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REVIEWS

Safety of transvaginal hybrid NOTES cholecystectomy: a systematic review and meta-analysis

Mikael H. Sodergren · Sheraz Markar · Philip H. Pucher · Ismail A. Badran · Long R. Jiao · Ara Darzi

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Abstract

Background Despite increasing data regarding clinical outcomes following transvaginal hybrid NOTES cholecystectomy (TVC), a consensus regarding safety based on comparative studies has yet to be reached. The aim of this systematic review and meta-analysis was to compare safety and clinical outcomes of TVC with conventional laparoscopic cholecystectomy (CLC) for the treatment of benign gallstone disease.

Methods A comprehensive search for published studies comparing TVC and CLC was performed. Review of each study was conducted and data were extracted. All pooled outcome measures were determined using random-effects models.

Results Data were retrieved from 14 studies describing 1,145 patients. There was no difference in total complications (POR = 0.68; 95 % CI 0.40–1.14; $P = 0.14$), incidence of bile duct injury (POR = 1.33; 95 % CI 0.31–5.66; $P = 0.70$), Clavien–Dindo Grade II (POR = 0.48; 95 % CI 0.14–1.60; $P = 0.23$) or Grade III (POR = 0.63; 95 % CI 0.24–1.65; $P = 0.34$) complications between TCV and CLC. Time of return to normal activities was significantly reduced in the TVC group (WMD = −4.86 days; 95 % CI −9.33 to −0.39; $P = 0.03$), and there was a non-significant reduction in post-operative pain on days 1 (WMD = −0.80; 95 % CI −1.60 to 0.01; $P = 0.05$) and 3 (WMD = −0.89; 95 % CI −1.77 to −0.01; $P = 0.05$).

Conclusions TVC is safe when performed by appropriately trained surgeons and may be associated with a faster return to normal activities and decreased postoperative pain.

Keywords Transvaginal hybrid cholecystectomy · Complications · Meta-analysis · NOTES

M. H. Sodergren (✉) · S. Markar · P. H. Pucher ·
I. A. Badran · L. R. Jiao · A. Darzi
Department of Surgery and Cancer, St Mary's Hospital, Imperial College London, London 10th Floor QEQM Building, St. Mary's Hospital South Wharf Road, London W2 1NY, UK
e-mail: m.sodergren@imperial.ac.uk

Since the first clinical description of hybrid transvaginal cholecystectomy in 2007 [1], the concept of natural orifice translumenal endoscopic surgery (NOTES) has gained widespread publicity. Theoretical advantages of NOTES include decreased post-operative pain and morbidity such as wound infection and incisional abdominal wall hernias, as well as improved cosmesis. The idea of performing scarless surgery has appealed to many clinicians as the ultimate step in the evolution of minimally invasive abdominal surgery; however, these techniques have not yet reached widespread clinical adaptation. This is not only partly related to concerns regarding disinfection [2] and reliable closure of any potential enterotomy for transgastric or transcolonic NOTES [3] but also due to the fact that technological evolution of surgical tools and platforms is yet to catch up with our ideological innovation. Despite this, even complex abdominal interventions such as NOTES pancreatectomy have been shown to be feasible in the animal model [4] and pure NOTES procedures (with no trans-abdominal assistance) in humans, such as appendectomy [5] and ventral hernia repair [6], have been reported from specialist centers.

Due to the established safety of colpotomy as an access route transvaginal hybrid cholecystectomy is currently the most commonly performed clinical application. Publications of large patient series and case registries [7, 8] [9] have suggested transvaginal hybrid NOTES cholecystectomy (TVC) to be a safe procedure when performed by appropriately specialist minimally invasive surgeons in selected centers. There are now a number of randomized controlled trials and comparative studies comparing conventional laparoscopic cholecystectomy (CLC) with TVC. The aim of this systematic review and meta-analysis is to compare safety and clinical outcomes of CLC with TVC for the treatment of benign gallstone disease.

Methods

An electronic search was performed using Embase, MEDLINE, Web of Science and Cochrane Library (Issue 1, 2014) databases from 2000 to 2014. The search terms, 'laparoscopy', 'cholecystectomy', 'transvaginal', 'natural orifice translumenal endoscopic surgery', 'NOTES', and medical subject headings (MeSH) terms 'Laparoscopy'(MeSH), 'cholecystectomy'(MeSH) and 'natural orifice endoscopic surgery (MeSH) were used in combination with Boolean operators AND or OR. Two authors performed electronic searches independently in January 2014. The reference lists of articles obtained were also searched to identify further relevant citations. Finally, the search included the Current Controlled Trials Register (http://www.controlled-trials.com) and the Cochrane Database of Controlled Trials. Abstracts of the citations identified by the search were then scrutinized by two of the authors to determine eligibility for inclusion in the pooled analysis.

Publications were included if they were randomized controlled trials or comparative studies in which patients underwent either transvaginal or conventional multiport laparoscopic cholecystectomy and reported one of the outcome measures identified below. Studies were excluded if they were non-comparative or compared transvaginal cholecystectomy (TVC) with single-incision laparoscopic cholecystectomy and no reference to conventional multiport cholecystectomy (CLC). Standard three or four-port laparoscopic cholecystectomy was used as the experimental arm in the majority of studies, with ports most commonly placed in the epigastrium, right upper quadrant, right middle quadrant and infra-umbilical region. Transvaginal cholecystectomy was most commonly performed as hybrid procedure with an infra-umbilical camera port placed for safety to ensure no intra-peritoneal injury of the transvaginal port and for deployment of the laparoscopic clip applicator.

Primary outcome measures were total postoperative complications, bile duct injury, Clavien–Dindo grade II and III complications. Secondary outcome measures were operative time (min), length of hospital stay (days), pain score on postoperative days 1 and 3, and return to normal activity.

Statistical analysis

Data from eligible trials were entered into a computerized spreadsheet for analysis. Statistical analysis was performed using RevMan 5.2 (Review Manager version 5.2). Pooled odds ratios (POR) were calculated for the effect of transvaginal cholecystectomy (TVC) on discrete variables such as total complications, incidence of bile duct injury, Clavien–Dindo grade II and III complications. Weighted mean differences (WMD) were calculated for the effect of TVC on continuous variables such as operative time, length of hospital stay, postoperative pain score day 1 and day 3, and return to normal activity. All pooled outcome measures were determined using random-effects model as described by DerSimonian and Laird [10]. Heterogeneity among trials was assessed by means of the I^2 statistic. Statistical significance was assigned when the P value was <0.05.

Results

The literature search identified 14 publications [11–24] that met the inclusion criteria for this pooled analysis. Figure 1 shows the preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram for the literature search. In total 1,145 cholecystectomy operations were included, 530 by TVC and 615 by CLC. Table 1 describes the method of TVC employed in each study included. Patient demographic data and indication for cholecystectomy are described in Table 2 where available. Tables 3 and 4 outline the main outcomes from each study.

Primary outcome measures

Total postoperative complications (Fig. 2)

Thirteen studies reported the incidence of postoperative complications [11–22, 24]. In total 5.6 % of patients in the TVC group developed a postoperative complication compared with 7.5 % in the CLC group. Pooled analysis showed no significant difference between the groups in the incidence of postoperative complications (POR = 0.68; 95 % CI 0.40–1.14; $P = 0.14$). There was no evidence of statistical heterogeneity ($I^2 = 0$ %).

Bile duct injury (Fig. 3)

Thirteen studies reported the incidence of bile duct injury [11–22, 24]. The incidence of bile duct injury was 0.6 % in the TVC group and 0.4 % in the CLC group. Pooled analysis showed no significant differences between the groups in the incidence of bile duct injury (POR = 1.33; 95 % CI

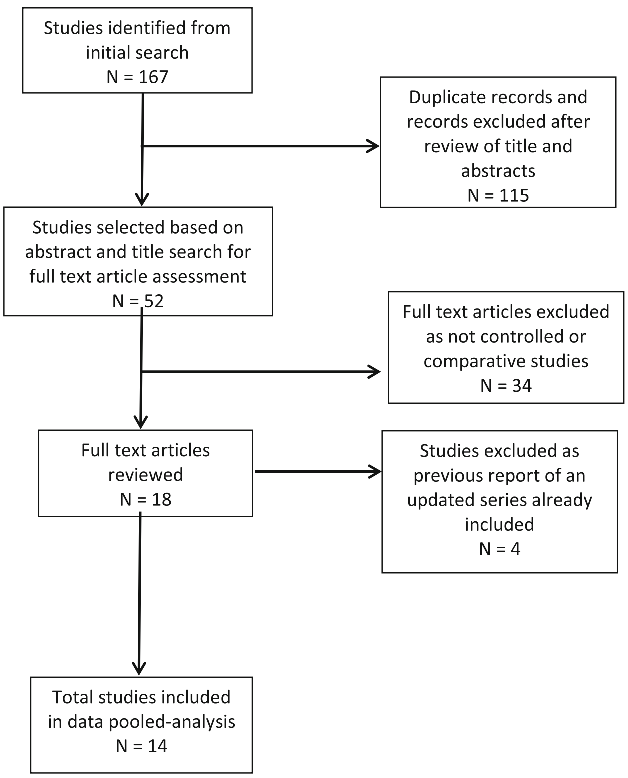


Fig. 1 PRISMA flowchart—systematic search and selection strategy

0.31–5.66; $P = 0.70$). There was no evidence of statistical heterogeneity ($I^2 = 0$ %).

Clavien–Dindo grade II complications (Fig. 4)

Thirteen studies classified complications by the Clavien–Dindo grading system [11–22, 24]. The incidence of Clavien–Dindo grade II complications was 0.4 % in the TVC group and 1.4 % in the CLC group. Pooled analysis showed no significant difference between the groups in the incidence of Clavien–Dindo grade II complications (POR = 0.48; 95 % CI 0.14–1.60; $P = 0.23$). There was no evidence of statistical heterogeneity ($I^2 = 0$ %).

Clavien–Dindo grade III complications (Fig. 5)

Thirteen studies classified complications by the Clavien–Dindo grading system [11–22, 24]. The incidence of Clavien–Dindo grade III complications was 1.5 % in the TVC group and 2.4 % in the CLC group. Pooled analysis showed no significant difference between the groups in the incidence of Clavien–Dindo grade III complications (POR = 0.63; 95 % CI 0.24–1.65; $P = 0.34$). There was no evidence of statistical heterogeneity ($I^2 = 0$ %).

Secondary outcome measures

Operative time (Fig. 6)

All 14 studies [11–24] reported the operative time for each procedure; however, three studies [15, 18, 24] failed to report standard deviations for the results and were therefore excluded from the results. Pooled analysis showed the operative time was significantly increased in the TVC group compared to the CLC group (WMD = 14.81 min; 95 % CI 8.58–21.04; $P < 0.00001$). There was evidence of significant statistical heterogeneity ($I^2 = 100$ %).

Length of hospital stay (Fig. 7)

Six studies reported the average length of hospital stay with standard deviations and were included in the pooled analysis [11, 14, 15, 17, 19, 22]. Pooled analysis demonstrated no significant difference between the groups in length of hospital stay (WMD = −0.14 days; 95 % CI −0.45–0.18; $P = 0.40$). There was evidence of significant statistical heterogeneity ($I^2 = 69$ %).

Time to return to normal activities (Fig. 8)

Four studies reported the average time taken to return to normal activity [13, 14, 20, 21]. Pooled analysis demonstrated the time to return to normal activities was significantly reduced in the TVC group (WMD = −4.86 days; 95 % CI −9.33 to −0.39; $P = 0.03$). There was evidence of significant statistical heterogeneity ($I^2 = 98$ %).

Postoperative pain score on day 1 (Fig. 9)

Five studies reported the postoperative pain score on day.11 [1, 12, 16, 20, 21]. Pooled analysis demonstrated a non-significant reduction in postoperative pain on day 1 in the TVC group (WMD = −0.80; 95 % CI −1.60 to 0.01; $P = 0.05$). There was evidence of significant statistical heterogeneity ($I^2 = 90$ %).

Postoperative pain score on day 3 (Fig. 10)

Four studies reported the postoperative pain score on day 3 [11, 12, 16, 21]. Pooled analysis demonstrated a non-significant reduction in postoperative pain on day 3 in the TVC group (WMD = −0.89; 95 % CI −1.77 to −0.01; $P = 0.05$). There was evidence of significant statistical heterogeneity ($I^2 = 93$ %).

Table 1 Surgical Technique employed for transvaginal cholecystectomy and study design

Publication	Method of transvaginal cholecystectomy	No of percutaneous abdominal trocars[a]	Pt no (TVC)	Pt no (CLC)	Study design	Conversions TVC to CLC	Conversions CLC to open
Borchert et al. [11]	Hybrid: 5-mm umbilical camera port initially used to ensure safe transvaginal access, then dissecting instrument used through this port. Transvaginal 10-mm port inserted for 42-cm long 45° laparoscope (Olympus Endo eye®), and long bent grasper through posterior vault adjacent to the 10-mm port. 5-mm multifire metaclip applicator introduce through the umbilicus for ligation of cystic duct and artery	Not available	95	96	Prospective controlled (non-randomized)	Not reported	Not reported
Borchert et al. [12]	Hybrid: 5-mm umbilical camera port initially used to ensure safe transvaginal access, then dissecting instrument used through this port. Transvaginal 12-mm port inserted for 42-cm long 45° laparoscope (Olympus Endo eye®), and long bent grasper through posterior vault adjacent to the 12-mm port. 5-mm multifire metaclip applicator introduce through the umbilicus for ligation of cystic duct and artery	1.3 (95 % CI 1.2–1.4)	41	51	Double-blind, randomized controlled trial	5	1
Bulian et al. [14]	Hybrid: 5-mm umbilical camera port initially used to ensure safe transvaginal access, then dissecting instrument used through this port. Transvaginal 10-mm port inserted for 42-cm long 45° laparoscope (Olympus Endo eye®), and long bent grasper through posterior vault adjacent to the 10-mm port. 5-mm multifire metaclip applicator introduce through the umbilicus for ligation of cystic duct and artery	1.2	20	20	Matched cohort-study	0	1
Bulian et al. [13]	Hybrid: 5-mm umbilical camera port initially used to ensure safe transvaginal access, then dissecting instrument used through this port. Transvaginal 10-mm port inserted for 42-cm long 45° laparoscope (Olympus Endo eye®), and long bent grasper through posterior vault adjacent to the 10-mm port. 5-mm multifire metaclip applicator introduce through the umbilicus for ligation of cystic duct and artery	1 (IQR: 1–1)	50	50	Prospective, randomized, non-blinded trial	0	0
Hensel et al. [15]	Hybrid: umbilical camera port initially used to ensure safe transvaginal access, then dissecting instrument used through this port. Transvaginal port inserted for endoscopic/laparoscopic camera, and long grasper through posterior vault	Not available	47	46	Retrospective case-controlled study	Not reported	Not reported
Kilian et al. [16]	Hybrid: 5-mm infraumbilical incision for introduction of trocar and creation of capnoperitoneum. Then 10-mm trocar and 5-mm laparoscopic forceps introduced under direct visualization, transvaginally through a double culdotomy. 5-mm infraumbilical camera then changed to a 10-mm camera through the 10-mm culdotomy trocar. The infraumbilical 5-mm trocar was further used as working trocar	1 (one additional 2 mm trocar used in one case to improve triangulation)	15	20	Prospective observational study	0	3
Navarra et al. [17]	Hybrid: 5-mm infraumbilical port used initially for camera to can safe access transvaginally. Flexible endoscope inserted into the pelvis through the vagina and advanced to expose the gallbladder. Three or more transabdominal sutures were placed through the gallbladder wall for retraction and 5-mm infraumbilical port used as a working port for dissecting instrumentation	1	6	74	Retrospective comparative study	0	0
Noguera and Curro [19]	Hybrid: umbilical veress peritoneum. Vaginal trocar introduced to enter the peritoneal cavity through the Douglas fornix, and a double channel video-endoscope was introduced through this trocar. Cystic artery and duct ligated with endoscopic clip, QucikClip2™ (Olympus endotherapy). 'Mouse teeth' type forceps that pass through the operating channel of the endoscope were used to close the plastic bag containing the gallbladder and extract it transvaginally	Not available	20	20	Non-randomized prospective clinical series	0	0

Table 1 continued

Publication	Method of transvaginal cholecystectomy	No of percutaneous abdominal trocars[a]	Pt no (TVC)	Pt no (CLC)	Study design	Conversions TVC to CLC	Conversions CLC to open
Noguera et al. [18]	Hybrid: umbilical veress peritoneum. Vaginal trocar introduced to enter the peritoneal cavity through the Douglas fornix, and a double channel video-endoscope was introduced through this trocar. Cystic artery and duct ligated with endoscopic clip, QucikClip2™ (Olympus endotherapy). 'Mouse teeth' type forceps that pass through the operating channel of the endoscope were used to close the plastic bag containing the gallbladder and extract it transvaginally	No additional ports included	20	20	Prospective randomized study	0	0
Santos et al. [20]	Hybrid: umbilical veress peritoneum. Colpotomy performed and dual-channel flexible gastroscope (2T160; Olympus, Tokyo, Japan) inserted. An internal retraction system EndoGrab (Virtual Ports, Misgav, Israel) was deployed through the umbilical laparoscopic port to suspend the gallbladder to the anterior abdominal wall using self-retaining clips. Laparoscopic clips applied through the umbilical port were used to ligate the cystic duct and artery	1 (1–2)	7	7	Comparative series	0	0
Solomon et al. [21]	Hybrid: umbilical veress peritoneum. 12-mm port introduced through the posterior fornix under direct visualization from the umbilical port. Following this a 10-mm 45° angled long endoscope was utilized. Transabdominal sutures were placed through the gallbladder wall for retraction and to ensure critical view was obtained prior to clipping and transection of the cystic duct and artery	Not available	11	14	Prospective cohort study	1	0
van den Boezem et al. [22]	Hybrid: 5-mm umbilical camera port initially used to ensure safe transvaginal access, then dissecting instrument used through this port. Transvaginal 10-mm port inserted for 42-cm long 45° laparoscope (Olympus Endo eye®), and long bent grasper through posterior vault adjacent to the 10-mm port. 5-mm multifire metaclip applicator introduce through the umbilicus for ligation of cystic duct and artery	Two patients required additional trocars in order to achieve critical view	30	30	Case–control study	0	0
Wood et al. [23]	Hybrid: umbilical veress peritoneum. 12-mm port introduced through the posterior fornix under direct visualization from the umbilical port. Following this a 10-mm 45° angled long endoscope was utilized. Two transabdominal sutures were placed through the gallbladder wall for retraction and to ensure critical view was obtained prior to clipping and transection of the cystic duct and artery	Not available	68	67	Comparative study	Not reported	Not reported
Zornig et al. [24]	Hybrid: 5-mm umbilical camera port initially used to ensure safe transvaginal access, then dissecting instrument used through this port. Transvaginal 10-mm port inserted for 42-cm long 45° laparoscope (Olympus Endo eye®), and long bent grasper through posterior vault adjacent to the 10-mm port. 5-mm multifire metaclip applicator introduce through the umbilicus for ligation of cystic duct and artery	4 cases required additional abdominal 2–5 mm trocar	100	100	Comparative study	0	0

IQR interquartile range, *95 % CI* 95 % confidence interval

[a] Presented as mean unless stated

Table 2 Patient demographics and indication for cholecystectomy from each study

Publication	Age (TVC) (years)	Age (CLC) (years)	BMI (TVC) (kg/m^2)	BMI (CLC) (kg/m^2)	ASA (TVC)	ASA (CLC)	Cholecystitis (TVC)	Cholecystitis (CLC)
Borchert et al. [11]	52.9 ± 12.6	54.7 ± 15.2	27.1 ± 4.9	27.8 ± 5.6	I:5, II:65, III:14	I:7, II:55, III:19	Not specified, patients with symptomatic cholecystolithiasis included	
Borchert et al. [12]	54 (49–59)[a]	54 (50–58)[a]	29 (27–30)[a]	30 (28–31)[a]	2.2 (2–2.3)[a]	2.2 (2–2.3)[a]	Acute cholecystitis excluded	
Bulian et al. [14]	46.3 (22–76)	48.8 (24–75)	26.7 (17–38)	28.7 (18–38)	I:17, II:33	I:9, II:41	Acute cholecystitis excluded	
Bulian et al. [13]	44.8 ± 15.2	47.5 ± 18.8	28.1 ± 4.2	28.5 ± 4.5	I:2, II:17, III:1	I:6, II:12, III:2	Acute cholecystitis excluded	
Hensel et al. [15]	49 ± 15	54 ± 16	28 ± 6	29 ± 7	1.9 ± 0.4	2.1 ± 0.5	10 (21.3 %)	6 (13 %)
Kilian et al. [16]	50(30–73)[b]	56(26–82)[b]	26(20–30)[b]	25(18–33)[b]	I:9, II:5, III:1	I:12, II:7, III:3	Acute cholecystitis excluded	
Navarra and Curro [17]	52(46–65)[b]	–	31(29–37)[b]	–	–	–	Not specified	
Noguera et al. [19]	42.7	45.2	–	–	–	–	Not specified	
Noguera et al. [18]	40.6	47.2	27.5	27.4	–	–	Acute cholecystitis excluded	
Santos et al. [20]	38 ± 6	34 ± 12	29 ± 5	27 ± 5	I:4, II:3	I:3, II:4	Acute cholecystitis excluded	
Solomon et al. [21]	33.5 ± 3	35.5 ± 4.1	28.8 ± 1.5	31.4 ± 2.2	–	–	Acute cholecystitis excluded	
van den Boezem et al. [22]	42 (18–62)[b]	46 (24–70)[b]	25 (18–33)	27 (20–40)	–	–	Acute cholecystitis excluded	
Wood et al. [23]	41 ± 13	41 ± 14.6	29.3 (25–32.8)[a]	31 (25.8–36.3)[a]	–	–	Not specified	
Zornig et al. [24]	49 (16–76)	50 (16–76)	26 (16–35)	26 (18–40)	–	–	12 (12 %)	12 (12 %)

Continuous variables presented as mean ± SD or mean (range) unless specified

[a] Mean and 95 % confidence interval/Interquartile range

[b] Median and range

Table 3 Primary outcome measures from each study included

Publication	Postoperative complications (TVC)	Postoperative complications (CLC)	Bile duct injury (TVC)[a]	Bile duct injury (CLC)[a]	CD complication II (TVC)	CD complication II (CLC)	CD complication III (TVC)	CD complication III (CLC)
Borchert et al. [11]	2	7	1 (A)	0	0	2	1	2
Borchert et al. [12]	13	15	0	0	0	0	1	5
Bulian et al. [14]	2	2	0	1 (B)	0	0	1	1
Bulian et al. [13]	2	2	1 (A)	0	0	1	2	1
Hensel et al. [15]	1	4	0	0	1	0	0	1
Kilian et al. [16]	1	1	1 (B)	0	0	0	1	1
Navarra and Curro [17]	0		0	0	0	0	0	0
Noguera et al. [19]	1	0	0	0	1	0	0	0
Noguera et al. [18]	1	2	0	0	0	1	0	0
Santos et al. [20]	1	2	0	0	0	0	0	0
Solomon et al. [21]	1	0	0	0	0	0	0	0
van den Boezem et al. [22]	0	1	0	0	0	1	0	0
Wood et al. [23]			0	0				
Zornig et al. [24]	1	5	0	1 (B)	0	3	1	2
TOTAL (%)	26 (5.6)	41 (7.5)	3 (0.6)	2 (0.4)	2 (0.4)	8 (1.4)	7 (1.5)	13 (2.4)

CD complication Clavien–Dindo graded complication

[a] Classified according to the Strasburg criteria for bile duct injuries

Table 4 Secondary Outcome measures for each study included

Publication	Operative time (TVC) (min)	Operative time (CLC) (min)	LOS (TVC) (days)	LOS (CLC) (days)	TRNA (TVC) (days)	TRNA (CLC) (days)	Pain POD 1 (TVC)	Pain POD1 (CLC)	Pain POD 3 (TVC)	Pain POD 3 (CLC)
Borchert et al. [11]	65.1 (22–204)	64.2 (29–168)	2.8 (2–7)	2.8 (1–7)	–	–	1.8 ± 1.9	2 ± 1.7	0.3 ± 0.8	0.7 ± 0.9
Borchert et al. [12]	75 (66–83)[a]	55 (48–61)[a]	2.4 (2.2–2.6)[a]	2.4 (2.2–2.7)[a]	–	–	1.7 ± 1.5	1.6 ± 1.2	0.8 ± 0.9	1.3 ± 1.6
Bulian et al. [14]	78 (36–150)	78 (25–282)	2.7	3.4	5.4 (0–16)	14.4 (2–90)	–	–	–	–
Bulian et al. [13]	50 (42–66)[b]	54.5 (46–62)[b]	2 (2–2)[b]	2 (2–2)[b]	5.5 (3.5–12.5)[b]	6.5 (6–11)	–	–	–	–
Hensel et al. [15]	45	60	3	4	–	–	–	–	–	–
Kilian et al. [16]	68 (35–98)[b]	55 (35–135)[b]	3 (3–12)[b]	4 (2–17)[b]	–	–	1 (1–3)[b]	3 (1–5)[b]	2.5 (1–4)[b]	2 (1–3)[b]
Navarra and Curro [17]	65 (45–75)	40 (25–60)	<2 (1–2)	<2 (1–5)	–	–	–	–	–	–
Noguera et al. [19]	69.5 (40–120)	46.3 (30–85)	0.8 (0–2)	0.8 (0–3)	–	–	–	–	–	–
Noguera et al. [18]	64.9	47			–	–	3.9	4.7	–	–
Santos et al. [20]	162 ± 29	68 ± 21	–	–	2 ± 2	4 ± 2	2 ± 2	6 ± 3	–	–
Solomon et al. [21]	67 ± 3.9	42.3 ± 3.9	–	–	6.4 ± 1.5	14.1 ± 1.4	4.1 ± 0.5	5.7 ± 0.4	2.9 ± 0.7	4.7 ± 0.3
van den Boezem et al. [22]	60 (44–87)[b]	46 (28–75)[b]	1 ± 0	1 ± 0	–	–	–	–	–	–
Wood et al. [23]	62.5 (51–75)[b]	45 (35–57)	–	–	–	–	–	–	–	–
Zornig et al. [24]	52	35	–	–	–	–	–	–	–	–

Continuous variables presented as mean ± SD or mean (range) unless specified

LOS length of hospital stay, *TRNA* time to return to normal activities, *POD* postoperative day

[a] Mean and 95 % confidence interval/interquartile range

[b] Median and range/interquartile range

Study or Subgroup	TVC Events	TVC Total	CLC Events	CLC Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Borchert 2012	13	41	15	51	25.9%	1.11 [0.46, 2.72]
Borchert 2014	2	95	7	96	19.3%	0.27 [0.06, 1.35]
Bulian 2013	2	20	2	20	5.1%	1.00 [0.13, 7.89]
Bulian 2014	2	50	2	50	5.4%	1.00 [0.14, 7.39]
Hensel 2012	1	47	4	46	11.2%	0.23 [0.02, 2.12]
Kilian 2011	1	15	1	20	2.3%	1.36 [0.08, 23.61]
Navarra 2010	0	6	0	74		Not estimable
Noguera 2009	1	20	0	20	1.3%	3.15 [0.12, 82.16]
Noguera 2012	1	20	2	20	5.4%	0.47 [0.04, 5.69]
Santos 2012	1	7	2	7	4.9%	0.42 [0.03, 6.06]
Solomon 2012	1	11	0	14	1.1%	4.14 [0.15, 112.06]
van den Boezem 2014	0	30	1	30	4.2%	0.32 [0.01, 8.24]
Wood 2014	0	68	0	67		Not estimable
Zornig 2011	1	100	5	100	14.0%	0.19 [0.02, 1.67]
Total (95% CI)		**530**		**615**	**100.0%**	**0.68 [0.40, 1.14]**
Total events	26		41			

Heterogeneity: Chi² = 7.58, df = 11 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.48 (P = 0.14)

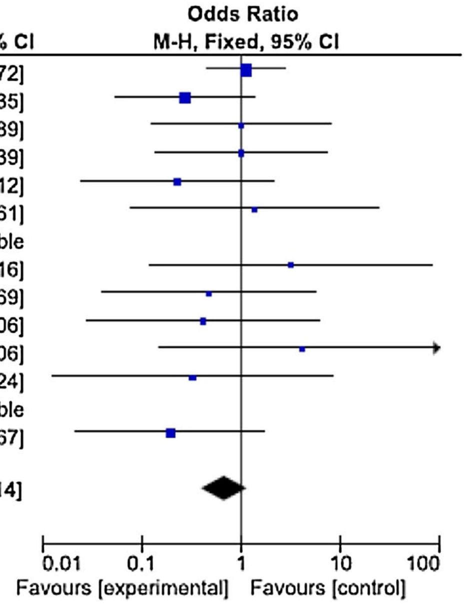


Fig. 2 Forrest plot showing no significant difference between the groups in the incidence of postoperative complications

Study or Subgroup	TVC Events	TVC Total	CLC Events	CLC Total	Weight	Odds Ratio M-H, Random, 95% CI
Borchert 2012	0	41	0	51		Not estimable
Borchert 2014	1	95	0	96	20.3%	3.06 [0.12, 76.15]
Bulian 2013	1	20	0	20	19.7%	3.15 [0.12, 82.16]
Bulian 2014	0	50	1	50	20.1%	0.33 [0.01, 8.21]
Hensel 2012	0	47	0	46		Not estimable
Kilian 2011	1	15	0	20	19.6%	4.24 [0.16, 111.65]
Navarra 2010	0	6	0	74		Not estimable
Noguera 2009	0	20	0	20		Not estimable
Noguera 2012	0	20	0	20		Not estimable
Santos 2012	0	7	0	7		Not estimable
Solomon 2012	0	11	0	14		Not estimable
van den Boezem 2014	0	30	0	30		Not estimable
Wood 2014	0	68	0	67		Not estimable
Zornig 2011	0	100	1	100	20.3%	0.33 [0.01, 8.20]
Total (95% CI)		**530**		**615**	**100.0%**	**1.33 [0.31, 5.66]**
Total events	**3**		**2**			

Heterogeneity: Tau² = 0.00; Chi² = 2.46, df = 4 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.39 (P = 0.70)

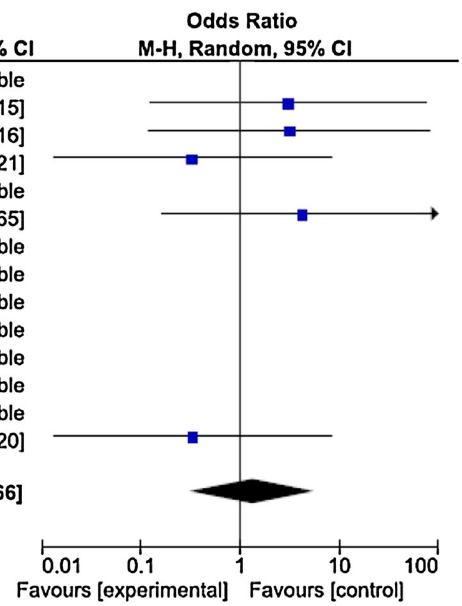


Fig. 3 Forrest plot showing no significant difference between the groups in the incidence of Bile duct injury

Discussion

Whilst it is clear that complex NOTES operations remain too technically challenging using currently available operating platforms, hybrid procedures have gained popularity with the aim of capitalizing on some of the benefits of decreased invasiveness. Although large case series have demonstrated TVC to be relatively safe, there has been a lack of high-powered comparative studies. With the introduction of novel surgical techniques, safety has to remain of paramount importance and any procedures have to be performed under ethically approved trial protocols by adequately trained surgeons. Importantly therefore, this meta-analysis demonstrated no significant differences in post-operative complications (including by Clavien–Dindo grades II & III) or rate of bile duct injury between CLC and TVC. It is important to recognize that the incidence of bile duct injury is low in CLC and very large numbers of patients would be required to demonstrate a statistical difference, nevertheless it is reassuring to see no

Study or Subgroup	TVC Events	TVC Total	CLC Events	CLC Total	Weight	Odds Ratio M-H, Random, 95% CI
Borchert 2012	0	41	0	51		Not estimable
Borchert 2014	0	95	2	96	15.5%	0.20 [0.01, 4.18]
Bulian 2013	0	20	1	20	13.6%	0.32 [0.01, 8.26]
Bulian 2014	0	50	0	50		Not estimable
Hensel 2012	1	47	0	46	13.8%	3.00 [0.12, 75.56]
Kilian 2011	0	15	0	20		Not estimable
Navarra 2010	0	6	0	74		Not estimable
Noguera 2009	1	20	0	20	13.6%	3.15 [0.12, 82.16]
Noguera 2012	0	20	1	20	13.6%	0.32 [0.01, 8.26]
Santos 2012	0	7	0	7		Not estimable
Solomon 2012	0	11	0	14		Not estimable
van den Boezem 2014	0	30	1	30	13.7%	0.32 [0.01, 8.24]
Wood 2014	0	68	0	67		Not estimable
Zornig 2011	0	100	3	100	16.3%	0.14 [0.01, 2.72]
Total (95% CI)		**530**		**615**	**100.0%**	**0.48 [0.14, 1.60]**
Total events	2		8			

Heterogeneity: Tau² = 0.00; Chi² = 3.70, df = 6 (P = 0.72); I² = 0%
Test for overall effect: Z = 1.19 (P = 0.23)

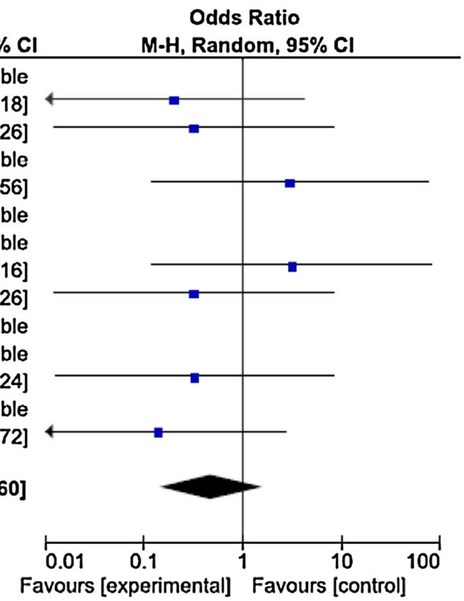


Fig. 4 Forrest plot showing no significant difference between the groups in the incidence of Clavien–Dindo grade II complications

Study or Subgroup	TVC Events	TVC Total	CLC Events	CLC Total	Weight	Odds Ratio M-H, Random, 95% CI
Borchert 2012	1	41	5	51	19.7%	0.23 [0.03, 2.05]
Borchert 2014	1	95	2	96	16.2%	0.50 [0.04, 5.61]
Bulian 2013	2	20	1	20	15.3%	2.11 [0.18, 25.35]
Bulian 2014	1	50	1	50	12.0%	1.00 [0.06, 16.44]
Hensel 2012	0	47	1	46	9.1%	0.32 [0.01, 8.04]
Kilian 2011	1	15	1	20	11.6%	1.36 [0.08, 23.61]
Navarra 2010	0	6	0	74		Not estimable
Noguera 2009	0	20	0	20		Not estimable
Noguera 2012	0	20	0	20		Not estimable
Santos 2012	0	7	0	7		Not estimable
Solomon 2012	0	11	0	14		Not estimable
van den Boezem 2014	0	30	0	30		Not estimable
Wood 2014	0	68	0	67		Not estimable
Zornig 2011	1	100	2	100	16.2%	0.49 [0.04, 5.55]
Total (95% CI)		**530**		**615**	**100.0%**	**0.63 [0.24, 1.65]**
Total events	7		13			

Heterogeneity: Tau² = 0.00; Chi² = 2.36, df = 6 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.95 (P = 0.34)

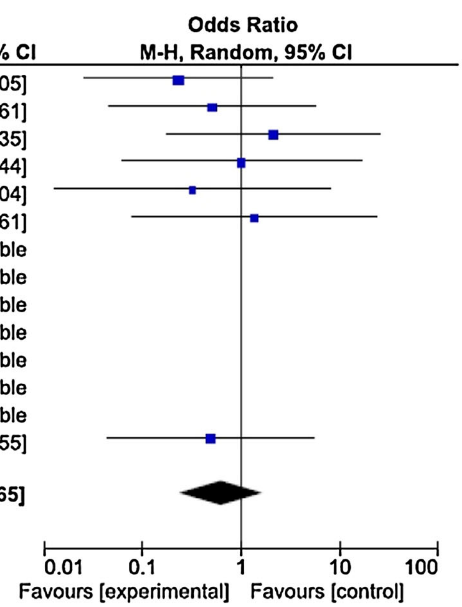
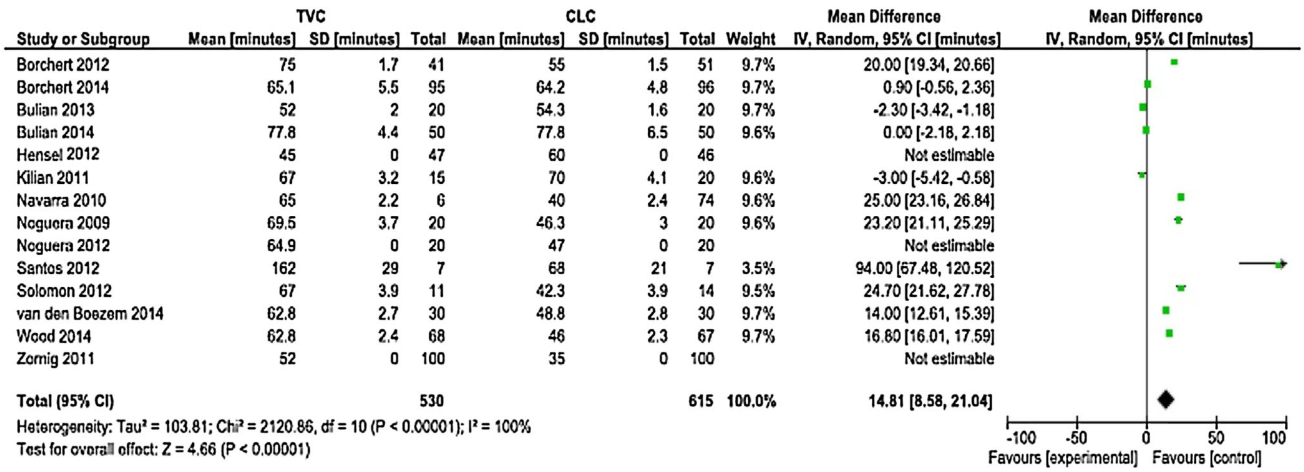


Fig. 5 Forrest plot showing no significant difference between the groups in the incidence of Clavien III complications

significant difference between both groups in this meta-analysis. As can be seen from Table 1, there were only a total of 6 reported conversions from TVC to CLC. There were five conversions from CLC to an open procedure in the reported cases. Naturally if there is doubt regarding safety during TVC these should at least be converted to CLC however this low level of conversion in the TVC group suggests that the technique is feasible and not associated with too high a level of technical difficulty in selected patient cohorts.

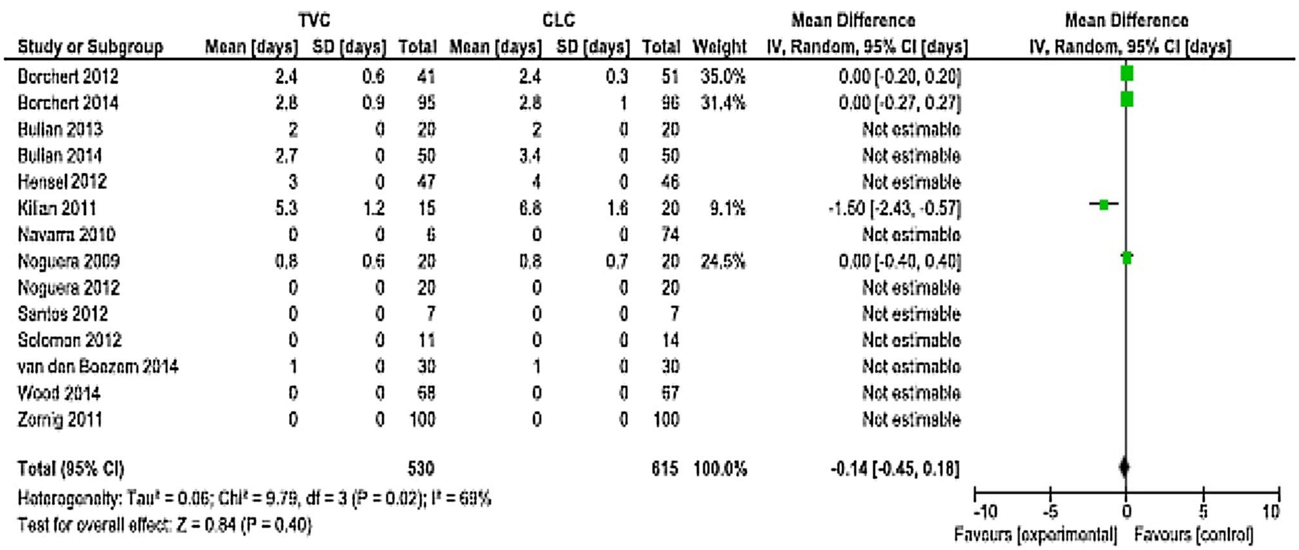
Despite evidence of significant statistical heterogeneity, the operative time was shown to be significantly greater in the TVC compared with the CLC group. This is likely to be related to the increased number of surgical steps associated with transvaginal cholecystectomy; however, there will also be a learning curve seen in surgeons performing TVC, as whilst the operative steps for cholecystectomy remain the same the instrument ergonomics will differ. As with the introduction of any novel technique, the operative time is likely to decrease as surgical workflow is streamlined.



Study or Subgroup	TVC Mean [minutes]	TVC SD [minutes]	TVC Total	CLC Mean [minutes]	CLC SD [minutes]	CLC Total	Weight	Mean Difference IV, Random, 95% CI [minutes]
Borchert 2012	75	1.7	41	55	1.5	51	9.7%	20.00 [19.34, 20.66]
Borchert 2014	65.1	5.5	95	64.2	4.8	96	9.7%	0.90 [-0.56, 2.36]
Bulian 2013	52	2	20	54.3	1.6	20	9.7%	-2.30 [-3.42, -1.18]
Bulian 2014	77.8	4.4	50	77.8	6.5	50	9.6%	0.00 [-2.18, 2.18]
Hensel 2012	45	0	47	60	0	46		Not estimable
Kilian 2011	67	3.2	15	70	4.1	20	9.6%	-3.00 [-5.42, -0.58]
Navarra 2010	65	2.2	6	40	2.4	74	9.6%	25.00 [23.16, 26.84]
Noguera 2009	69.5	3.7	20	46.3	3	20	9.6%	23.20 [21.11, 25.29]
Noguera 2012	64.9	0	20	47	0	20		Not estimable
Santos 2012	162	29	7	68	21	7	3.5%	94.00 [67.48, 120.52]
Solomon 2012	67	3.9	11	42.3	3.9	14	9.5%	24.70 [21.62, 27.78]
van den Boezem 2014	62.8	2.7	30	48.8	2.8	30	9.7%	14.00 [12.61, 15.39]
Wood 2014	62.8	2.4	68	46	2.3	67	9.7%	16.80 [16.01, 17.59]
Zornig 2011	52	0	100	35	0	100		Not estimable
Total (95% CI)			530			615	100.0%	14.81 [8.58, 21.04]

Heterogeneity: Tau² = 103.81; Chi² = 2120.86, df = 10 (P < 0.00001); I² = 100%
Test for overall effect: Z = 4.66 (P < 0.00001)

Fig. 6 Forrest plot showing the operative time was significantly increased in the TVC group compared to the CLC group (WMD = 14.81 min; 95 % CI 8.58–21.04; $P < 0.00001$)



Study or Subgroup	TVC Mean [days]	TVC SD [days]	TVC Total	CLC Mean [days]	CLC SD [days]	CLC Total	Weight	Mean Difference IV, Random, 95% CI [days]
Borchert 2012	2.4	0.6	41	2.4	0.3	51	35.0%	0.00 [-0.20, 0.20]
Borchert 2014	2.8	0.9	95	2.8	1	96	31.4%	0.00 [-0.27, 0.27]
Bulian 2013	2	0	20	2	0	20		Not estimable
Bulian 2014	2.7	0	50	3.4	0	50		Not estimable
Hensel 2012	3	0	47	4	0	46		Not estimable
Kilian 2011	5.3	1.2	15	6.8	1.6	20	9.1%	-1.50 [-2.43, -0.57]
Navarra 2010	0	0	6	0	0	74		Not estimable
Noguera 2009	0.8	0.6	20	0.8	0.7	20	24.5%	0.00 [-0.40, 0.40]
Noguera 2012	0	0	20	0	0	20		Not estimable
Santos 2012	0	0	7	0	0	7		Not estimable
Solomon 2012	0	0	11	0	0	14		Not estimable
van den Boezem 2014	1	0	30	1	0	30		Not estimable
Wood 2014	0	0	68	0	0	67		Not estimable
Zornig 2011	0	0	100	0	0	100		Not estimable
Total (95% CI)			530			615	100.0%	-0.14 [-0.45, 0.18]

Heterogeneity: Tau² = 0.06; Chi² = 9.79, df = 3 (P = 0.02); I² = 69%
Test for overall effect: Z = 0.84 (P = 0.40)

Fig. 7 Forrest plot demonstrating no significant difference between the groups in the length of hospital stay

Furthermore there was a decreased time to return to normal activities in the TVC group although again there was significant statistical heterogeneity seen amongst the studies, and there was a non-significant reduction in post-operative pain on days 1 and 3. These results clearly need to be interpreted with caution; however, pain is widely known to correlate with return to normal activities and it is also the authors' observation from a local case series that the vaginal incision is associated with very limited post-operative discomfort.

Although pooled analysis showed no difference in length of stay, it is important to consider that local clinical governance and reimbursement arrangements may be a significant contributing factor to this, which is exemplified by the lack of ambulatory cholecystectomy procedures in Germany, largely driven by financial incentives. This may therefore not be an optimal clinical end-point particularly when pooling results from several countries.

Due to the novelty of the TVC technique and the lack of operative standardization, there is some heterogeneity between the studies in relation to operative techniques and trans-abdominal assistance, as demonstrated in Table 1; however, the majority of studies used a 5-mm umbilical incision for initial laparoscopic visualization and deployment of a laparoscopic clip applicator. This step is important as flexible endoscopic clips have yet to prove reliable for closure of the cystic duct.

Colpotomy for peritoneal access has been proven to be safe from large case series in the gynaecology literature with no significant sequelae on sexual function [25]. Several studies in this meta-analysis reported no dyspareunia or difference in return to sexual activity between TVC and

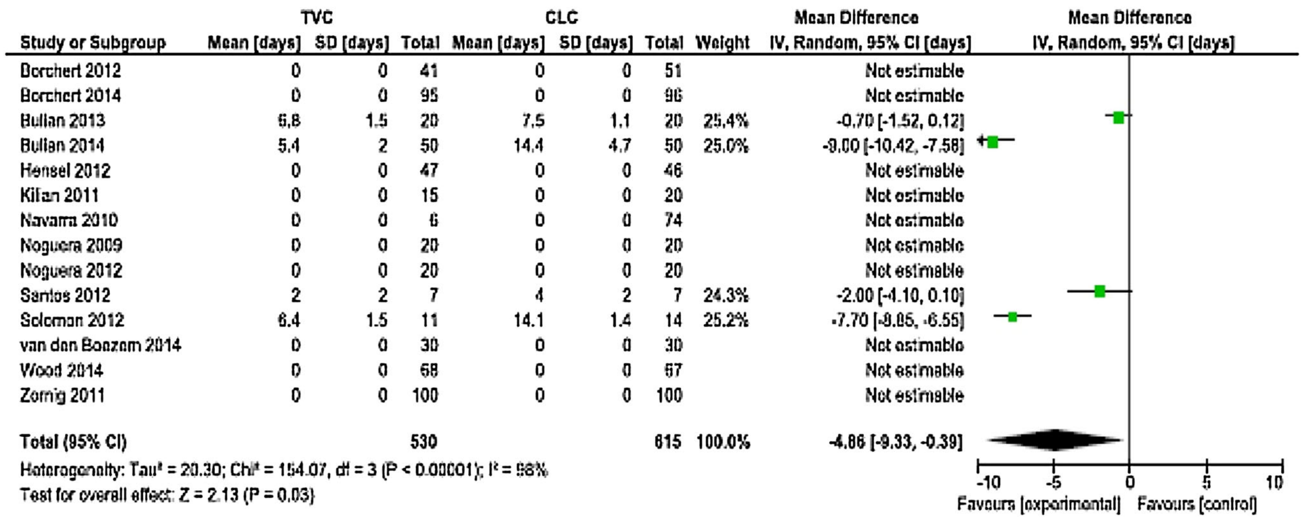


Fig. 8 Forrest Plot demonstrating the time to return to normal activities was significantly reduced in the TVC group (WMD = −4.86 days; 95 % CI −9.33 to −0.39; $P = 0.03$)

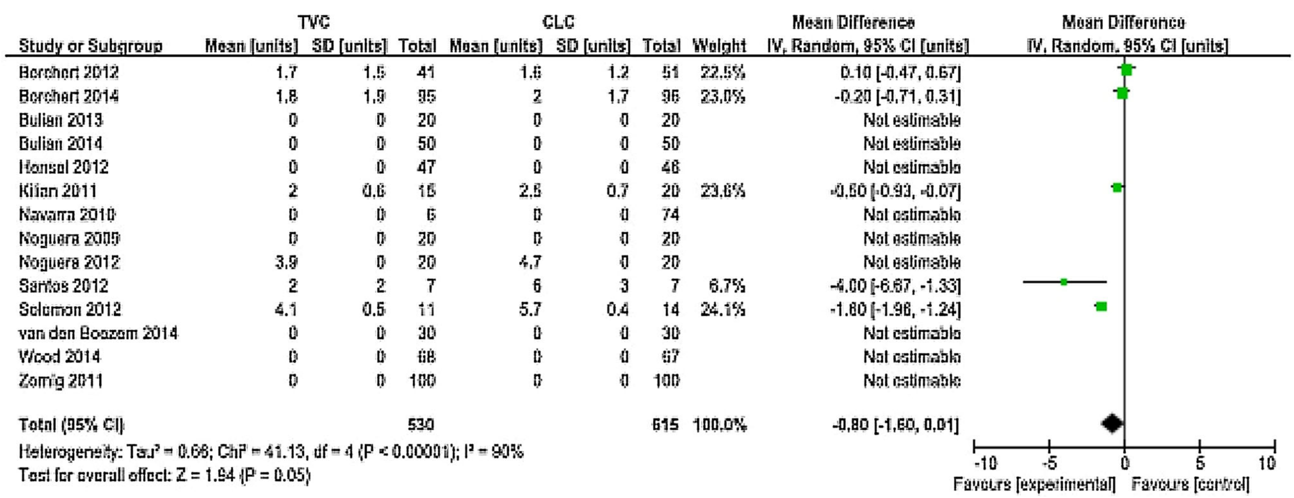


Fig. 9 Forrest plot demonstrating a non-significant reduction in postoperative pain on day 1 in the TVC group (WMD = −0.80; 95 % CI −1.60 to 0.01; $P = 0.05$)

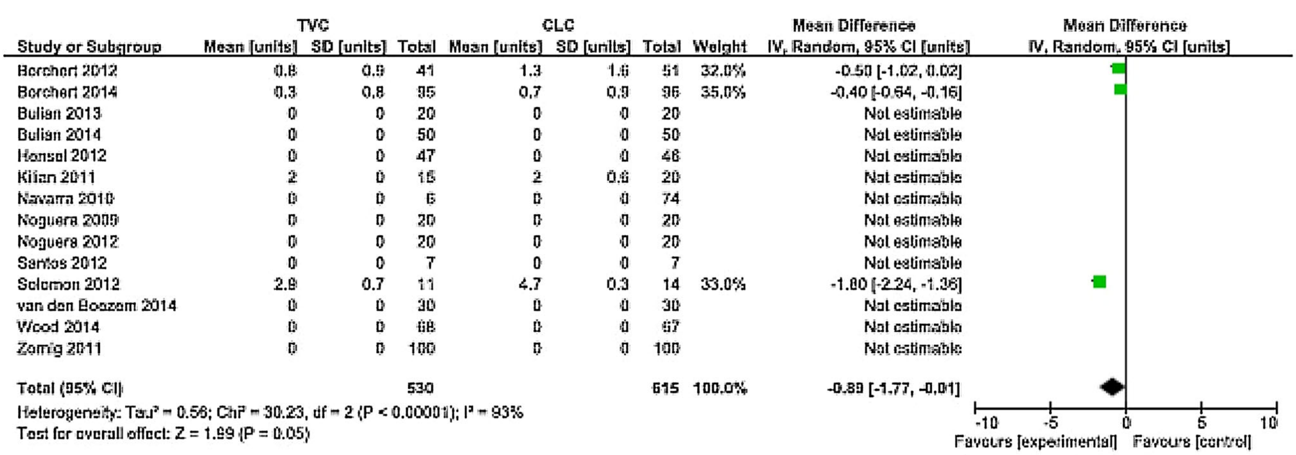


Fig. 10 Forrest plot demonstrating a non-significant reduction in postoperative pain on day 3 in the TVC group (WMD = −0.89; 95 % CI −1.77 to −0.01; $P = 0.05$)

CLC groups [11, 14, 18, 22, 24] and this was objectively evaluated through item 26 of GIQOL questionnaire [11] as well as the German version of Female Sexual Function Index (FSFI-d) [14] with no differences shown between the groups. In one study [20], evaluation using a sexual function questionnaire showed worse sexual function at 3 months post-operatively in the TVC group in 2 of 7 domains; however, this was thought to be related to the fact that 86 % of patients in their TVC group were not sexually active compared with 0 % in the CLC group.

Quality of life was objectively evaluated in three studies [11, 13, 20]. Brochert et al. [11] showed no difference in SF36 and GIQOL scores between the groups and Santos et al. [20] showed no difference in SF36 scores; however, Bulian et al. [13] showed a significantly better GIQOL score in the TVC group. Due to the low morbidity of the intervention in the long-term, quality of life evaluation is not likely to be significantly different however trials comparing short-term quality of life perceptions are currently lacking.

One clear advantage of TVC is cosmetic appearance and this was reported in three studies [13, 14, 22] all showing significantly better perception of cosmesis in the TVC group and v den Boezem et al. [22] reported significantly higher scores for both body image and cosmetic subscales in a validated body image questionnaire.

There are some limitations to this meta-analysis. There is heterogeneity in study design and therefore quality of the comparative studies that were included as indicated in Table 1. Although there was one prospective, double-blind randomized controlled trial [12] and two prospective non-blinded randomized trials [13, 18] the other studies were prospective cohort or case-controlled studies which will inherently introduce the possibility of selection bias and lower level of evidence. Furthermore, these trials have also been conducted in centers of excellence in minimally invasive surgery by very skilled surgeons who often have many years of experience in laparoscopic surgery and have undertaken significant simulator, bench-top and animal training prior to embarking on the first human studies, which is likely to have an effect on applicability of the results. Importantly the majority of studies included in this pooled analysis excluded patients with cholecystitis, and focused on patients with benign non-inflamed gallstone disease. Therefore, the applicability of a transvaginal technique to cholecystectomy in more advanced gallstone disease with inflammation remains to be determined and is an important area for future assessment. Additionally, quantification of the effect of medical co-morbidities upon the outcomes of this meta-analysis would ideally be presented as a meta-regression; however, it was not possible to provide this type of analysis due to heterogeneity in the description and quantification of medical co-morbidities within the studies included.

Despite these limitations, these data suggest that TVC is safe in selected patient groups when performed by appropriately skilled surgeons with a similar morbidity and complication profile to CLC. Furthermore TVC may be associated with a decrease in post-operative pain and a faster return to normal activities. Further standardization of the operative technique will aid in the training and adoption of TVC and allow for more meaningful comparisons. Due to the paucity of high-quality data, there is a need for larger multi-center randomized controlled trials to elicit the true potential advantages of this technique.

Disclosure Drs. Sodergren, Markar, Pucher, Badran, Jiao and Darzi have no conflicts of interest or financial ties to disclose. All authors have read and approved the final manuscript.

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