Systematic review

Meta-analysis of hybrid natural-orifice transluminal endoscopic surgery *versus* laparoscopic surgery

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Background: **Hybrid natural-orifice transluminal endoscopic surgery (NOTES), combining access through a natural orifice with small-sized abdominal trocars, aims to reduce pain and enhance recovery. The objective of this systematic review and meta-analysis was to compare pain and morbidity in hybrid NOTES and standard laparoscopy.**

Methods: **A systematic literature search was performed to identify RCTs and non-RCTs comparing hybrid NOTES and standard laparoscopy. The main outcome was pain on postoperative day (POD) 1. Secondary outcomes were pain during the further postsurgical course, rescue analgesia, complications, and satisfaction with the cosmetic result. The results of meta-analysis in a random-effects model were presented as odds ratio (ORs) or standard mean differences (MDs) with 95 per cent confidence intervals.**

Results: **Six RCTs and 21 non-randomized trials including 2186 patients were identified. In hybrid NOTES the score on the numerical pain scale was lower on POD 1 (−0·75, 95 per cent c.i. −1·09 to −0·42; $P = 0·001$) and on POD 2–4 (−0·58, −0·91 to −0·26; $P < 0·001$) than that for standard laparoscopy. The need for rescue analgesia was reduced in hybrid NOTES (OR 0·36, 0·24 to 0·54; $P < 0·001$). The reduction in complications found for hybrid NOTES compared with standard laparoscopy (OR 0·52, 0·38 to 0·71; $P < 0·001$) was not significant when only RCTs were considered (OR 0·83, 0·43 to 1·60; $P = 0·570$). The score for cosmetic satisfaction was higher after NOTES (MD 1·14, 0·57 to 1·71; $P < 0·001$).**

Conclusion: **Hybrid NOTES reduces postoperative pain and is associated with greater cosmetic satisfaction in selected patients.**

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Introduction

Since the first report of transgastric peritoneoscopy in 2004, natural-orifice transluminal endoscopic surgery (NOTES) has evolved[1,2]. However, pure NOTES with complete omission of transabdominal trocars is associated with a number of difficulties and has not gained wide acceptance[3–5]. Hybrid NOTES combines access through a natural orifice with small-sized abdominal trocars (*Fig. 1*). In hybrid NOTES, the omission of the minilaparotomy for organ retrieval may be associated with improved pain, recovery, wound complications and cosmetic outcomes[6–9]. However, RCTs have yielded conflicting results[9–14], and opponents highlight the risk of access-related complications[15].

The objective of this meta-analysis was to elucidate differences in postoperative pain and morbidity between hybrid NOTES and standard laparoscopy. As hybrid NOTES is thought to reduce the trauma of the access to the abdominal cavity, the meta-analysis was not limited to specific interventions.

Methods

The reporting of this systematic review and meta-analysis adheres to the PRISMA guidelines[16].

Literature search strategy, study selection and data collection

A comprehensive search of the electronic databases MEDLINE (via PubMed), Current Contents and the Cochrane Central Register of Controlled Trials was carried out to identify studies published up to 6 July 2016.

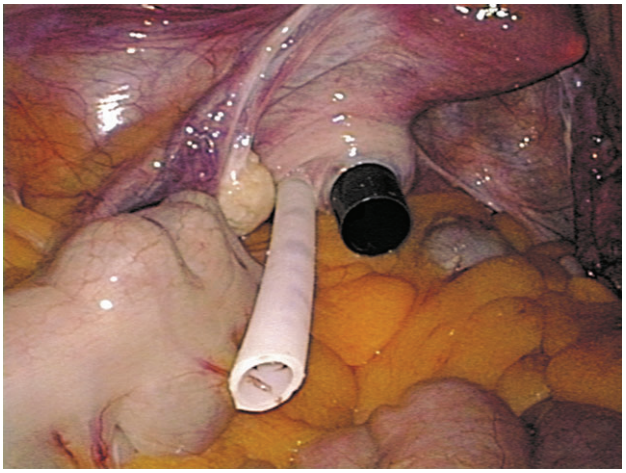

Fig. 1 Intraoperative image showing the port positioning for NOTES cholecystectomy. A 12-mm (VersaStep) (VersaStep™; Medtronic, Dublin, Ireland) and a 5-mm (V-Port™; A.M.I, Feldkirch, Austria) trocar are inserted through the posterior vaginal fornix during transvaginal cholecystectomy

The keyword algorithm used is depicted in *Appendix S1* (supporting information). Additionally, the bibliographies of all included studies and existing systematic reviews were searched by hand for appropriate references. Data extraction, critical appraisal and quality assessment were performed by two investigators independently. Any disagreement was resolved by consulting a third reviewer.

Data from the included studies were entered in an Excel™ (Microsoft Corporation, Redmond, Washington, USA) database. To avoid errors in data extraction, a double data-entry method was used. The two investigators compared the data and discussed discrepancies until consensus was achieved.

Eligibility criteria

The two investigators who performed data extraction independently considered the titles and abstracts of the identified articles for eligibility. For inclusion, a study needed to be comparative, either an RCT or a non-randomized trial. It had to report on at least one of the defined outcome measures.

Inclusion criteria were: RCT or non-randomized trial with a comparison group (type of study); published in full in English or German in a peer-reviewed journal on or before 6 July 2016; study of hybrid NOTES *versus* standard laparoscopic approach in general surgery with assessment of difference in surgical outcomes (type of intervention); including only adult patients (aged over 18 years) (type of participants).

Exclusion criteria were: duplicated RCT or non-RCT; non-randomized trial with no comparison group; experimental study in animals; none of the defined outcome measures analysed.

Outcome measures

The main outcome analysed was postsurgical pain on postoperative day (POD) 1. Pain as a surrogate for postoperative recovery is the most important aim of hybrid NOTES in current understanding of the technique. Secondary outcome measures were postoperative pain on POD 2–4, postoperative pain on POD 5–10, need for analgesia additional to predefined standard painkillers in the case of breakthrough pain (rescue analgesia), cumulative opioid dose, duration of surgery, length of hospital stay, overall complication rate, rate of major complications (grade III or higher in the Dindo–Clavien classification[17]), wound complications and the cosmetic result. Subgroup analyses were performed separately for RCT and non-randomized trials. In addition, specific procedures were analysed separately.

Methodological quality

The methodological quality of RCTs was evaluated using the Cochrane Collaboration tool for assessing risk of bias. Random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessment, incomplete outcome data, selective reporting, and other sources of bias were considered. For each domain, the risk of bias was classified as low, unclear or high according to the Cochrane Handbook for Systematic Reviews of Interventions[18]. Non-randomized trials were rated according to the Newcastle–Ottawa quality assessment scale for case–control studies[19]. Up to nine stars could be awarded: selection of study groups (maximum 4 stars); comparability of the groups (maximum 2 stars); and ascertainment of outcome of interest (maximum 3 stars).

Statistical analysis and risk of bias across studies

Meta-analyses were performed using odds ratios (ORs) for dichotomous outcomes and standardized mean differences (MDs) for continuous measures. Data were pooled using a Mantel–Haenszel model for dichotomous outcomes and an inverse variance method for continuous outcomes. A random-effects model was used to combine the summary data.

Heterogeneity among studies was calculated using the I^2 index. A high level of heterogeneity was assumed

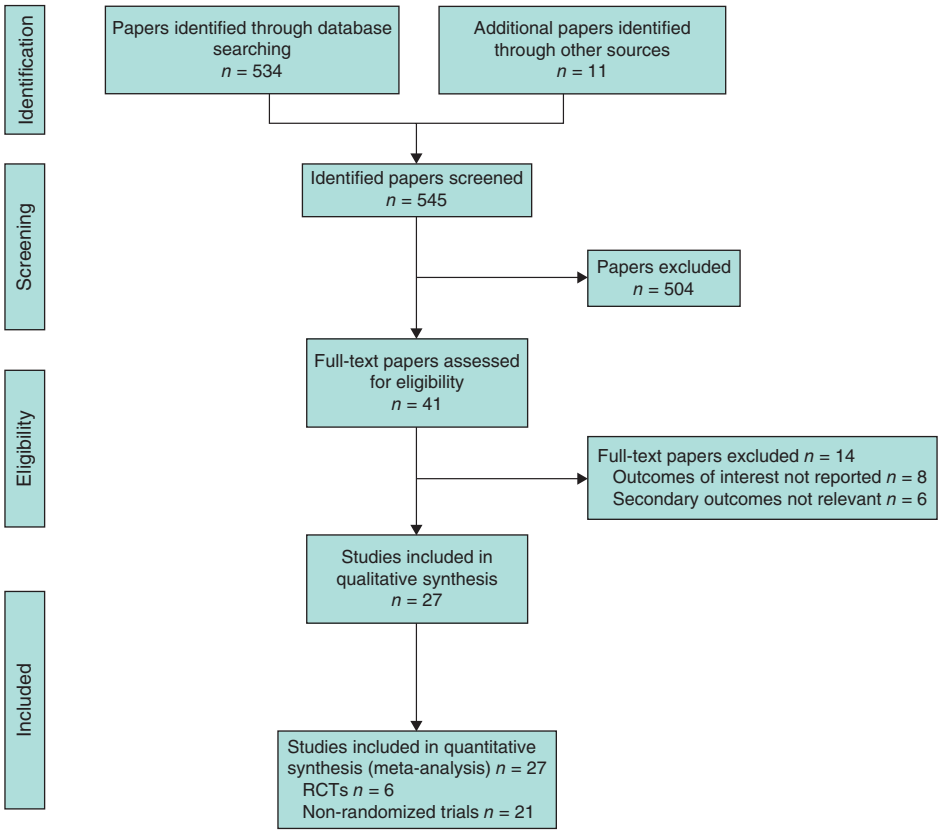

Fig. 2 PRISMA flow diagram for the systematic review

Table 1 RCTs included in the systematic review

			Study group		BMI (kg/m^2)*	
	Country	*n*	NOTES (*n* = 179)	Control (*n* = 179)	NOTES	Control
Cholecystectomy						
Borchert *et al.*[10]	Germany	102	Transvaginal cholecystectomy	4-port laparoscopic cholecystectomy	29 (27–30)†	30 (28–31)†
Bulian *et al.*[35,37]	Germany	40	Transvaginal cholecystectomy	Needlescopic cholecystectomy	28·1(4·2)	28·5(4·5)
Noguera *et al.*[14]	Spain	40	Transvaginal cholecystectomy	3-port laparoscopic cholecystectomy	27·5	27·4
Colectomy						
Leung *et al.*[13]	China	70	Transrectal left-sided colectomy	Multiport left-sided colectomy	n.a.	n.a.
Wolthuis *et al.*[38]	Belgium	40	Transrectal left-sided colectomy	Multiport left-sided colectomy	23·5 (18–29)‡	24 (20–29)‡
Gynaecology						
Ghezzi *et al.*[12]	Italy	66	Transvaginal organ retrieval	Transumbilical organ retrieval	23·8(3·6)	24·1(3·9)

*Values are mean(s.d.) unless indicated otherwise; values are †median (i.q.r.) and ‡median (range). NOTES, natural-orifice transluminal endoscopic surgery; n.a., not available.

when I^2 was 60 per cent or greater. To pool continuous data, mean(s.d.) values for each study are required. However, some of the published clinical trials did not report mean(s.d.) values, but the size of the trial, the median, and range or i.q.r. values. Using the available statistics, estimates of the mean(s.d.) values were obtained using formulas proposed by Hozo and colleagues[20].

Publication bias was assessed by visual evaluation of funnel plots and Egger's linear regression test. All estimates were obtained using Review Manager version 5.3 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Egger's linear regression[21] was calculated using Comprehensive Meta Analysis version 3.3.070 (Biostat, Englewood, New Jersey, USA).

Table 2 Non-randomized trials included in the systemic review

				Study group		BMI (kg/m²)*		Newcastle–Ottawa scale		
	Country	Type of study	*n*	NOTES (*n* = 845)	Control (*n* = 983)	NOTES	Control	S	C	E
Cholecystectomy										
Borchert *et al.*[40]	Germany	CCT	275	Transvaginal cholecystectomy	Multiport cholecystectomy	27·1(4·9)	27·8(5·6)	★☆☆☆	★☆	★★★
Bulian *et al.*[11,59]	Germany	PCH	100	Transvaginal cholecystectomy	Multiport cholecystectomy	26·7 (17–38)†	29 (18–38)†	★★☆☆	★☆	★★☆
Hensel *et al.*[41]	Germany	CCT	60	Transvaginal cholecystectomy	Multiport cholecystectomy	27(5·4)	28(5·2)	★★☆☆	★☆	★★☆
Kilian *et al.*[42]	Germany	CCT	35	Transvaginal cholecystectomy	Multiport cholecystectomy	26 (20–30)†	25 (18–31)†	★★☆☆	★☆	★★☆
Niu *et al.*[54]	China	RCH	91	Transvaginal cholecystectomy	Multiport cholecystectomy	21·5(6·2)	n.a.	★☆☆☆	★☆	★★☆
Santos *et al.*[50]	USA	PCH	14	Transvaginal cholecystectomy	Multiport cholecystectomy	29(5)	27(5)	★☆☆☆	★☆	★★☆
Solomon *et al.*[44]	USA	CCT	25	Transvaginal cholecystectomy	Multiport cholecystectomy	28·8(1·5)	31·4(2·2)	★☆☆☆	★☆	★★☆
van den Boezem *et al.*[48]	The Netherlands	PCH	60	Transvaginal cholecystectomy	Multiport cholecystectomy	25 (18–33)†	27 (20–40)†	★★☆☆	★★	★★★
Wood *et al.*[55]	USA	RCH	135	Transvaginal cholecystectomy	Multiport cholecystectomy	29·3 (25–32·8)‡	31 (26–36)‡	★☆☆☆	★☆	★★☆
Zornig *et al.*[49]	Germany	PCH	200	Transvaginal cholecystectomy	Multiport cholecystectomy	26 (16–35)†	26 (18–40)†	★☆☆☆	★★	★★☆
Appendicectomy										
Roberts *et al.*[43]	USA	CCT	40	Transvaginal appendicectomy	Multiport appendicectomy	23·7(1·2)	23·6(0·7)	★★☆☆	★☆	★★★
Colectomy										
Awad[57]	USA	RCH	40	Transvaginal right hemicolectomy	Multiport right hemicolectomy	25·1(6·7)	31·6(8·3)	★★☆☆	★☆	★★☆
Christoforidis *et al.*[58]	Switzerland	RCH	33	Transrectal left-sided colectomy	Multiport left-sided colectomy	27·6 (20–31)†	26 (19–32)†	☆☆☆☆	☆☆	☆☆☆
Costantino *et al.*[39]	France	CCT	26	Transrectal left-sided colectomy	Multiport left-sided colectomy	25·5(3·0)	30·6(4·2)	★★☆☆	★★	★★★
Fernández-Hevia *et al.*[45]	Spain	PCH	74	Transanal anterior resection	Laparoscopic anterior resection	23·7(3·6)	25·1(4)	★★☆☆	★☆	★★☆
Hisada *et al.*[51]	Japan	RCH	70	Transanal anterior resection	Laparoscopic anterior resection	n.a.	n.a.	★☆☆☆	★☆	★★☆
Kang *et al.*[52]	Korea	RCH	119	Transanal anterior resection	Laparoscopic anterior resection	< 25 in 83%	< 25 in 77%	★☆☆☆	★☆	★★☆
Kim *et al.*[53]	Korea	RCH	116	Transvaginal left-sided colectomy	Multiport left-sided colectomy	23·5(2·9)	23·2(3·3)	★★☆☆	★★	★★☆
Park *et al.*[46]	Korea	PCH	68	Transvaginal right hemicolectomy	Multiport right hemicolectomy	23·9(3·1)	23·1(2·7)	★★☆☆	★★	★★☆
Perdawood and Al Khefagie[47]	Denmark	PCH	50	Transanal anterior resection	Laparoscopic anterior resection	28 (18–46)†	26 (19–38)†	★★☆☆	★★	★★☆
Xingmao *et al.*[56]	China	RCH	197	Transrectal left-sided colectomy	Multiport left-sided colectomy	23·7(2·9)	23·1(3·1)	★☆☆☆	★☆	★★☆

*Values are mean(s.d.) unless indicated otherwise; values are †median (range) and ‡median (i.q.r.). NOTES, natural-orifice transluminal endoscopic surgery; S, selection of cases and controls; C, comparability of cases and controls; E, ascertainment of exposure; CCT, prospective controlled clinical trial; PCH, prospective cohort with historical control; RCH, retrospective cohort with historical control; n.a., not available.

The level of significance was defined at 5 per cent ($P \leq 0{\cdot}050$).

Results

Data extraction from electronic databases yielded a total of 534 abstracts, and hand searches of reference lists in available studies on the topic[7–9,15,22] yielded a further 11 studies. After exclusion of non-relevant citations, 41 citations of potential relevance remained for full-text screening. Fourteen of these studies were excluded, either because they did not report outcome parameters of interest ($n = 8$)[23–30] or because they reported secondary outcomes that were not relevant for this analysis for the same

Table 3 Summary statistics of pooled odds ratio and mean differences for clinical outcomes

	No. of studies	No. of patients	Pooled result*	Test for overall effect		Test for heterogeneity		
				Z	*P*	τ^2	d.f.	I^2 (%)
Pain on day 1	21	1593	−0·75 (−1·09, −0·42)	4·38	0·001	0·53	20	90
RCTs	6	348	−0·45 (−0·78, −0·12)	2·68	0·007	0·09	5	55
Non-RCTs	15	1245	−0·88 (−1·32, −0·43)	3·86	< 0·001	0·67	14	92
Pain on days 2–4	10	628	−0·58 (−0·91, −0·26)	3·48	< 0·001	0·17	9	69
RCTs	2	130	−0·67 (−1·43, 0·08)	1·75	0·080	0·22	1	73
Non-RCTs	8	498	−0·57 (−0·97, −0·17)	2·78	0·005	0·21	7	73
Pain on days 5–10	7	409	−0·41 (−0·89, 0·06)	1·69	0·090	0·31	6	80
RCTs	4	208	−0·23 (−1·10, 0·64)	0·52	0·610	0·69	3	88
Non-RCTs	3	201	−0·54 (−0·82, −0·25)	3·70	< 0·001	0·00	2	0
Need for rescue analgesia	7	800	0·36 (0·24, 0·54)†	5·00	< 0·001	0·00	6	0
RCTs	2	106	0·09 (0·02, 0·44)†	3·00	0·003	0·00	1	0
Non-RCTs	5	694	0·40 (0·26, 0·60)†	4·38	< 0·001	0·00	4	0
Cumulative opioid dose	7	428	−0·41 (−0·86, 0·04)	1·77	0·080	0·28	6	78
RCTs	2	80	−0·22 (−1·44, 1·00)	0·36	0·720	0·67	1	86
Non-RCTs	5	348	−0·48 (−1·02, 0·05)	1·76	< 0·001	0·28	4	79
Duration of surgery	27	2181	0·50 (0·21, 0·79)	3·39	< 0·001	0·49	26	90
RCTs	6	348	−0·06 (−0·58, 0·46)	0·22	0·830	0·34	5	82
Non-RCTs	21	1833	0·66 (0·34, 0·98)	3·99	< 0·001	0·47	20	90
Duration of hospital stay	23	1888	−0·39 (−0·63, −0·15)	3·24	0·001	0·26	22	83
RCTs	5	282	−0·14 (−0·40, 0·11)	1·09	0·270	0·01	4	14
Non-RCTs	18	1606	−0·45 (−0·73, −0·17)	3·11	0·002	0·30	17	86
Complications	27	2173	0·52 (0·38, 0·71)†	4·11	< 0·001	0·00	24	0
RCTs	6	348	0·83 (0·43, 1·60)†	0·56	0·570	0·00	5	0
Non-RCTs	21	1825	0·45 (0·32, 0·65)†	4·37	< 0·001	0·00	18	0
Wound complications	12	1039	0·21 (0·09, 0·49)†	3·69	< 0·001	0·00	10	0
RCTs	2	110	0·13 (0·02, 1·12)†	1·86	0·060	0·00	1	0
Non-RCTs	10	929	0·23 (0·10, 0·56)†	3·23	0·001	0·00	8	0
Cosmetic satisfaction	6	354	1·14 (0·57, 1·71)	3·93	< 0·001	0·42	5	83
RCTs	3	166	1·00 (−0·08, 2·08)	1·81	0·070	0·82	2	90
Non-RCTs	3	188	1·28 (0·66, 1·91)	4·01	< 0·001	0·22	2	72

Values in parentheses are 95 per cent confidence intervals. *Values are mean differences unless indicated otherwise; †values are odds ratios.

cohort as studies that were included ($n = 6$)[31–36]. A total of six RCTs[10,12–14,35,37,38] comprising 358 patients and 21 non-randomized trials[11,39–59] comprising 1828 patients were included in the meta-analysis (*Fig. 2*).

Three RCTs and ten non-randomized trials reported on cholecystectomy, two RCTs and ten non-randomized trials on colectomy, one RCT on gynaecological procedures and one non-randomized trial on appendicectomy. Details of the 27 included trials are shown in *Tables 1* and *2*.

Methodological quality

The risk of bias in included RCTs, according to the Cochrane Collaboration risk-of-bias tool, was unclear for random sequence generation but low for all other domains. Several trials[10,14,37,38] did not report how many patients were screened for inclusion in the trial, how many declined to participate, and how many possibly eligible patients were not asked to participate. There is therefore an unclear risk of selection bias due to inadequate generation of a randomized sequence. Four[10,12,13,38] of the six RCTs were double-blinded, and all except one[14] reported on incomplete outcome data.

For non-randomized trials, a median of 5 of 9 stars were awarded (range 4–9). There was one non-RCT[39] with a matched concurrent control, five[40–44] with a non-matched concurrent control, six[11,45–49] with a matched historical control, one[50] with a non-matched historical control and eight[51–58] retrospective non-randomized trials. The quality rating of the included non-randomized studies is shown in *Table 2*.

Outcome analysis

The results of meta-analyses of the defined outcome measures, including subgroup analyses, are shown in *Table 3*.

Pain on postoperative day 1

Six RCTs[10,12–14,37,38] and 15 non-randomized trials[11,39–42,44,46,48,50,52–57] reported on postoperative pain on day 1 using a numerical rating scale (NRS) (0, no pain; 10, strongest pain). In a random-effects model, the

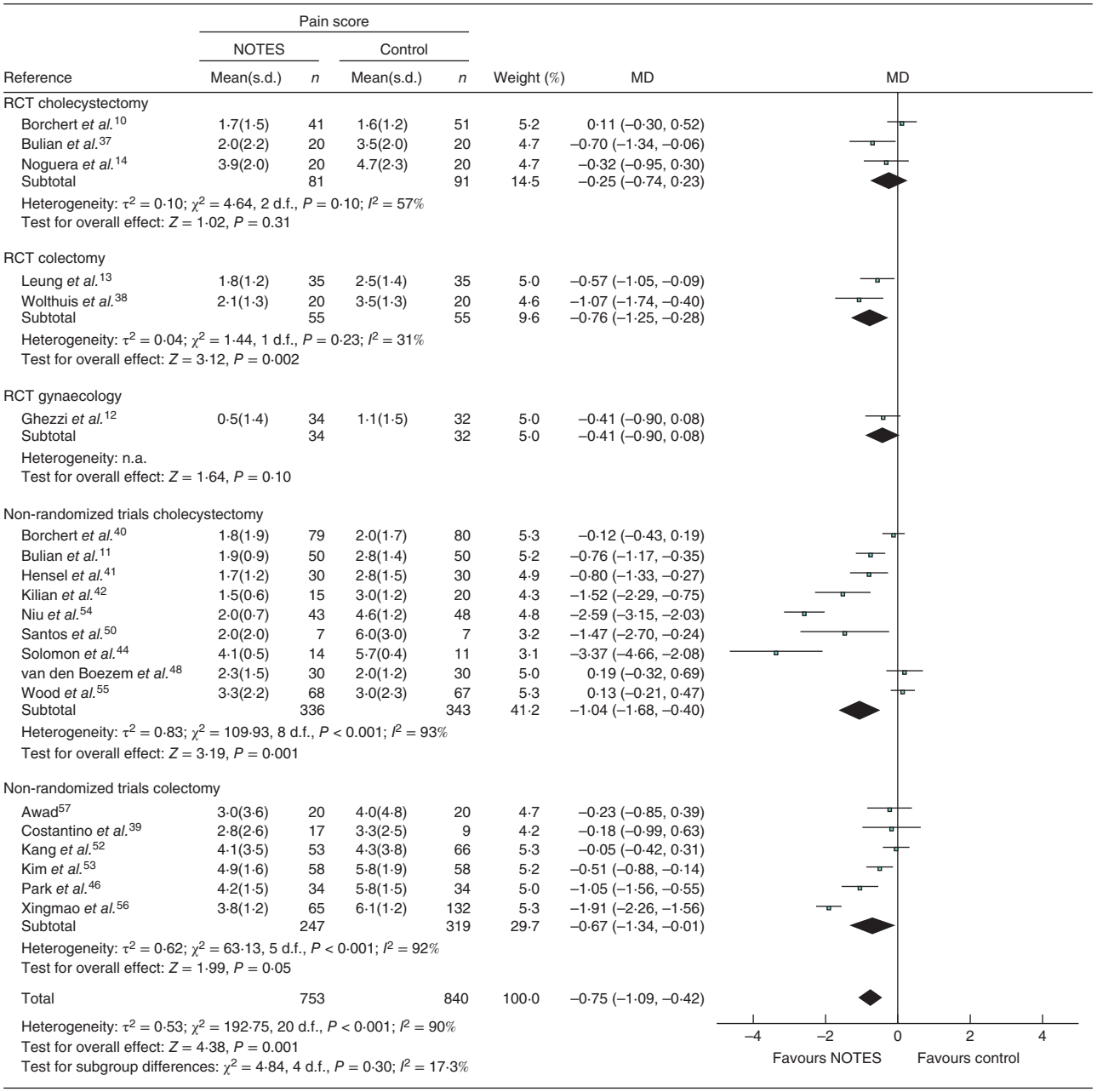

Fig. 3 Forest plot of pain on postoperative day 1, measured on a numerical rating scale (0, no pain; 10, strongest pain), in RCTs and non-randomized trials that compared natural-orifice transluminal endoscopic surgery (NOTES) with standard laparoscopy (control). An inverse variance random-effects model was used for meta-analysis. Mean differences (MDs) are shown with 95 per cent confidence intervals. n.a., Not applicable

NRS score for hybrid NOTES was lower than for standard laparoscopy (MD −0·75, 95 per cent c.i. −1·09 to − 0·42; $P = 0·001$) (*Fig. 3*). In the subgroup analysis involving only RCTs, the NRS score was also lower for hybrid NOTES (MD −0·45, −0·78 to −0·12; $P = 0·007$) (*Table 3*).

Pain on postoperative days 2–4

The level of pain on days 2–4 after surgery was reported by two RCTs[10,38] and eight non-RCTs[40–42,44,46,50,52,57]. Heterogeneity among the trials was high ($I^2 = 69$ per cent). The NRS score was lower for hybrid NOTES

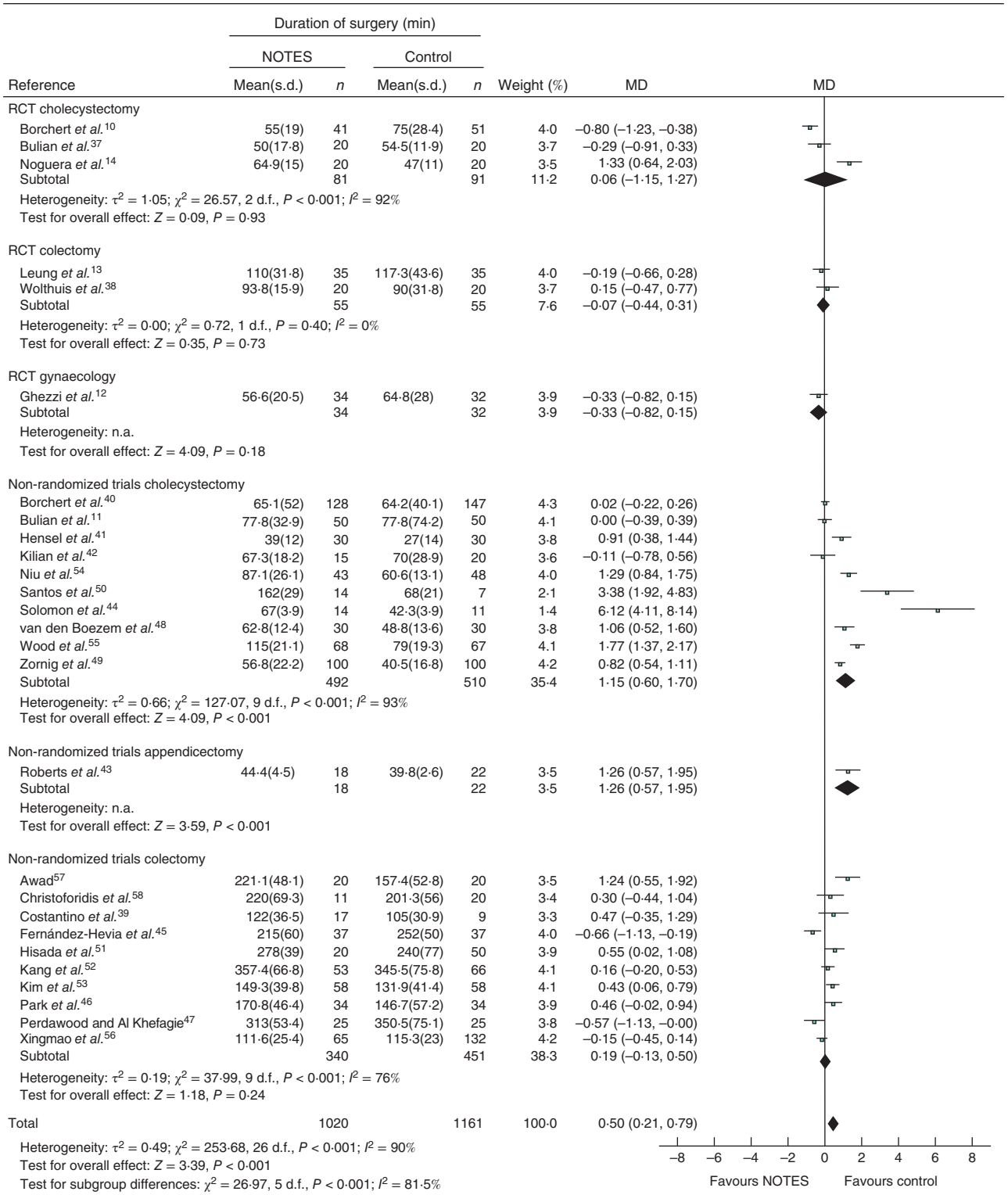

Fig. 4 Forest plot of duration of surgery in RCTs and non-randomized trials that compared natural-orifice transluminal endoscopic surgery (NOTES) with standard laparoscopy (control). An inverse variance random-effects model was used for meta-analysis. Mean differences (MDs) are shown with 95 per cent confidence intervals. n.a., Not applicable

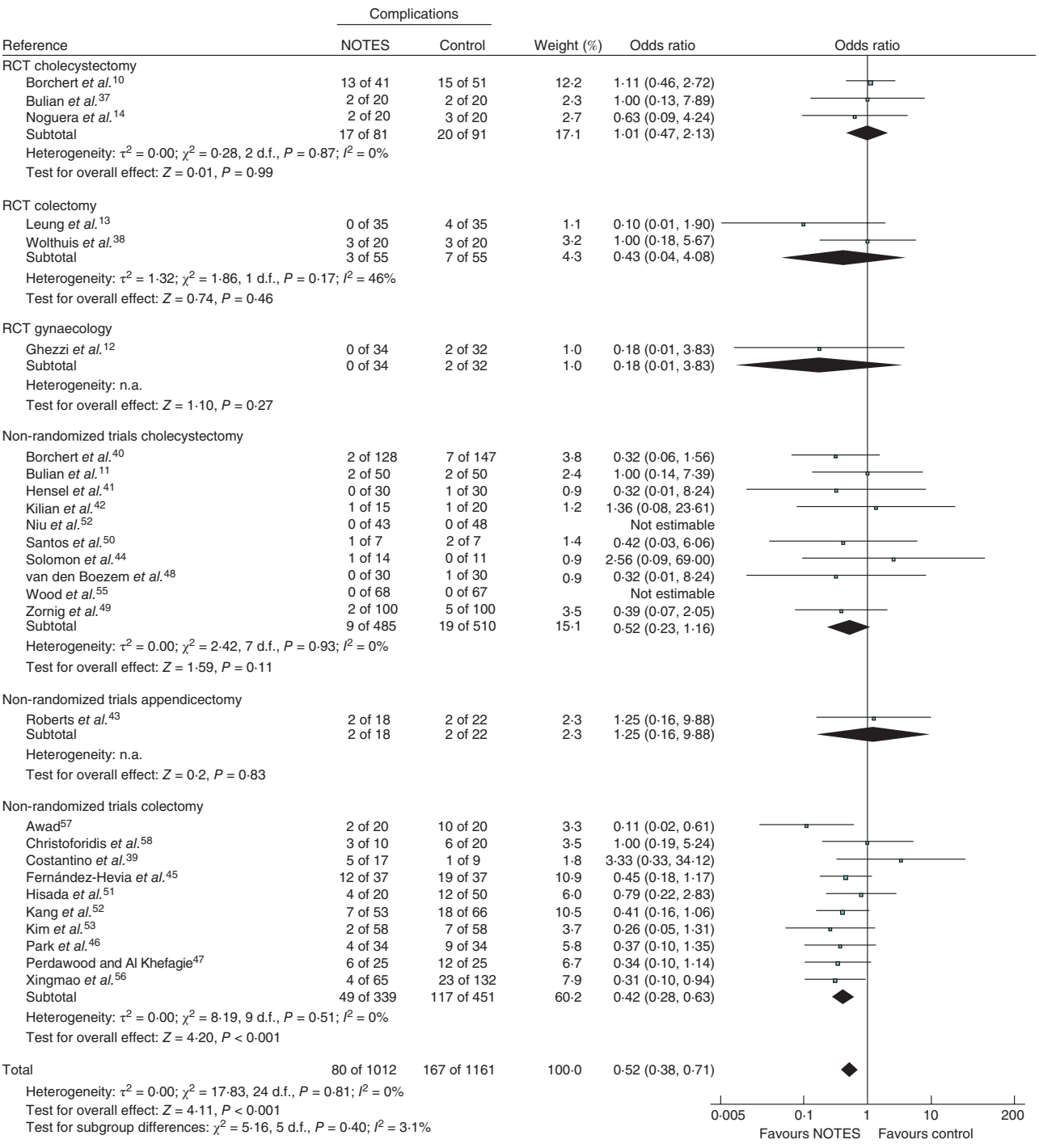

Fig. 5 Forest plot of overall complication rates in RCTs and non-randomized trials that compared natural-orifice transluminal endoscopic surgery (NOTES) with standard laparoscopy (control). A Mantel–Haenszel random-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals. n.a., Not applicable

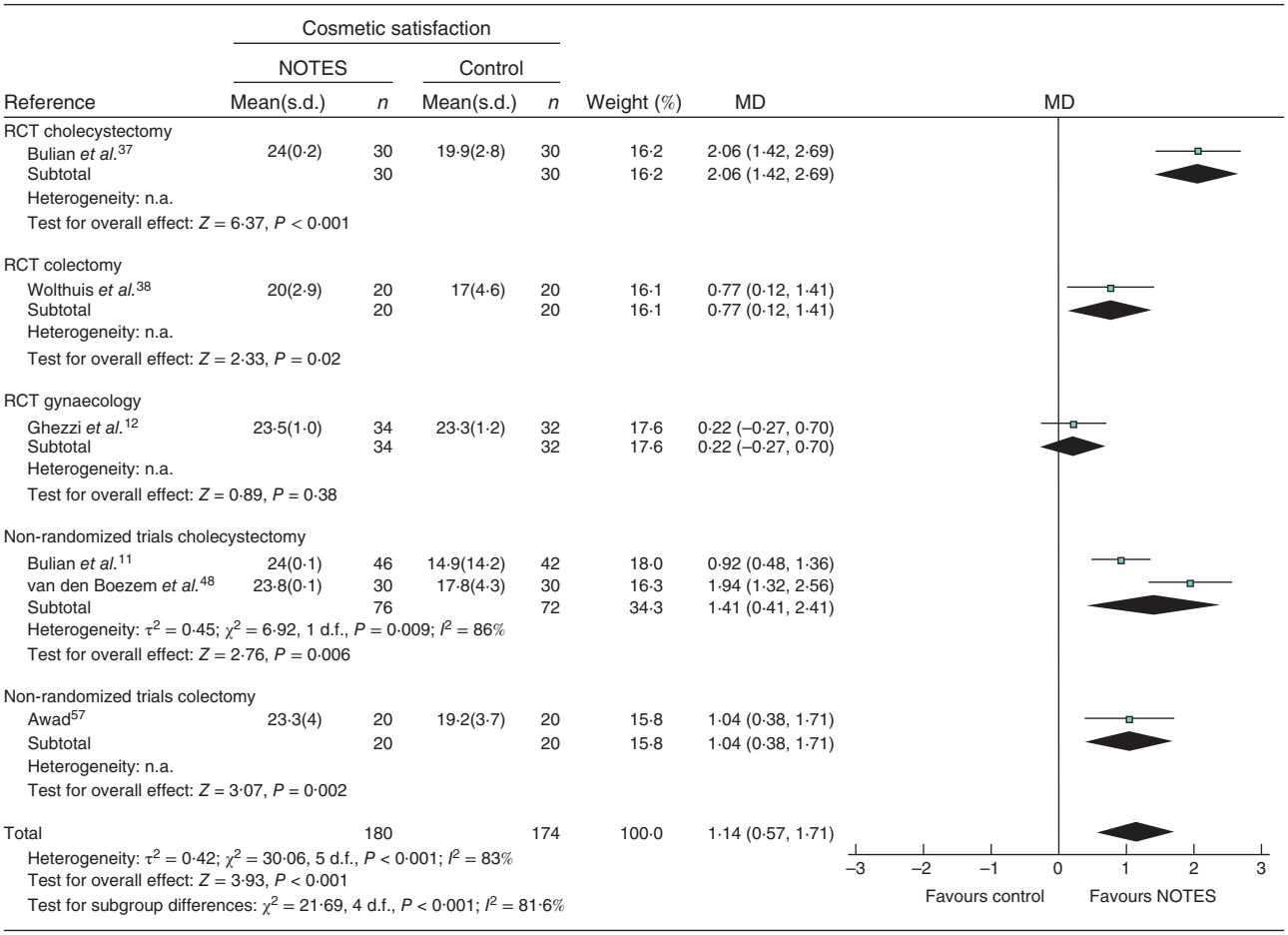

Fig. 6 Forest plot of cosmetic satisfaction, measured on a scale ranging from 3 (lowest level) to 24 (highest level), in RCTs and non-randomized trials that compared natural-orifice transluminal endoscopic surgery (NOTES) with standard laparoscopy (control). An inverse variance random-effects model was used for meta-analysis. Mean differences (MDs) are shown with 95 per cent confidence intervals. n.a., Not applicable

than for standard laparoscopy (MD −0·58, 95 per cent c.i. −0·91 to −0·26; $P < 0·001$) (*Fig. S1*, supporting information).

Pain on postoperative days 5–10

Four RCTs[10,14,37,38] and three non-randomized trials[46,50,52] assessed pain on POD 5–10. The level of heterogeneity was high ($I^2 = 80$ per cent). No significant difference was observed between NOTES and standard laparoscopy (*Fig. S2*, supporting information). In the subgroup of colectomy, however, the pain level was lower for hybrid NOTES (MD −0·65, 95 per cent c.i. −1·02 to −0·27; $P < 0·001$), with a moderate level of heterogeneity ($I^2 = 45$ per cent).

Need for rescue analgesia

Two RCTs[12,38] and five non-randomized trials[11,40,46,53,55] reported the need for rescue analgesia. Hybrid NOTES was associated with a significant reduction in the need for rescue analgesia compared with standard laparoscopy (OR 0·36, 95 per cent c.i. 0·24 to 0·54; $P < 0·001$) (*Fig. S3*, supporting information).

Cumulative opioid dose

Two RCTs[37,38] and five non-RCTs[39–41,51,58] reported the cumulative opioid dose. No significant difference between the groups was observed (MD −0·41, 95 per cent c.i. −0·86 to 0·04; $P = 0·080$) (*Fig. S4*, supporting information).

Duration of surgery

The duration of surgery was longer for hybrid NOTES than for standard laparoscopy (MD 0·50, 95 per cent c.i. 0·21 to 0·79; $P < 0·001$) (*Fig. 4*). In the subgroup analysis of RCT only, no difference in operating time was

observed between the two groups (MD −0·06, −0·58 to 0·46; $P = 0·830$) (*Table 3*).

Length of hospital stay

Duration of hospital stay was shorter with hybrid NOTES than with standard laparoscopy (MD 0·39, 95 per cent c.i. −0·63 to −0·15; $P = 0·001$) (*Fig. S5*, supporting information). On analysis of RCTs alone, hospital stay was shorter for hybrid NOTES, but not significantly so (MD −0·14, −0·40 to 0·11; $P = 0·270$) (*Table 3*).

Complications

The overall rate of complications was lower in the hybrid NOTES group (OR 0·52, 95 per cent c.i. 0·38 to 0·71; $P < 0·001$) (*Fig. 5*), but there was no difference in the rate of major complications (OR 0·65, 0·41 to 1·02; $P = 0·060$) (*Fig. S6*, supporting information). For the subgroup of RCTs there was no difference in overall complications (OR 0·83, 0·43 to 1·60; $P = 0·570$) (*Table 3*) or major complications (OR 0·77, 0·24 to 2·50; $P = 0·670$). The number of wound infections was fourfold lower for hybrid NOTES (OR 0·21, 0·09 to 0·49; $P < 0·001$) (*Fig. S7*, supporting information).

Cosmetic satisfaction

Aesthetic outcome, measured using a cosmetic scale ranging from 3 (lowest level of satisfaction) to 24 (highest level of satisfaction), was reported by three RCTs[12,37,38] and three non-randomized trials[48,57,59]. Patients in the hybrid NOTES group had a higher score on the cosmetic scale than patients in the standard laparoscopy group (MD 1·14, 95 per cent c.i. 0·57 to 1·71; $P < 0·001$) (*Fig. 6*). The cosmetic score was higher for hybrid NOTES cholecystectomies (MD 1·61, 0·84 to 2·39; $P < 0·001$) and colectomies (MD 0·90, 0·44 to 1·36; $P = 0·001$).

Publication bias

For all meta-analyses, neither funnel plots nor Egger's linear regression demonstrated any publication bias (*Fig. S8*, supporting information).

Discussion

Pain was recorded in most of the included studies[10–14,37–42,44,46,48,50,52–57]. As an outcome measure, pain can be assessed early after operation and can be objectified well using the NRS, a test with high validity[60]. Previous meta-analyses[8,22] on postoperative pain after transvaginal cholecystectomy have shown conflicting results. In contrast to cholecystectomy, following colectomy a significantly lower pain level for hybrid NOTES is detectable until the end of the first week after surgery. The most important factor in pain reduction for hybrid NOTES is probably omission of the minilaparotomy used in standard laparoscopy. Lower postoperative pain and lower analgesia requirements are associated with a better health status. This may lead to swifter recovery, and earlier return to work and normal activities of daily life. The time needed for postoperative recovery has been reported by only a few studies, precluding meta-analysis. For transvaginal cholecystectomy, the two studies[37,49] found no significant difference in the time taken to return to everyday life. In contrast, in non-randomized trials a significantly faster return to everyday activities was reported following transvaginal cholecystectomy and transvaginal appendicectomy compared with standard laparoscopy[43,44,48,59].

In the present analysis, the overall complication rate was lower for hybrid NOTES than for standard laparoscopy. When only RCTs were compared, however, no difference in morbidity was found. The lower complication rate for hybrid NOTES in non-RCTs is probably due to selection bias, with healthier patients being chosen for the novel technique. However, RCTs and non-randomized trials consistently report no difference in major morbidity. Access-related complications specific to NOTES are reported to the German NOTES registry[61]. These complications are mostly intraoperative. A lower wound infection rate was found for hybrid NOTES in this meta-analysis. It may be assumed that the rate of incisional hernia is lower after hybrid NOTES, but few studies have reported on this outcome[35,59]. Given the low incidence of trocar site hernia, a very high sample size would be needed to demonstrate a possible reduction in incisional hernia by NOTES[62].

Duration of hospital stay was slightly shorter for hybrid NOTES. This finding has been reported previously in meta-analyses, including predominantly non-randomized trials of cholecystectomy[8,22] and colectomy[7]. However, analysis of RCTs alone did not show any difference in length of hospital stay. Again, a selection bias must be assumed in non-randomized studies, favouring assignment of low-risk patients to the novel technique.

In line with previous systematic reviews[7,8,22], a minimally longer duration of surgery was found for hybrid NOTES in non-randomized trials, but not in RCTs. Obviously non-RCTs were performed at an early stage after introduction of the novel technique and within the learning curves of the surgeons involved. RCTs are usually performed later, when surgeons are experienced with the new procedure.

It might be inferred that, once hybrid NOTES is routine, the operating time will be no greater than for standard laparoscopy.

None of the previous meta-analyses has included different general surgical procedures, and none has featured subgroup analysis of RCTs alone[7,8,22]. The subgroup analysis revealed important differences between non-randomized trials and RCTs. In RCTs there was no difference in morbidity, length of hospital stay or duration of surgery between NOTES and standard laparoscopy. However, the difference in early postoperative pain was confirmed in the meta-analysis of RCTs at a moderate level of heterogeneity. In contrast to commonly voiced concerns[15], hybrid NOTES is not associated with more complications than standard laparoscopy.

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Supporting information

Additional supporting information may be found in the online version of this article:

Appendix S1 Keyword search algorithm (Word document)

Fig. S1 Forest plot of pain on postoperative days 2–4 (Word document)

Fig. S2 Forest plot of pain on postoperative days 5–10 (Word document)

Fig. S3 Forest plot of need for rescue analgesia (Word document)

Fig. S4 Forest plot of cumulative opioid dose (Word document)

Fig. S5 Forest plot of duration of hospital stay (Word document)

Fig. S6 Forest plot of major complications (Clavien–Dindo grade III or above) (Word document)

Fig. S7 Forest plot of wound complications (Word document)

Fig. S8 Funnel plots showing no evidence of publication bias for all groups in Egger's test (Word document)