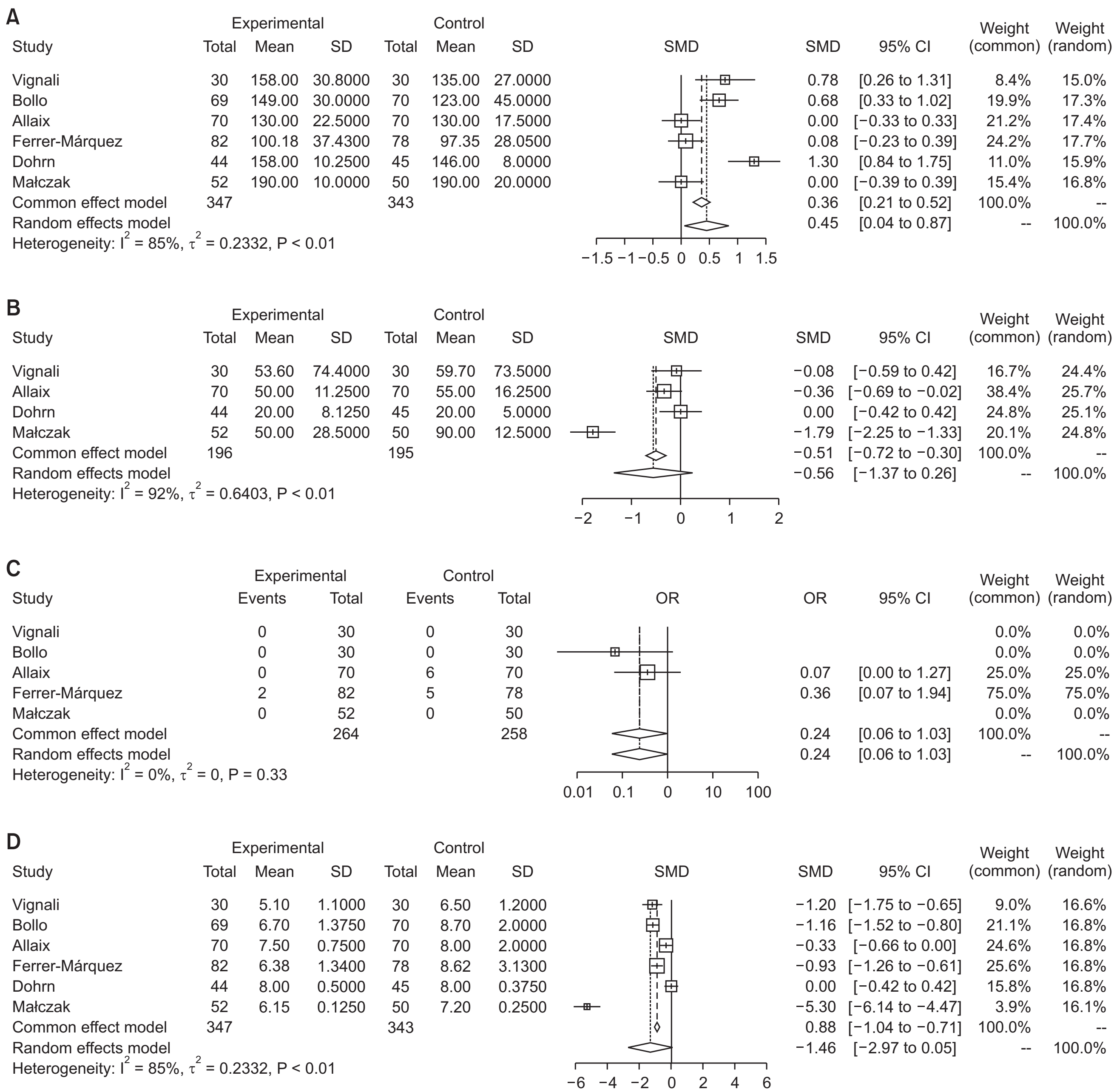

Fig. 2. Forest plot of intraoperative outcomes between intracorporeal and extracorporeal anastomosis. (A) Operation time (min). (B) Intraoperative blood loss (mL). (C) Conversion rate. (D) Length of incision (cm). SD, standard deviation; SMD, standardized mean difference; CI, confidence interval; OR, odds ratio.

and the operation time was significantly longer in the ICA group (SMD, 0.873 [95% CI, 0.630–1.116]; P < 0.001). Intraoperative blood loss also differed between the groups (SMD, –0.271 [95% CI, –0.499 to –0.044]; P = 0.019), with a heterogeneity of 51% when the study by Dohrn et al. [16] was excluded. In the analysis of incision length, we excluded the study by Małczak et al. [17], but the heterogeneity did not decrease from 96% to 85%. However, the length of the incision was significantly different between the ICA and ECA groups, being smaller in the ICA group than in the ECA group (SMD, –0.715 [95% CI, –1.177 to –0.254]; P = 0.002).

DISCUSSION

In this systematic review and meta-analysis, we compared the outcomes of ICA and ECA in RHC with MIS in 7 RCTs. There was no significant difference in the overall perioperative and recovery outcomes, including postoperative complications and anastomotic leakage. The operation time was significantly longer in patients who underwent ICA than in those who

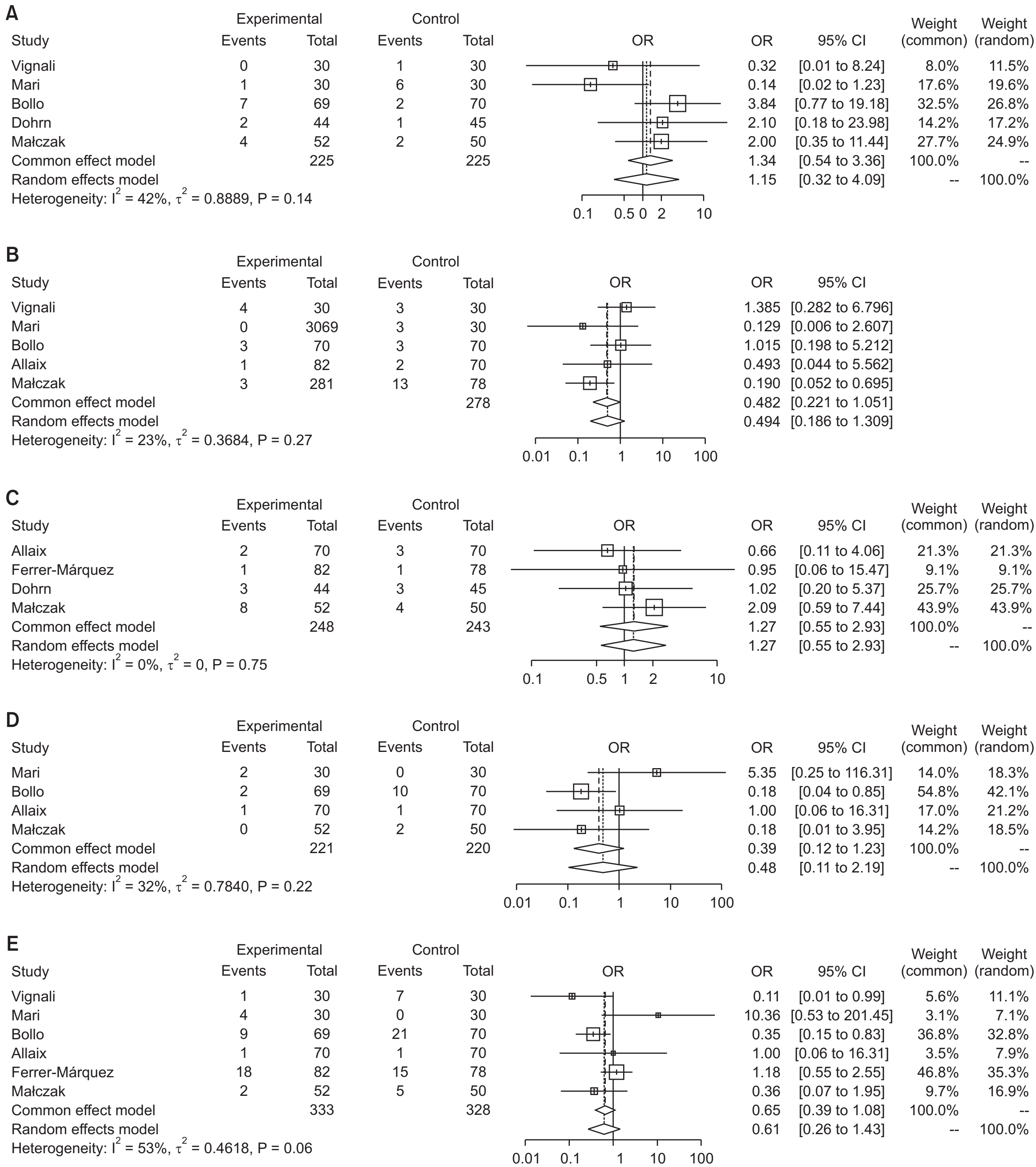

Fig. 3. Forest plot of perioperative outcomes between intracorporeal and extracorporeal anastomosis. (A) Clavien-Dindo classification of ≥III. (B) Surgical site infection. (C) Pulmonary complication. (D) Postoperative bleeding. (E) Ileus. (F) Anastomosis leakage. (G) Reoperation. (H) Hospitalization (days). (I) Readmission. OR, odds ratio; SMD, standardized mean difference; CI, confidence interval; SD, standard deviation.

underwent ECA ($P = 0.034$). Although postoperative pain was significantly decreased in ICA ($P = 0.003$) on POD 2, it was similar between the groups on POD 3 ($P = 0.152$).

Previous studies have demonstrated comparable outcomes between ICA and ECA in terms of morbidity and mortality in patients who underwent laparoscopic RHCs [18-22]. Our study

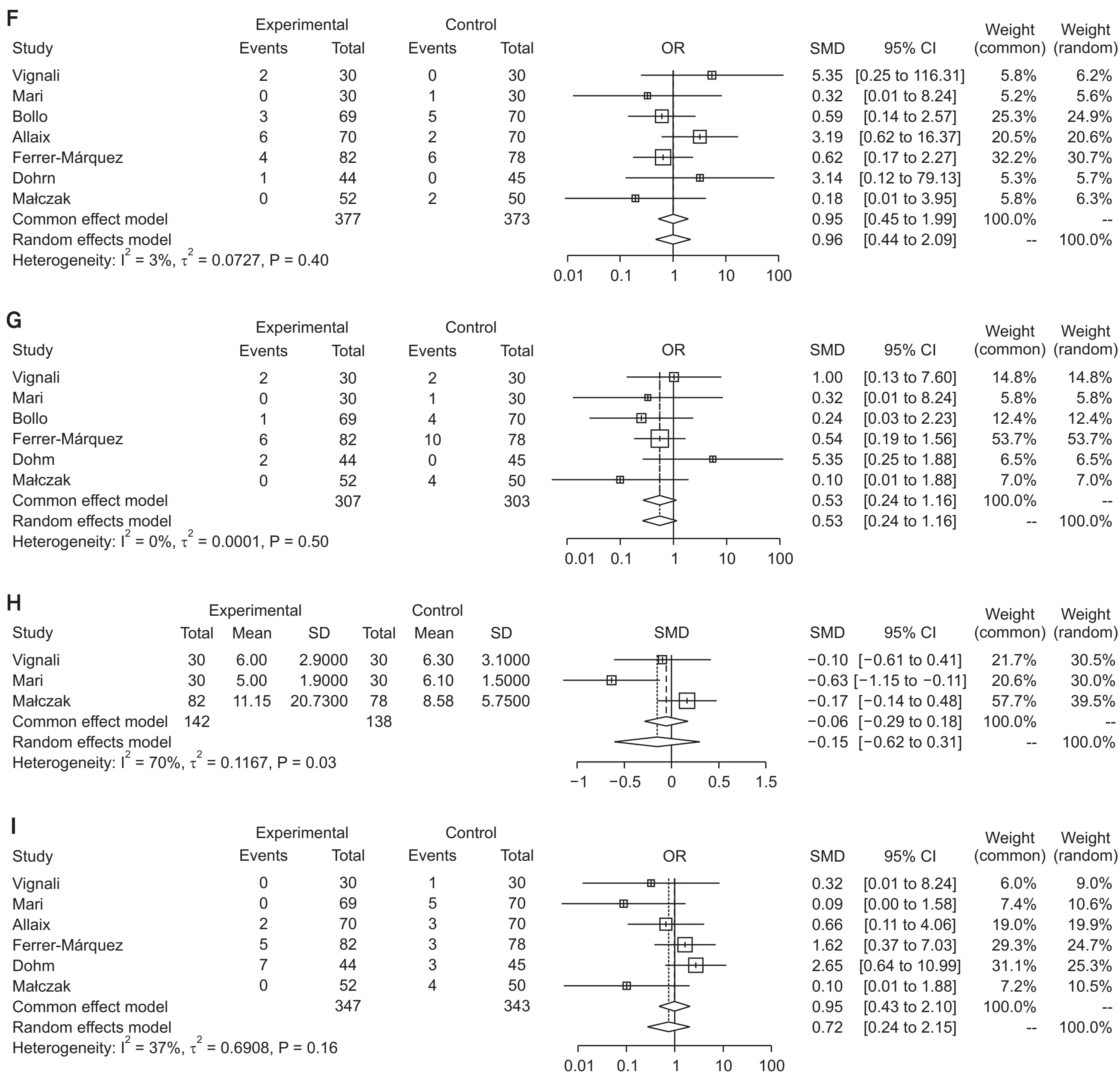

Fig. 3. Continued.

also confirmed that intraoperative blood loss and conversion rates were not different. Our study showed a significant difference in the extraction sites between the 2 modalities. In the ICA group, the Pfannenstiel incision was the most common (54.1%), while the RUQ and midline incision were more common in the ECA group (RUQ, 44.0%; midline, 42.1%). When considering the location of the tumor, the RUQ or midline incision was convenient for pulling out the dissected colon from the abdomen in the ECA group. In cases of ICA, the Pfannenstiel incision may be preferred by surgeons for cosmetic reasons. In addition, it might be selected because of the lower possibility of incisional hernia compared with the midline incision [23,24]. Irrespective of the reason, one advantage of ICA over ECA is the possibility of selecting an extraction site.

Although our study showed reduced postoperative pain on POD 2 in patients after ICA, it was similar between both groups on POD 3. Thus, we could not conclude whether there was a benefit with regard to postoperative pain in ICA, and the main reason for this phenomenon remains unclear. When our previous study compared the natural-orifice specimen-extraction procedure with conventional robotic surgeries in rectal cancer patients, a significant reduction of postoperative pain was confirmed [25]. We believe that the pain is relieved because the pain felt by the compatible person was reduced

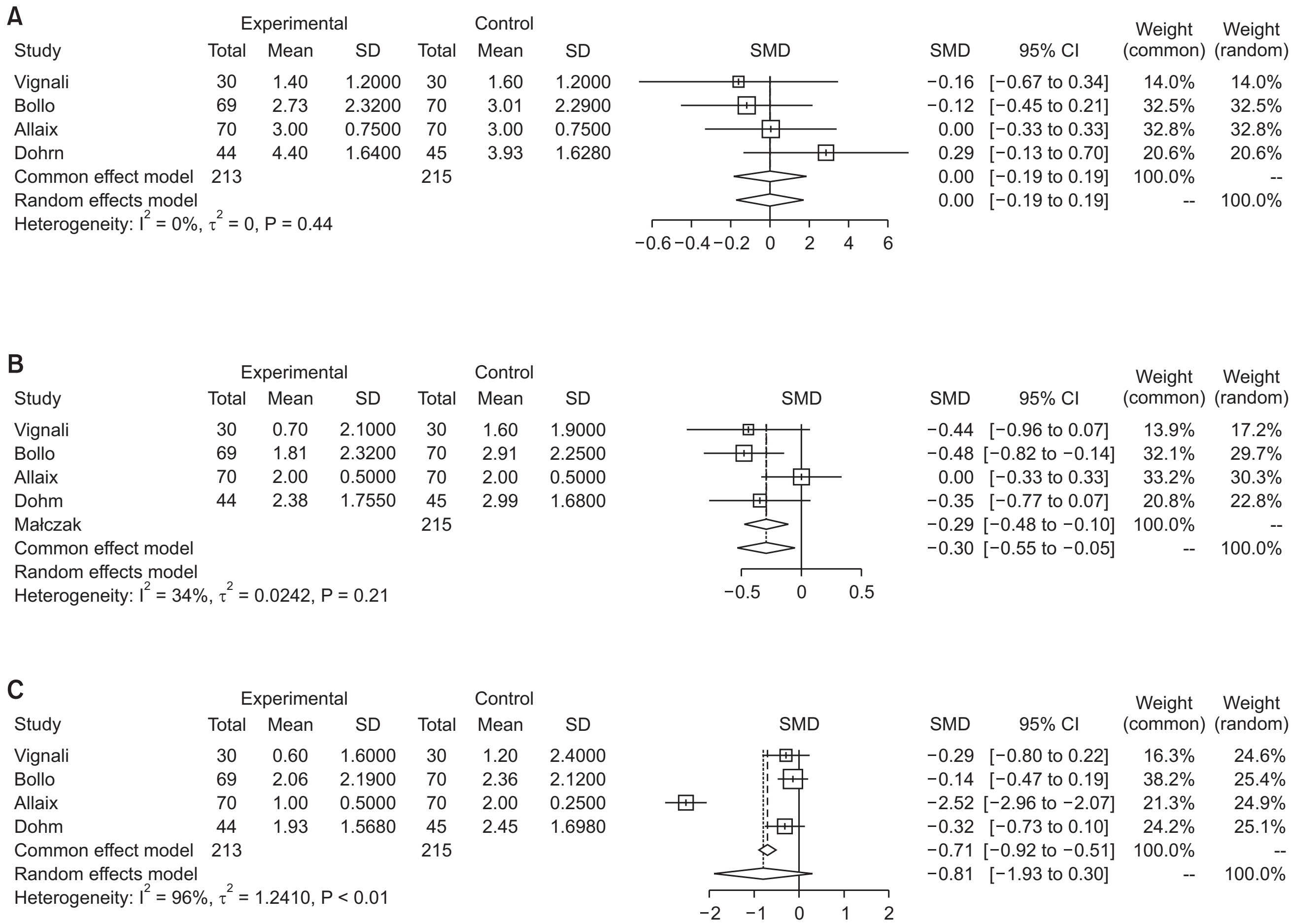

Fig. 4. Forest plot of postoperative pain (visual analogue scale) between intracorporeal and extracorporeal anastomosis. (A) Postoperative pain in postoperative day (POD) 1. (B) Postoperative pain in POD 2. (C) Postoperative pain in POD 3. SD, standard deviation; SMD, standardized mean difference; CI, confidence interval.

by removing the tumor-extraction skin area. However, in this meta-analysis, there was no significant difference in the total incision length between the ICA and ECA groups. Therefore, it is important to determine whether there is a difference in postoperative pain depending on the tumor-extraction site. Existing studies have yielded inconsistent results [26,27], making it difficult to draw precise conclusions. Nevertheless, in the sensitivity analysis, except for 1 study, there were results showing differences in the length of the incision site. Therefore, additional research is required to determine whether the incision length can be sufficiently reduced through ICA.

During surgery for colorectal disease, anastomosis leakage is one of the major complications, with values as high as 20% [28]. There is a concern that ICA might increase anastomosis leakage because reinforcement suturing is difficult when performing ICA in MIS. Similar to the results of a previous study, there was no significant difference in anastomotic leakage between the ICA and ECA groups. Therefore, anastomosis leakage is not an important complication to worry about when performing ICA. However, when ICA is first implemented, it is predicted that a learning curve period will be required. Therefore, the extent to which these learning curves were considered in the studies included in this meta-analysis is questionable. In RCTs, the results would be from experienced surgeons who might be more skilled in MIS than beginners. For beginners without much experience in ICA, the results of anastomotic leakage may differ. Thus, this should be considered carefully before concluding about the safety of ICA.

In our study, there was no significant difference in the body mass indices [BMIs] of included patients between the ICA and ECA groups. Obese patients with a higher BMI may benefit from ICA because they will be spared from the additional dissections associated with ECA. Vignali et al. [29] reported that ICA did not differ from ECA in short-term outcomes, except for the rate of incisional hernia (in patients with BMI of >30 kg/m^2). Lendzion and Gilmore [30] reported the results of obese patients (BMI of >30 kg/m^2) after laparoscopic RHC with ICA and showed a short duration of hospitalization and low morbidity. However, they demonstrated the outcomes of only 11 patients and did not compare them with the ECA group. Therefore, a study on whether the advantages of performing ICA in obese patients can be highlighted more than those of performing ECA seems to be a very interesting topic.

This study had some limitations. The high heterogeneity among studies, including operation time, intraoperative blood loss, length of incision, and length of hospitalization, should be considered. Although we performed a sensitivity analysis by a one-on-one exclusion, high or moderate heterogeneity was still found. Because we included only 1 study on robotic RHC, it is necessary to analyze whether the results will differ when more studies using robotic surgery are included. Finally, each study reported different continuous data that were sometimes missing. Therefore, we needed the mean and its standard deviation or the median and interquartile range using the equation by Hozo et al. [31].

In conclusion, this meta-analysis showed that laparoscopic or robotic right hemicolectomy with ICA showed perioperative outcomes and safety comparable to those of ECA. There was a difference in the incision type and postoperative pain on POD 2 between the ICA and ECA groups. We suggest that laparoscopic or robotic surgery with ICA is feasible and not inferior to surgery with ECA. Nevertheless, whether these advantages are sufficient to overcome the disadvantage of longer operation time is questionable.

SUPPLEMENTARY MATERIALS

Supplementary Table 1 and Supplementary Figs. 1 and 2 can be found via https://doi.org/10.4174/astr.2024.106.1.1.

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Conflict of Interest

Jeonghyun Kang is been a member of editorial board of *Annals of Surgical Treatment and Research*. He was were not involved in the review process of this article. No other potential conflict of interest relevant to this article was reported.

ORCID iD

Chinock Cheong: https://orcid.org/0000-0002-7723-0053
Na Won Kim: https://orcid.org/0000-0003-1710-4183
Hye Sun Lee: https://orcid.org/0000-0001-6328-6948
Jeonghyun Kang: https://orcid.org/0000-0001-7311-6053

Author Contribution

Conceptualization: CC, JK
Data curation: CC, NWK, JK
Investigation, Visualization: CC
Formal Analysis: HSL
Supervision: JK
Writing – Original Draft: CC
Writing – Review & Editing: JK

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