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Safety Outcomes of NOTES Cholecystectomy Versus Laparoscopic Cholecystectomy: A Systematic Review and Meta-Analysis

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Objective: Natural orifice transluminal endoscopic surgery (NOTES) is an endoscopic technique whereby surgical interventions can be performed with a flexible endoscope passed through a natural orifice (mouth, vulva, urethra, anus) then through a transluminal opening of the stomach, vagina, bladder, or colon. Although in the early stage of research and development, NOTES has been clinically applied across the globe, above all the transvaginal cholecystectomy is among the most frequently performed procedures. In the existing 2 types of transvaginal routes, the hybrid NOTES cholecystectomy (NC) is more likely to be accepted. However, there has been controversy regarding the safety outcomes of hybrid NC in comparison with classical laparoscopic cholecystectomy (LC). The primary objective of this meta-analysis is to compare the characteristics between NC and classical LC.

Materials and Methods: A meta-analysis of eligible studies comparing NC with classical LC was performed to evaluate the safety outcomes including wound complications, other postoperative complications and intraoperative conversion between the 2 groups.

Results: Pooling 3 randomized controlled trials (n = 157) and 7 nonrandomized trial (n = 593) demonstrated that the rates of wound complications and other postoperative complications in NC group did not significantly differ from those of classical LC group [wound complications: ratio difference (RD) = −0.02, 95% confidence interval (CI) −0.04to 0.01, $P = 0.23$; other postoperative complication: RD = −0.01; 95% CI, −0.03 to 0.02; $P = 0.6$]. The intraoperative conversion rate in NC groups was higher than that of LC groups (RD = 0.03; 95% CI, 0.01-0.06; $P = 0.02$).

Conclusions: There is no significate difference between the safety of NC and laparoscope cholecystectomy. NC is associated with a higher rate of intraoperative conversion when compared with LC. It is worthy of further promotion and validation in clinical settings.

Key Words: natural orifice transluminal endoscopic surgery, NOTES, transvaginal cholecystectomy, laparoscopic cholecystectomy, meta-analysis, safety outcomes

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Humans always have an obsession for the pursuit of minimally invasive procedures. With the rapid development of minimally invasive surgical techniques, a great interest has arisen for natural orifice transluminal endoscopic surgery (NOTES). NOTES is an endoscopic technique whereby surgical interventions can be performed with a flexible endoscope passed through a natural orifice (mouth, vulva, urethra, anus) then through a transluminal opening of the stomach, vagina, bladder, or colon.[1] Compared with laparoscopic procedure, the new NOTES technique has the potential not only to avoid abdominal wall incisions and eliminate related complications but also to reduce postoperative pain and lead to ideal cosmetic outcomes.[2] However, nowadays surgeons are still facing several technical challenges, such as how to achieve a safe access, a leak proof closure, and a spatial orientation barrier and to avert potential abdominal infectious complications.

Nearly one third of many general surgeons' work in clinical is cholecystectomy, it is always chosen as a model when a new operation method need to be evaluated. Just like laparoscopic cholecystectomy (LC), which is the "golden standard" technique in gallbladder disease treatment. The first operation successfully accomplished by NOTES method was also cholecystectomy.[3] With more and more cases about NOTES cholecystectomy (NC) being reported, the comparison between NC and classical LC is an urgently needed. Because of the lack of large sample randomized controlled study, we took the systematic review and meta-analysis method to process the published clinical trials.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

Inclusion criteria: (1) published randomized controlled clinical studies or observational studies; (2) all the patients diagnosed gallbladder stone or gallbladder polyps; (3) the observation outcomes including wound complications, other postoperative complications, and intraoperative conversion rate; (4) the age of all patients range from 18 to 80 years old. Exclusion criteria: (1) received cholecystectomy by different NOTES operation methods; (2) patients with other serious complications.

Search Strategy

MEDLINE, EMBASE, and Cochrane libraries were independently searched by 2 reviewers for potentially eligible studies from the earliest available date to November

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TABLE 1. Characteristics of the Studies Included in This Meta-Analysis (LC/NC)

References	Noguera et al[7]	Borchert et al[8]	Solomon et al[9]	Zornig et al[10]	Kilian et al[11]
Publish time	2012	2014	2012	2010	2011
Trial type	RCT	RCT	RCT	nRCT	nRCT
LC patients	20	51	11	100	20
NC patients	20	41	14	100	15
Jada score/NOS	3/5	4/5	2/5	S4C1O3	S2C1O3
Sex (F;M)	F	F	—	F	25:10
Age (y)	47.2/40.6*	54 ± 4/54 ± 5	35.5 ± 4.1/33.5 ± 3	50/49*	56/50†
BMI	27.4/27.5*	30 ± 1/29 ± 2	31.4 ± 2.2/28.8 ± 1.5	26/26*	25/26†

BMI indicates body mass index; F, female; LC, laparoscopic cholecystectomy; M, male; NC, NOTES cholecystectomy; NOS, Newcastle-Ottawa Scale; RCT, randomized controlled trial; nRCT, nonrandomized controlled trial; *, mean value; †, median value.

30, 2014. The search terms used either alone or in combination included "Cholecystectomy," "laparoscopic Cholecystectomy," "Natural orifice transluminal endoscopic surgery," "NOTES," "LC," "prospective," "RCTs" or "observational studies." Reference lists from retrieved articles were also manually searched for articles meeting our criteria. Abstracts identified using our search strategies were reviewed separately by 2 reviewers. The full-text articles that potentially met criteria were then reviewed in duplicate to determine the inclusion in the analysis. Disagreements between reviewers were resolved by consensus among all the authors.

Data Extraction

According to the predesigned data extraction form, data extraction were performed independently by 2 reviewers. Extracted data included the rate of wound complications, the incidence of postoperative complication, and the rate of intraoperative conversion, the operation time, postoperative pain, and length of stay in hospital. Any disagreements between the 2 researchers were resolved through discussion or consultation with the third person, the lack of data to be added through a variety of ways of seeking assistance. The quality of studies was assessed with the Newcastle-Ottawa scale for observational studies[4,5] and with the Jadad scale for randomized controlled trials (RCTs).[6] The Jadad scale uses a set of 5 criteria to determine the quality of a RCT with a score ≥ 3 denoting high quality of the study. The Newcastle-Ottawa scale assesses the study on 3 aspects, 4 stars for the selection of the study group (S), 2 stars for the comparability (C) of the groups and 3 stars for outcomes (O).

Statistical Analysis

Statistical analysis was carried out using RevMan 5.0 software (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Danish) provided by the Cochrane Collaboration. For wound complications, other postoperative complications, and intraoperative conversion, because the number of positive event is too small, and seldom zero-event, we calculated the rate difference (RD) with 95% confidence interval (CI). A 2-sided *P*-values <0.05 were considered to be statistically significant. The pooled results of studies included in the meta-analysis and statistical homogeneity between trials were assessed using the fixed-effects model where a χ^2 test $P > 0.1$ indicated no heterogeneity. The random-effects model of meta-analysis was used when statistical heterogeneity exited (χ^2 test $P \leq 0.1$). We also used the I^2 statistic, which estimates the percentage of total variation across studies, to estimate the inconsistencies between included studies. For the I^2 metric, $I^2 > 50\%$ indicates significant heterogeneity. Agreement assessment between reviewers was evaluated using the Cohen *k* statistic. Furthermore, we hypothesized the heterogeneity between different study designs (RCT or observational study) and subgroup analysis was therefore carried out. Moreover, κ statistics were applied to assess the agreement between reviewers.

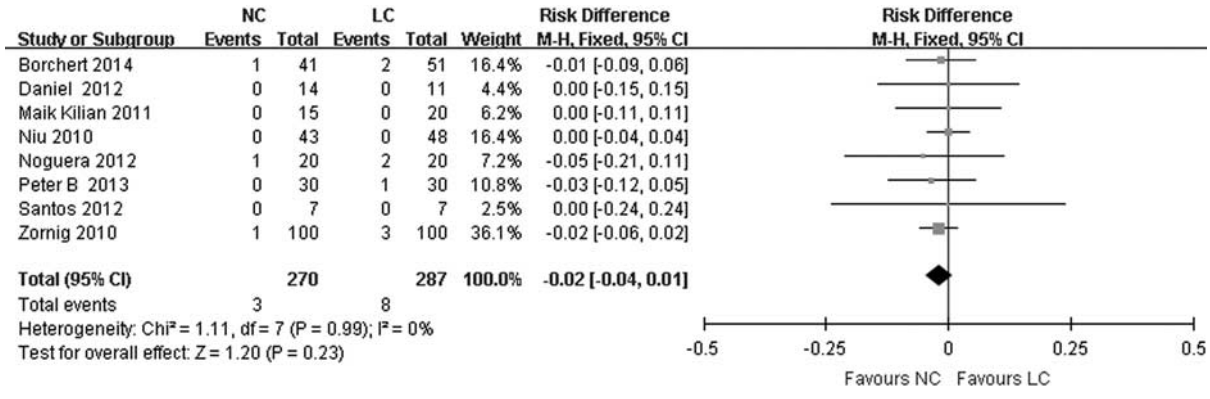

FIGURE 1. Meta-analysis of wound complications between NC and LC groups. NC indicates NOTES cholecystectomy; LC, laparoscopic cholecystectomy.

TABLE 1. *(continued)*

van den Boezem et al[12]	Santos et al[13]	Niu et al[2]	Hensel et al[6]	Bulian et al[14]
2013	2012	2010	2012	2012
nRCT	nRCT	nRCT	nRCT	nRCT
30	7	48	46	50
30	7	43	47	50
S4C1O3	S3C1O3	S2C1O2	S2C1O3	S3C1O3
F	F	F	F	F
46/42†	34 ± 12/38 ± 6	—/47.2 ± 9.6	54 ± 16/49 ± 15	48.8/46.3
27/25†	27 ± 5/29 ± 5	—/21.5 ± 6.2	29 ± 7/28 ± 6	28.7/26.7

RESULTS

Eligible Studies

A total of 420 potential eligible citations were identified with the literature search. Titles of these citations were reviewed and 286 were rejected, leaving 134 potentially eligible studies. After review of abstracts, an additional 128 were rejected. Ten studies (3 RCTs and 7 nonrandomized studies) were then retrieved in full-text to determine the inclusion. Assessment agreement of study selection of full-text papers between 2 reviewers led to a k score of 0.83 (95% CI, 0.78-0.88) initially. Then a further discussion was conducted among all the authors with regard to the studies upon which the 2 reviewers disagreed. Finally, corporate review of full-text papers excluded 2 studies for not reporting our endpoints.

Paper Description

According to the inclusion and exclusion criteria, we detected the 10 literatures (Table 1). Three RCTs[7–9] with 157 patients and 7 observational studies[2,6,10–14] with 593 patients met the inclusion criteria, the number of NOTES group patients is 367, and the number of laparoscopic group is 383.

The detailed characteristics of the included studies are shown in Table 1.

Wound Complications

Wound complications incision infection, incision hemorrhage, and incision hernia occurred in 11 patients after operation, including 3 patients who received NC and 8 patients after LC, respectively. Pooling the results of 8 studies[2,7–13] (n = 557) showed no significant difference in wound complications occurrence rate between the 2 groups (RD = −0.02; 95% CI, −0.04 to 0.01; $P = 0.23$; P heterogeneity = 0.23; $I^2 = 0\%$) (Fig. 1). There was no significant difference between 2 groups neither divided by RCT nor by non-RCT clinical trials (data does not show).

Other Postoperative Complications

Common complications of cholecystectomy are postoperative hemorrhage, bile leak, and server abdominal pain. Because the sample of single postoperative complication is too small for statistical analysis, we gathered all the complications together. Pooling the results of 10 studies[2,6–14] (n = 750) indicated no significant difference in aspect of other postoperative complications in 2 groups. (RD = −0.01; 95% CI, −0.03 to 0.02; $P = 0.61$). No significant heterogeneity was shown as well (P heterogeneity = 0.8; $I^2 = 0$) (Fig. 2). There was no significant difference between 2 subgroups neither divided by RCT nor by non-RCT clinical trial (data not shown).

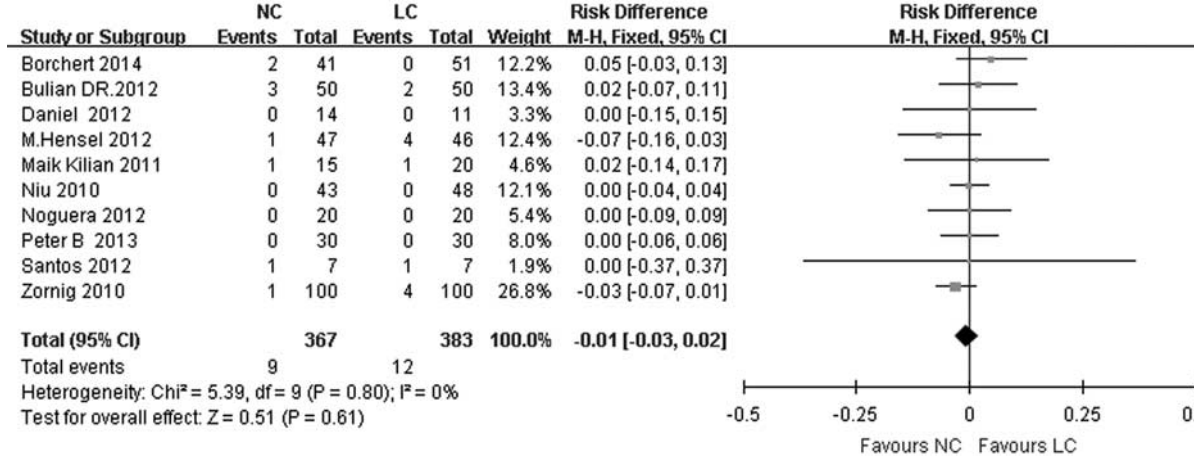

FIGURE 2. Meta-analysis of other postoperative complications between NC and LC groups. CI indicates confidence interval; NC, NOTES cholecystectomy; LC, laparoscopic cholecystectomy.

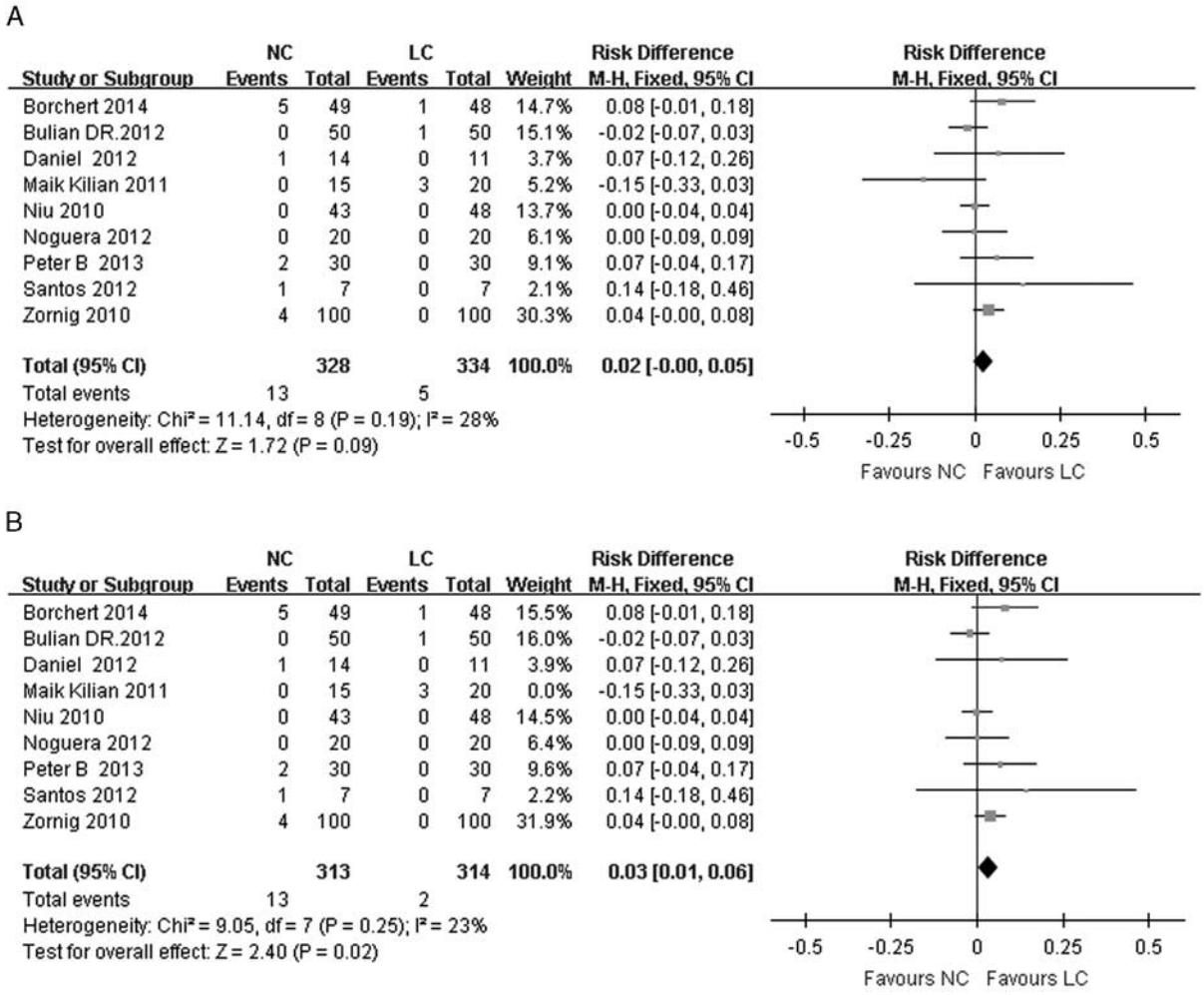

FIGURE 3. A, Meta-analysis of intraoperative conversion between NC and LC groups. B, Meta-analysis of intraoperative conversion between NC and LC groups without the Maik Kilian's trial. CI indicates confidence interval; NC, NOTES cholecystectomy; LC, laparoscopic cholecystectomy.

Intraoperative Conversion

The pooled analysis (9 studies,[2,7–14] n = 662) indicated that the intraoperative conversion rates in the groups of NC is increasing (RD = 0.02; 95% CI, 0.00-0.05; $P = 0.09$). There was no obvious heterogeneity between groups (P heterogeneity = 0.19; $I^2 = 28\%$). According to the forest graph, we found that the heterogeneity of Kilian et al's[11] trial is relatively large, there were 3 patients who received LC had intraoperative conversion because of severe preoperative disease. (One was perforation of gallbladder, the second subject had accepted many abdominal operations before, and the third one was Mirrizi syndrome.) So we

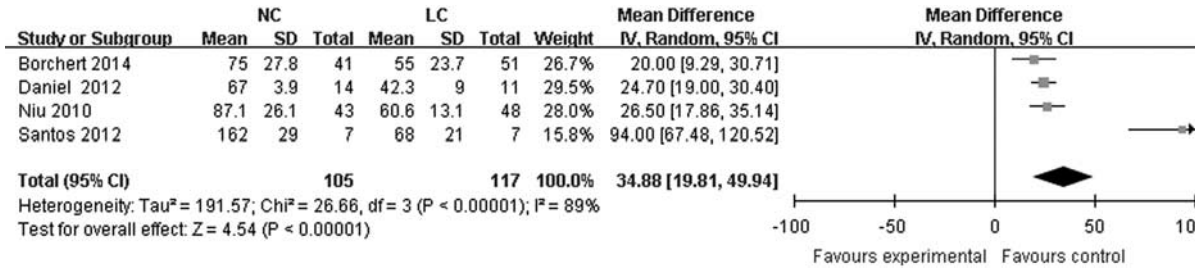

FIGURE 4. Meta-analysis of operation time between NC and LC groups. CI indicates confidence interval; NC, NOTES cholecystectomy; LC, laparoscopic cholecystectomy.

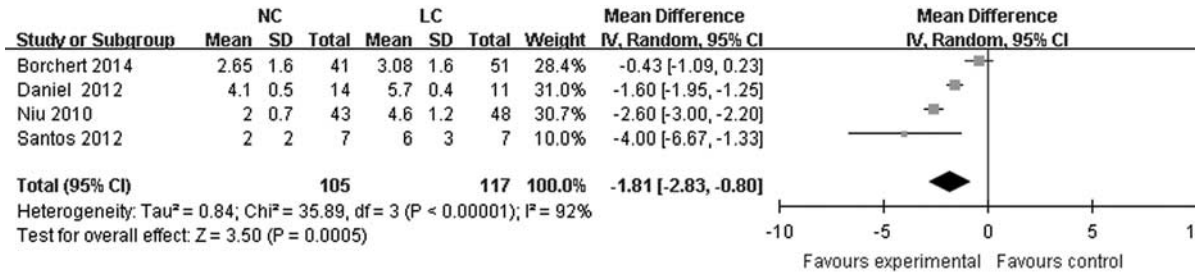

FIGURE 5. Meta-analysis of postoperative pain between NC and LC groups. CI indicates confidence interval; NC, NOTES cholecystectomy; LC, laparoscopic cholecystectomy.

eliminated this trial and did the analysis again. The second analysis showed that the rate of intraoperative conversion of LC group is lower than that of NC group. Significant statistical difference was shown (RD = 0.03; 95% CI, 0.01-0.06; $P = 0.02$), and there was no obvious heterogeneity between groups (P heterogeneity = 0.25; $I^2 = 23\%$) (Figs. 3A, B).

Operation Time, Postoperative Pain, and Length of Stay in Hospital After Operation

We noticed that there was no primary data in some original papers. Then we contacted with related authors, but seldom got responses. Therefore we just pool part of trials to process the statistics. For example, the operation time, postoperative pain, and length of stay in hospital. The results showed that the operation time in NC group was longer than LC group [mean difference (MD) = 34.88, $P < 0.001$], the pain score of postoperative of NC group is lesser than LC group (MD = −1.81, $P < 0.001$), and the length of stay in hospital between 2 groups is of no statistical difference (MD = −1.06, $P = 0.3$) (Figs. 4–6). However, the heterogeneity of all these 3 comparisons is significant. To facilitate the comparison, we listed the relevant data, including the means or medians. We could see that the operation time in NC group was longer than the LC group, and most of this difference is significant. Most researches showed that the pain score of postoperative of NC group is lesser than the LC group. The length of stay in hospital in 2 groups are both very short (1 to 2 d) and no significant difference was shown (Table 2).

Publication Bias Analysis

We assessed the publication bias of selected studies by Begg funnel plot. Using the postoperative complications analysis, the reverse funnel chart showed that experimental comparison of evenly distributed in both sides. So we thought that there was no obvious publication bias analysis in our study. Other indicators analysis revealed no obvious bias exists in this study (data not shown) (Fig. 7).

DISCUSSION

Open cholecystectomy was first recorded in 1882. A hundred years later, a famous French surgeon named Mouret, performed the first LC.[15] At the present time, LC have become the today's golden standard technique in gallbladder disease treatment. NOTES is a hotspot in the research of minimally invasive surgery. Compared with open and laparoscopic surgical procedures, NOTES has the potential advantage to provide no obvious scar, lesser pain and faster patient recovery.

NOTES have many routes into the peritoneal cavity. The transvaginal route met most of the expectations of surgeons for a safe and reliable access to the peritoneal cavity, most surgeons involved in the development of NOTES proposed to move forward by starting clinical series with the transvaginal approach. Cholecystectomy had already been a standard surgical procedure that could be easily translated from the laparoscopic to the NOTES approach. In 2007, Ricardo Zorron (Rio de Janeiro, Brazil) published the first report of transvaginal hybrid NOTES cholecystectomy.[16] In the same year, both Jacques Marescaux (Strasbourg, France) and Mark Bessler (New York) reported the first NOTES cholecystectomy without any laparoscopic assistance (pure NOTES).[17] These major achievements received a large echo in the media, favoring further development and evaluation of the technique. In the following years, many transvaginal hybrid NOTES cholecystectomy were reported in 2008.[18,19] Since May 2009, we also have successfully performed transvaginal endoscopic

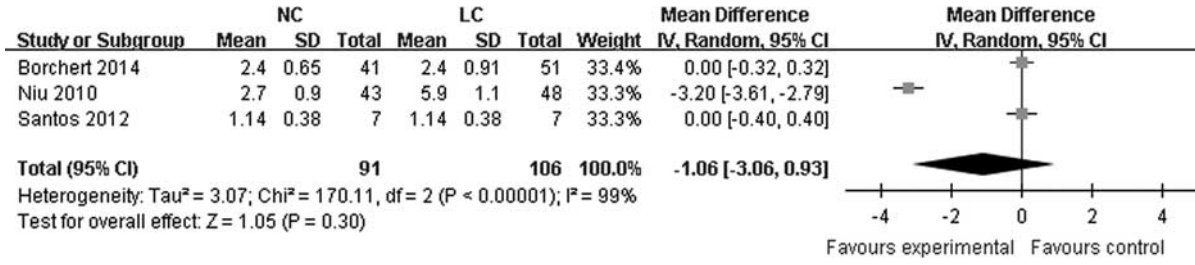

FIGURE 6. Meta-analysis of length of stay in hospital between NC and LC groups. CI indicates confidence interval; NC, NOTES cholecystectomy; LC, laparoscopic cholecystectomy.

TABLE 2. Major Outcomes (LC/NC)

References	Noguera et al[7]	Borchert et al[8]	Solomon et al [9]	Zornig et al[10]	Kilian et al[11]
Wound complications	2/1	2/1	0/0	3/1	0/0
Other complications	0/0	0/2	0/0	4/1	1/1
Intraoperative conversion	0/0	1/5	0/1	0/4	3/0
Operation time (min)	47/65 (mn)*	55 ± 6/75 ± 8*	42.3 ± 9/67 ± 3.9	35/52 (mn)*	55/68 (md)
Postoperative hospital stay (d)	1/1	2.4 ± 2/2.4 ± 2	—/—	2.3/2.1 (mn)	4/3 (md)*
Postoperative pain (scores)	4.65/3.94	1.56/1.71 (mn)	5.7 ± 0.4/4.1 ± 0.5*	—/—	3/1 (md)*

*Statistical significance.
LC indicates laparoscopic cholecystectomy; NC, NOTES cholecystectomy; md, median value; mn, mean value.

cholecystectomies in a consecutive series of 43 cases using a laparoscopically assisted method, which was published in 2011.[2]

In view of the present situation of the development of the mini-invasive operative instrument and the habits of the surgeon, generalized transvaginal route method including 2 major techniques categories. The first category is pure NOTES technique. A flexible endoscope enter the peritoneal cavity through the posterior vaginal fornix puncture point, and using the flexible instruments passed in endoscope working channel finish the cholecystectomy. The second category is hybrid NOTES technique, including the hybrid technique with a flexible endoscope and the hybrid technique with rigid laparoscopic instruments. The hybrid technique with a flexible endoscope refer that a rigid laparoscope enter the peritoneal cavity through the umbilical and making a small incision in posterior vaginal fornix, under the laparoscopic vision, insert a flexible endoscope into peritoneal cavity. Using the laparoscopic instruments without the laparoscope passed through the umbilical and posterior vaginal fornix finished the cholecystectomy under the endoscope vision. The hybrid technique with rigid laparoscopic instruments refer that a long rigid 45 degrees laparoscope and 5 mm dissector inserted into peritoneal cavity through the posterior vaginal fornix small incision. Another dissector passed through the umbilical into peritoneal cavity. Using the 2 laparoscopic instruments finish the cholecystectomy under the laparoscope vision.

In this review, we only compared the advantage between the LC and the hybrid NC, which has been described above the second category. We found that there is no different between wound complications of NC group and LC group. Even in some studies, the NC group is lower than LC. Similarly, there is no significant difference on the incidences of other postoperative complications of between the 2 groups. As matter of fact, transvaginal access to the abdominal cavity is not a new concept. This access has been used routinely by gynecologists to perform diagnostic and therapeutic procedures. We analyzed this results may resulted from 2 reasons. The first is that gynecologists accumulated rich experience for posterior colpotomy, they could control wound complications well. The second reason is that the healing ability of vaginal mucosa is better than skin.

We also found that the incidence of other postoperative complications in NC group is not higher than LC group. Postoperative bleeding and bile leak often resulted from bad exposure of anatomic structure or lack of enough experience. But in beginning of NOTES, these pioneer were the elites in this field, and the transvaginal route has been considered particularly suitable for the upper abdominal operation. It provides a straight view of the liver and gallbladder without the need for retroflection of the endoscope.

It could be easily accepted that intraoperative conversion incidence in NC group is higher than LC group. In the early stage of the NC development, operator were lack of experience, special instruments for NOTES procedure were also lacked. In addition, the operating team could cooperate well, and the selection of patients contributed to this result. Similarly, the operation time in NC group is longer than LC group. As for the better postoperative pain control in NC group, we speculate that vaginal incision is less sensitive than abdominal wounds and the nerve endings around the umbilical fundus are fewer.[2] To the obvious heterogeneity, we attributed it to the different therapeutic schedule and data collection method of each medical center.

In conclusion, even in the initial stage of NOTES, our meta-analysis shows that transvaginal NOTES cholecystectomy is also safe, and it is worthy of further promotion and validation in clinical works and in clinical practice. Until specifically designed endoscopic instruments for pure NOTES are available, we think that the best approach is the hybrid technique using a single umbilical trocar for laparoscopic assistance in present. We believe that with the further studies of NOTES, it would be provided to a wider range of the patients, with the promise of abolishing the traditional concept of pain and scars associated with surgery.

Limitations

There are several limitations to our meta-analysis and the findings should be interpreted with caution. First, the

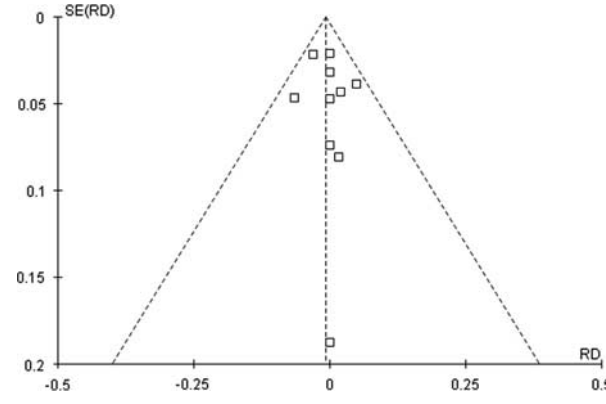

FIGURE 7. Begg funnel plot for publication bias of selected studies. RD indicates rate difference.

TABLE 2. *(continued)*

van den Boezem et al[12]	Santos et al[13]	Niu et al[2]	Hensel et al[6]	Bulian et al[14]
1/0	0/0	0/0	—/—	—/—
0/0	1/1	0/0	4/1	2/3
0/2	0/1	0/0	0/0	1/0
46/60 (md)*	68 ± 21/162 ± 29*	60.6 ± 13.1/87.1 ± 26.1*	60/45 (md)*	77.75/77.8 (mn)
1/1 (md)	1.14/1.14	5.9 ± 1.1/2.7 ± 0.9*	4/3 (md)*	3.4/2.7 (mn)*
2/2 (md)	6 ± 3/2 ± 2*	4.6 ± 1.2/2.0 ± 0.7*	—/—	2.8/1.9*

number of studies included in this paper is small, which means the inevitably bias. Second, inclusion of observational studies inevitably introduced a source of potential bias that inherently exists in nonrandomized, unblinded design. The combined and isolated groups might not be comparable in all the influencing factors. Third, differences between the included studies regarding surgical types (with a flexible endoscope or rigid endoscope), severity of cholecystitis and the therapy during perioperative period have also been several confounders. Fourth, the included studies might be underpowered to determine significant differences in rare events such as the other postoperative complications. Finally, our study did not make the meta-analysis of continuous variables, such as operation time, postoperative pain, and length of stay in hospital after operation, thus the results are unconvincing.

CONCLUSIONS

There is no significate difference on safety between NOTES cholecystectomy and laparoscope cholecystectomy. NOTES cholecystectomy is associated with a higher rate of intraoperative conversion and longer operation time when compared with LC, however, patients feel less pain in NOTES group. It is worthy of further promotion and validation in clinical settings.

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