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Laparoscopic versus open surgery for adhesional small bowel obstruction: a systematic review and meta-analysis of case–control studies

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Abstract

Background Small bowel obstruction (SBO) due to adhesions is a common acute surgical presentation. Laparoscopic adhesiolysis is being performed more frequently. However, the clear benefits of laparoscopic adhesiolysis (LA) compared with traditional open adhesiolysis (OA) remain uncertain. The aim of this study was to compare the outcomes of LA versus OA for SBO due to adhesions.
Methods A systemic literature review was conducted using PRISMA guidelines. A search was conducted using MEDLINE, EMBASE, PubMed and Cochrane Databases of all randomised controlled trials (RCT) and case-controlled studies (CCS) that compared LA with OA for SBO. Data were extracted using a standardised form and subsequently analysed.
Results There were no RCT. Data from 18 CCS on 38,927 patients (LA = 5,729 and OA = 33,389) were analysed. A meta-analysis showed that LA for SBO has decreased overall mortality (LA = 1.6% vs. OA = 4.9%, $p < 0.001$) and morbidity (LA = 11.2% vs. OA = 30.9%, $p < 0.001$). Similarly, the incidences of specific complications are significantly lower in the LA group. There are significantly lower reoperation rate (LA = 4.5% vs. OA = 6.5%, $p = 0.017$), shorter average operating time (LA = 89 min vs. OA = 104 min, $p < 0.001$) and a shorter length of stay (LOS) (LA = 6.7 days vs. OA = 11.6 days, $p < 0.001$) in the LA group. In the CCS, there is likely to be a selection bias favouring less complex adhesions in the LA group that may contribute to the better outcomes in this group.
Conclusions Although there is a probable selection bias, these results suggest that LA for SBO in selected patients has a reduced mortality, morbidity, reoperation rate, average operating time and LOS compared with OA. LA should be considered in appropriately selected patients with acute SBO due to adhesions.

Keywords Bowel obstruction · Laparoscopic · Open surgery · Meta-analysis · Case–control studies

Acute small bowel obstruction (SBO) is a common emergency surgical presentation in the developed world, accounting up to 20% of surgical admissions with an acute abdomen [1, 2]. The most common aetiology of SBO is intra-abdominal post-operative adhesions, followed by abdominal wall hernias, tumours, Crohn's disease, volvulus and post radiation stricture [1, 3, 4]. In the Western community, up to 80% of SBO are caused by post-operative intra-abdominal adhesions [3, 4].

Up to 75% cases of adhesional SBO can be initially treated with non-operative management, although up to half of these patients shall fail non-operative management and require surgical intervention [5, 6]. Traditionally, the surgical treatment is open adhesiolysis (OA) via laparotomy. However, OA may result in further intra-abdominal adhesions [7] and subsequent recurrent SBO. It is known that 14–17% of patients developed adhesional SBO within 2 years of open colorectal or other gastrointestinal surgery [8].

The improved techniques of laparoscopic surgery have resulted in laparoscopic adhesiolysis (LA) becoming an alternative surgical treatment for adhesive SBO. The first case of LA was in the early 1970s by Mouret [9]. In 1991, Bastug reported successful LA in adhesional SBO in

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America [10]. Since then, LA has become more widespread as laparoscopic surgery gained popularity. The purported benefits of LA are reduced risk of morbidity (in particular pneumonia and wound infection), mortality and length of hospital stay [11, 12]. Although many case-controlled studies and cohort studies have been published in the past, no randomised controlled trial (RCT) has been conducted comparing the benefits of LA with OA. A recent meta-analysis reported reduced risk of morbidity, mortality and surgical infections but there were concerns regarding the duration of operation and the incidence of iatrogenic enterotomy [12]. Apart from that, surgeons generally prefer OA in selected group of patients such as extensive dense adhesions, multiple previous laparotomies or patients with multiple medical co-morbidities given the lack of conclusive studies [11]. The aim of this study was to compare LA and OA for the surgical treatment of SBO and provide evidence-based guidance to the selection of the most appropriate operative technique.

Methods

Study protocol

Ethics approval is not required for meta-analysis/systematic reviews as it is based on published literature. A systemic search was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [13]. The following databases were searched for relevant studies: PubMed (from 1946), EMBASE (from 1949), Google Scholar and Google. The search terms "laparoscopic", "laparoscopy", "open", "adhesiolysis", "intestinal obstruction" and "small bowel obstruction" were used in combinations. The reference lists of selected articles were searched for relevant studies. No language restrictions were used, and no other exclusions were placed.

Study selection

All RCT and case-controlled studies (CCS) that compared LA with OA for SBO from 1990 to 2017 were included in this meta-analysis for further data analysis. All other non-comparative studies such as case series and case reports were excluded.

Data extraction

The data were extracted and critically appraised by two independent authors (GS and GE). The following data were extracted using a standardised data extraction form: Patient characteristics included age, BMI, American Society of Anaesthetists (ASA) classification, previous abdominal surgery, average number of previous abdominal surgeries, previous episodes of SBO and duration of symptoms. Primary outcomes included conversion from LA to OA, intra-operative complications, reoperation rates, mortality and various types of morbidity. Secondary outcomes included mean operating time, length of stay (LOS), solid food resumption and resumption of bowel movement.

Statistical analysis

Pooled odds ratios and 95% confidence intervals were calculated for patient outcomes for SBO using a random effects model [14]. Weighted mean difference was calculated for continuous variables such as mean operating time and total LOS [15]. Relative risk ratios were calculated for dichotomous variables such as post-operative morbidity and mortality [15]. Intention-to-treat analysis was performed where patients were converted to open adhesiolysis or when there were missing data. Yates half correction was used in studies that reported no events for outcomes [15, 16]. Heterogeneity was tested with Cochran's Q statistic, with $p<0.10$ indicating heterogeneity, and the degree of heterogeneity was quantified using the I^2 statistic, which represents the percentage of the total variability across studies which is due to heterogeneity [16, 17]. I^2 values of 25, 50 and 75% corresponded to low, moderate and high degrees of heterogeneity, respectively [16, 17]. All statistical analyses were performed with Comprehensive Meta-analysis (version 2.0), Biostat, Englewood, NJ (2005).

Results

The literature search generated a total of 1421 articles. Out of this, articles were excluded based on titles, abstracts, full texts or a combination of these (Fig. 1). There were no published RCT. Two studies that satisfied our inclusion criteria were excluded: a current RCT was still recruiting participants [18] and a CCS where the journal could not be located [19]. A total of 18 CCS were included in this meta-analysis [20–37] (Fig. 1). 11 (61.1%) CCS were from North America and all studies were from tertiary referral teaching hospitals.

The total number of patients were 38,927 with 5729 patients in the LA group and 33,389 patients in the OA group (Table 1). The average age of patients was 59 years in LA group and 63.3 years in OA group ($p=0.13$). Approximately one-third of the patients were male. ASA classifications were provided in 5 studies [29–31, 35, 36]. There was a significantly higher proportion of patients with ASA 1 and 2 in the LA group, and significantly higher proportion of patients with ASA 3 and 4 in the OA group (Table 2). There were no significant differences in both groups for BMI (24.9 for LA vs. 23.9 for OA, $p=0.39$), duration of symptoms (LA = 1.74 days vs. 2.07 days, $p=0.58$), average number

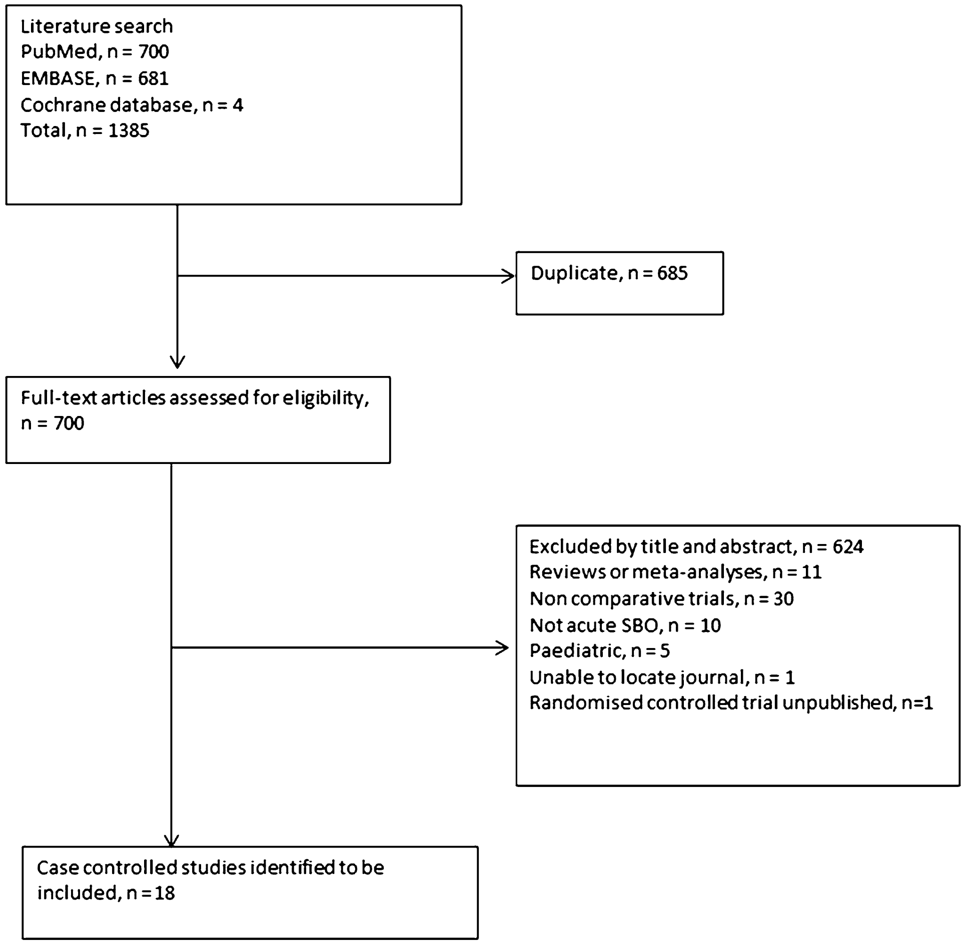

Fig. 1 PRIMSA diagram

Table 1 Study demographics and comparisons

Author	Year	Country	No of pt.			AGE (years)		Male gender (%)	
			Total	Lap	Open	Lap	Open	Lap	Open
Chopra [20]	2003	USA	75	34	52	59.7	58.7	–	–
Wullstein [21]	2003	Germany	104	52	52	59.3	64.8	14 (26.9)	12 (23.1)
Khaikin [22]	2007	USA	62	31	31	54.6	63	13 (41.9)	9 (29)
Mancini [23]	2008	USA	6165	702	5643	56.6	63.1	218 (31.1)	2021 (35.8)
Grafen [24]	2010	Switzerland	93	90	3	59	75	29 (32.2)	2 (66.7)
Johnson [25]	2011	USA	119	63	56	67	69	24 (38.1)	26 (46.4)
Okamoto [26]	2012	Japan	53	28	25	62	58.8	15 (53.6)	11 (44)
Davies [27]	2014	USA	102	38	64	52.5	57	13 (34.2)	28 (43.8)
Kelly [28]	2014	USA	9619	1434	8185	58.2	63.5	458 (31.9)	3109 (38)
Lombardo [29]	2014	USA	6762	1256	5506	57.4	63.4	415 (33)	2077 (37.7)
Saleh [30]	2014	Canada	4616	919	3697	57	62.3	285 (31)	1381 (37.4)
Byrne [31]	2015	USA	269	83	186	65.1	66.5	41 (49.4)	71 (38.2)
Sharma [32]	2015	USA	1750	51	1699	65.3	66	14 (27.5)	658 (38.7)
Lin [33]	2016	China	202	101	101	57.3	58.1	48 (47.5)	50 (49.5)
Hackenberg [34]	2016	Finland	91	25	66	63.8	72	13 (52)	22 (33)
Nordin [35]	2016	Sweden	105	71	34	34	34	13 (38.2)	13 (38.2)
Yao [36]	2017	Japan	156	78	78	69	77	42 (53.8)	39 (50)
Behman [37]	2017	Canada	8584	673	7911	63.4	67.2	287 (42.6)	3075 (38.9)
Total			38,927	5729	33,389	59 ± 7.7	63.3 ± 9.2	1942 (33.9)	12,604 (37.8)

Table 2 Patient co-morbidities and operative findings

	LA	OA	*p* value
ASA 1, *n* (%)	118 (2.1)	259 (0.8)	< 0.01
ASA 2, *n* (%)	1168 (20.4)	3295 (9.9)	< 0.01
ASA 3, *n* (%)	938 (16.4)	4749 (50)	< 0.01
ASA 4, *n* (%)	110 (1.9)	1126 (3.4)	< 0.01
ASA 5, *n* (%)	1 (0.02)	20 (0.06)	N/A
ASA = not defined, *n* (%)	3394 (59.2)	23,840 (71.6)	N/A
BMI	24.9	23.9	0.39
Duration of symptoms (Days)	1.74	2.07	0.58
Average number of previous abdominal surgery	1.4	2.3	0.14
Average number of previous SBO	0.7	0.8	0.9
No. of bowel resections	150 (2.6%)	2708 (8.1%)	< 0.001
Estimated blood loss (ml)	49.2	102.2	< 0.001

of previous abdominal surgeries (LA = 1.4 vs. OA = 2.3, $p = 0.14$) and average number of previous SBO (LA = 0.7 vs. OA = 0.8, $p = 0.9$) (Table 2).

Primary outcomes

Conversion to open surgery

Twelve studies reported the incidence of conversions from laparoscopic to open surgery [20–27, 29, 31, 35, 36]. A total of 706 patients (12.32%) in the LA group needed a conversion to open surgery. The most frequent reason for conversion to open surgery was dense adhesions ($n = 71$). Other reasons for conversion included inability to assess viability of bowel ($n = 27$), bowel injury ($n = 22$), technical difficulties ($n = 11$), bowel requiring resection ($n = 8$), tumour/mass ($n = 7$), bowel perforation ($n = 6$), unable to achieve pneumoperitoneum ($n = 2$), bleeding ($n = 1$) and pus ($n = 1$). Unfortunately, the indication was not defined in 527 (74.6%) cases. All patients having conversion to open surgery were included in LA group for analysis on an intention-to-treat basis.

Intra-operative complications

Four studies reported the incidence of intra-operative complications; bowel or mesenteric injury and bleeding [20, 21, 24, 34]. The overall intra-operative morbidity for LA and OA combined was 17.1%. There was no significant difference in the overall intra-operative morbidity in both groups (LA = 13.4% vs. OA = 20.1%, OR 0.82, 95% CI 0.27–2.53, $p = 0.73$) (Table 3). The most frequent intra-operative complication was bowel injury (LA = 96.3% and OA = 97.5%) with no significant difference between the two groups (LA = 12.9%, OA = 19.7%, OR 0.82; Cl 0.26–2.61, $p = 0.74$). There were significantly more bowel resections in the OA group (n = 2708, 8.1%) compared with the LA group ($n = 150$, 2.6%, $p < 0.001$) (Table 2). The estimated mean blood loss was significantly lower in the LA group ($n = 49.2$ ml) compared with the OA group ($n = 102.2$ ml, $p < 0.001$) (Table 2).

Post-operative morbidity

Sixteen studies reported the incidence of post-operative complications [20–23, 26–34, 36, 37]. The overall morbidity for both groups was 28.1%. The overall morbidity was significantly lower in the LA group ($n = 627$, 11.2%) compared with the OA group ($n = 10{,}297$, 30.9%), (OR = 0.23, 95% CI 0.16–0.34, $p < 0.001$) (Fig. 2; Table 3). The reported complications in studies included wound, respiratory, cardiac, incisional hernia, sepsis, leakage, abscess, ileus, urinary tract infection, renal complications, venous thromboembolism (VTE) and neurological complications (Table 3). The majority of these had a significantly lower incidence in the LA group with no evidence of statistical heterogeneity for any particular complication (Table 3).

Twelve studies reported the incidence of reoperations [20, 21, 24, 25, 27–33, 35]. The reoperation rate was significantly lower in the LA group ($n = 187$, 4.5%) compared with the OA group ($n = 1268$, 6.5%), (OR 0.71, 95% CI 0.53–0.94, $p = 0.017$). There was evidence of statistical heterogeneity, but it was not statistically significant ($I^2 = 36.12\%$, $p = 0.1$). The indications for reoperation included unresolved SBO, anastomotic leak, bowel injury, bowel ischemia and haemorrhage.

Mortality

All studies reported the mortality rate [20–37]. The mortality rate was significantly lower in the LA arm (1.6%) compared with the OA arm (4.9%) (OR 0.34, 95% CI 0.25–0.45, $p < 0.001$) (Table 3; Fig. 3). There was evidence of statistical heterogeneity, but it was not statistically significant ($I^2 = 14.71\%$, $p = 0.28$). The reported causes of mortality were multi-organ failure, respiratory complications, sepsis and bowel ischemia.

Secondary outcomes

Sixteen studies reported the operative duration [20–22, 24–37]. The mean operative duration was longer in the OA group (104.7 min ± 25.09) compared with the LA group (89.2 min ± 39.25) ($p < 0.001$) (Table 4). When the mean operative time was further assessed after 2014, there was a

Table 3 Primary outcomes

Morbidity	# of studies	LA (%)	OA (%)	OR	95% CI	*p* value	I^2 (p)
Overall intra-operative morbidity	4	13.4	20.2	0.82	0.27–2.53	0.73	54.12 (0.09)
Bowel injury	4	12.9	19.7	0.82	0.26–2.61	0.74	55.29 (0.08)
Mesentery injury	1	0	0.6			N/A	N/A
Haemorrhage	1	0.5	0			N/A	N/A
Overall post-operative morbidity	16	11.2	30.9	0.23	0.16–0.4	< 0.001	91.47 (< 0.001)
Respiratory complications	11	1.8	8.6	0.22	0.18–0.28	< 0.001	0 (0.83)
Cardiac complications	8	0.4	1.3	0.39	0.24–0.64	< 0.001	0 (0.73)
Wound complications	11	2.2	11.5	0.26	0.14–0.47	< 0.001	0 (0.83)
Post-operative sepsis	5	2.7	8.7	0.31	0.24–0.39	< 0.001	0 (0.74)
Intra-abdominal abscess	5	1.3	3.1	0.4	0.29–0.57	< 0.001	0 (0.72)
Venous thromboembolism (VTE)	8	0.8	2.5	0.34	0.23–0.49	< 0.001	0 (0.65)
Incisional hernia	3	1.9	10.8	0.17	0.11–0.24	< 0.001	0 (0.77)
Urinary tract infections (UTI)	4	1.6	5.5	0.31	0.21–0.48	< 0.001	0 (0.94)
Renal complications	4	0.3	1.4	0.28	0.14–0.56	< 0.001	0 (0.46)
Post-operative ileus	5	7.0	13.6	0.44	0.17–1.17	0.09	55.55 (0.06)
Leakage	2	1.5	2.5	0.89	0.03–26.07	0.95	61.04 (0.11)
Neurological complications	4	0.3	0.4	0.78	0.41–1.47	0.44	0 (0.55)
Bleeding	2	0.9	3.9	0.41	0.19–0.87	0.02	14.46 (0.28)
Haematoma	1	6.3	12.8			N/A	N/A
Seroma	1	18.8	4.3			N/A	N/A
Fistula	2	6.9	1.3	1.53	0.12–19.7	0.75	39.49 (0.2)
Unclassified	3	12.5	22.7	0.35	0.12–0.98	0.05	0 (0.99)
Reoperations	12	4.5	6.5	0.71	0.53–0.94	0.017	36.12 (0.1)
Mortality	16	1.6	4.9	0.34	0.25–0.45	< 0.001	14.71 (0.28)

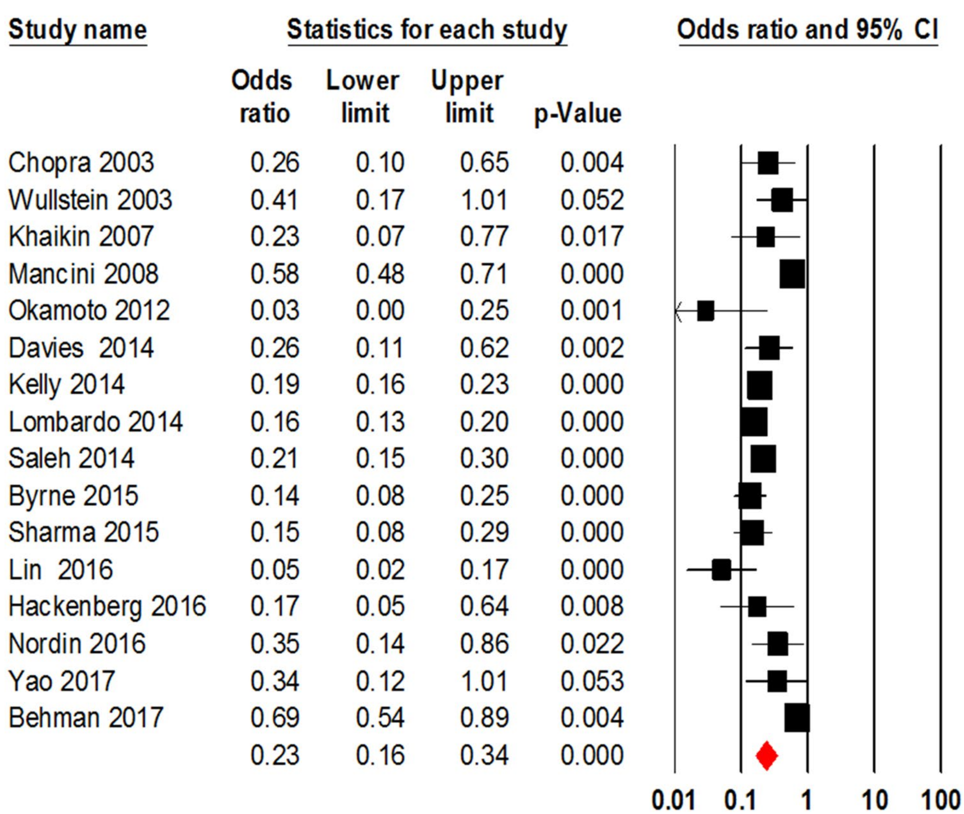

Fig. 2 Forest plot for overall post-operative morbidity. This favours LA with OR 0.23 (95% CI 0.16–0.34, $p < 0.001$)

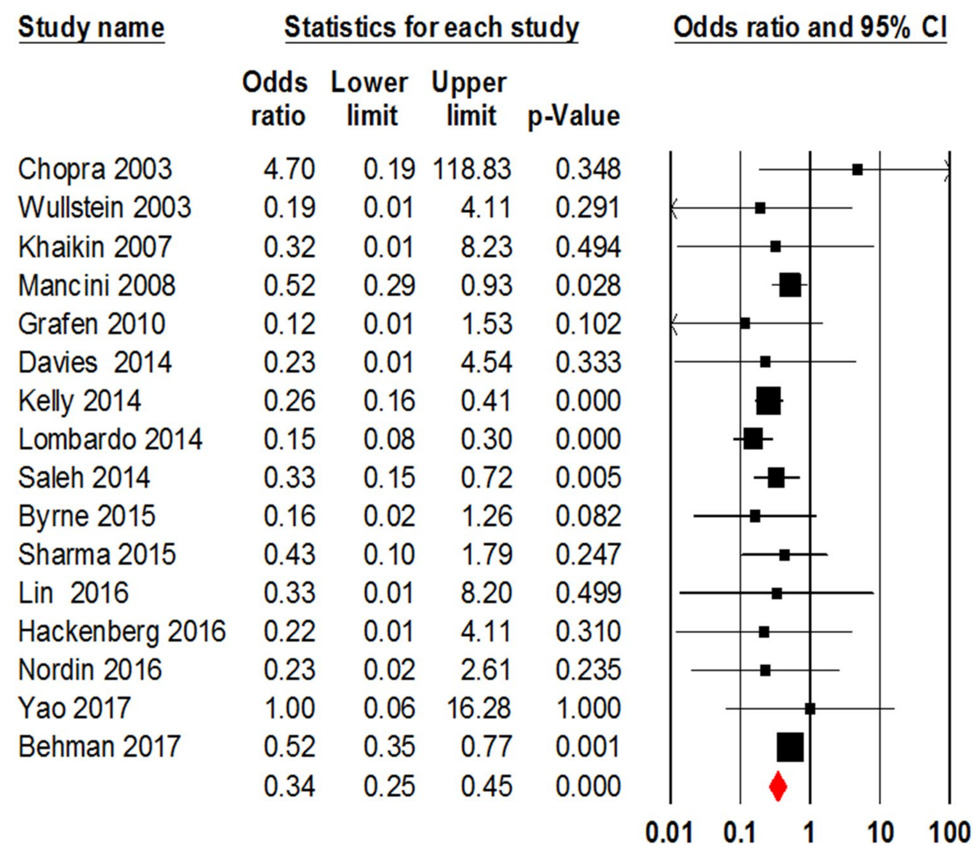

Fig. 3 Forest plot for mortality. This favours LA with OR 0.34 (95% CI 0.25–0.45, $p < 0.001$)

Table 4 Secondary outcomes

	# of studies	LA	OA	*p* value
Mean length of hospital stay (days)	17	6.7 ± 2.34	11.6 ± 4.62	< 0.001
Mean operative duration (OT) (min)	16	89.2 ± 25.09	104.7 ± 39.25	< 0.001
Mean OT before 2014 (min)	6	100.2 ± 23.55	112.3 ± 49.49	N/A
Mean OT after 2014 (min)	10	82.6 ± 24.74	100.1 ± 33.82	N/A
Solid food resumption (days)	3	3.7 ± 1.21	6 ± 0.84	0.05
Return of bowel movement (day)	4	2.8 ± 0.72	4.1 ± 1.48	0.19
NGT usage (days)	1	2.3	3.2	N/A

slight reduction in the LA group (LA = 82.6 min ± 24.74 vs. OA = 100.1 min ± 33.82).

Seventeen studies reported the LOS [20–29, 31–37]. The average LOS was significantly lower for the LA group (6.7 ± 2.3 days) compared with in the OA group (11.6 ± 4.6 days) ($p < 0.01$) (Table 4).

There was no significant difference between LA and OA for solid food resumption, nasogastric tube use and return to normal activities (Table 4).

Discussion

Since the introduction of laparoscopic surgery into general surgical practice in early 1990s, it has become the routine technique in gallstone surgery [38], elective colorectal surgery [39] and appendicectomy [40]. The advantages of laparoscopic surgery include decreased overall morbidity, mortality, cost, LOS, post-operative pain, an earlier return to work and resumption of normal daily activity [38, 40–43]. The results of this meta-analysis show a significant benefit in performing LA in adhesional SBO in a selected group of patients. We found a statistically significant reduction in the overall mortality and morbidity in the LA group. The incidence of specific post-operative complications including respiratory, cardiac, wound, sepsis, abscess, VTE, incisional hernia, UTI, renal complications and bleeding were significantly lower in the LA group compared to the OA group. There was a significantly shorter LOS and a lower reoperation rate in the LA group.

As all the studies used in the present study were CCS, there is likely to be a bias in the selection of patients for LA that favours a better outcome in the LA group. We tried to assess this bias by the number of previous abdominal operations performed and the incidence of previous episodes of SBO. Although the OA group had more previous surgeries, this difference was not significant. There was no difference in the incidence of previous episodes of SBO. No study reported the types, clinical indications and frequency of previous laparotomies. The threefold higher incidence of bowel resections in the OA group would indicate that the OA group had a high incidence of strangulation, perforation and / or a higher incidence of more complex adhesions requiring a more extensive dissection, supporting there was a selection bias that favoured LA. Furthermore, the higher incidence of bowel resection shall be associated with an increased risk of morbidity and mortality. The significantly higher proportion of ASA 1 and ASA 2 patients in the LA group is further evidence of a selection bias that favours better outcomes in the LA group. A potential confounding factor for more frequent selection of OA in the ASA 3 and ASA 4 patients is some of these patients may have been unwell with strangulation or perforation which was the reason for selecting OA over LA.

Having acknowledged the likely selection bias in favour of LA, it is difficult to ascertain the extent of patient selection bias in our study, as the majority of studies did not report their selection criteria for LA or OA. However, of those studies that reported choice of surgery [21, 22, 25, 26, 34, 36], patient's clinical situation and surgeon preference were the major influence in determining type of surgery performed pre-operatively. It is likely that surgeons preferentially selected patients who had a higher likelihood of a more complex adhesive SBO with strangulation, perforation or multiple adhesions to have OA. Other reported exclusion criteria for LA include degree of abdominal distension, diffuse peritonitis and abdominal surgery within 30 days [21, 34]. Patients selected for LA may include cases with a higher likelihood of a single band or localised adhesions such as patients with a prior history of appendicectomy or gynaecological surgery [3].

Although there is a selection bias that confounds the interpretation of the outcomes, it is clear that an initial laparoscopic approach is an acceptable strategy in selected patients. The selection criteria for LA are not able to be clearly determined, but are likely to include those with a low risk of strangulation or perforation, a reasonable possibility of single or a low number of adhesions and no severe distension. Conversely, OA selection criteria would be cases of probable strangulation or perforation, known extensive adhesions or a high likelihood of extensive adhesions. Conversion to open surgery should not be considered as a failure of the laparoscopic approach, as it is usually required for pathology that cannot be safely managed at LA, as was noted by the indications for conversions reported in this study.

Another confounding factor is the patients' co-morbidities. We found significant bias of ASA 1 and 2 towards LA approach and ASA 3 and 4 towards OA approach. Previous studies have found association between higher ASA classifications and higher post-operative complications [44, 45]. Therefore, the reduced morbidity in the LA group may be related in part to the lower ASA classifications in the LA group. Given the higher proportion of ASA 3 and ASA 4 patients in the LA group, a subgroup analysis of these patients was attempted. Unfortunately, although there were five studies that defined the ASA classification [29–31, 35, 36], there were no morbidity or mortality data for these ASA classifications preventing the subgroup analysis. The indication and type of previous abdominal surgery may also be an important influence for many surgeons whether LA or OA is selected to treat an adhesional SBO. However, we were unable to assess this, as most studies did not include the relevant information.

One of the concerns for laparoscopic surgery in adhesional SBO is iatrogenic bowel injury, either by inadvertent enterotomy during port insertion, while dividing adhesions or during laparoscopic manipulation of the bowel. A recent meta-analysis showed a trend towards higher incidence of intra-operative bowel injury in the LA group [12]. The present study found the opposite trend with a slightly higher risk of intra-operative bowel injury in the OA group (19.7%) compared with the LA group (12.9%) that was not significant ($p = 0.74$). This difference between studies may be attributed to improved laparoscopic techniques or better patient selection in the additional four studies used in the present study. However, it may also reflect a selection bias where more complex cases that are more likely to have an inadvertent bowel injury are treated with OA.

Another early criticism of LA for adhesional SBO was the longer average operating time (OT) compared with OA. Previous meta-analyses [11, 12] showed a trend towards longer OT in the LA group, although not statistically significant. In our study, we found the opposite with a significantly shorter operating time in LA (89.2 min) compared with OA (104.7 min). When studies were further subcategorised to before and after 2014, when the most recent meta-analysis

[12] was performed, there was a reduction in average OT in both groups, especially in the LA group (82.6 min) compared with the OA group (100.1 min). Once again, the likely explanation for the reduced OT is a selection bias where patients more likely to have less complex adhesions that take less time to dissect are selected for LA. These cases may include adhesive SBO subsequent to appendicectomy or gynaecological surgery [3], whereas patients having had complex gastrointestinal resections or multiple previous laparotomies are more likely to be selected for OA.

The conversion rate for LA in this study (12.3%) was much lower than conversion rates reported in earlier studies (40%) [11]. This reduction in conversion rates is expected with better laparoscopic skills and experience, as has been demonstrated in other emergency gastrointestinal surgeries where laparoscopic surgery has become routine such as laparoscopic cholecystectomy where conversion rates now ranges between 2.6 and 7.7% [46, 47] and laparoscopic appendectomy with conversion rates between 4.2 and 9.5% [48, 49]. The most common cause of conversion to open was dense adhesions (10.1%), followed by inability to assess the viability of bowel (3.8%), ischaemic bowel (3.3%) or a bowel injury (3.1%). The lower conversion rate may also reflect the use of better selection criteria for LA.

Our meta-analysis provides evidence that LA is a safe method in treating adhesional SBO in selected group of patients compared with the traditional OA approach with reduced mortality, morbidity, reoperation rate, average operating time and LOS. These results are no doubt effected by the selection bias that easier cases of adhesive SBO are treated with LA. Randomised controlled trials with long-term follow-up such as the first RCT comparing LA with OA currently underway by Sallinen et al. [18] are required to further validate the findings of this meta-analysis on case-controlled studies.

Compliance with ethical standards

Disclosures Gaik S. Quah, Guy D. Eslick and Michael R. Coxhas have no conflicts of interest and financial ties to disclose.

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