

## Systematic analysis of the safety and benefits of transvaginal hybrid-NOTES cholecystectomy

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**Author contributions:** Bulian DR and Lehmann KS designed research; Bulian DR, Knuth J, Lehmann KS and Sauerwald A performed research; Bulian DR and Heiss MM checked the data analysis and reviewed the article; Bulian DR and Knuth J wrote the paper.

**Conflict-of-interest statement:** Bulian DR, Knuth J, Lehmann KS, Sauerwald A and Heiss MM do not report any conflict of interest.

**Data sharing statement:** The technical appendix, statistical code, and dataset are available from the corresponding author at [buliand@kliniken-koeln.de](mailto:buliand@kliniken-koeln.de). Participants gave informed consent for data sharing. No additional data are available.

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Received: April 26, 2015  
Peer-review started: April 27, 2015  
First decision: June 23, 2015  
Revised: July 21, 2015  
Accepted: September 14, 2015  
Article in press: September 14, 2015  
Published online: October 14, 2015

### Abstract

**AIM:** To evaluate transvaginal hybrid-NOTES cholecystectomy (TVC) during its clinical establishment and compare it with the traditional laparoscopic technique (LC).

**METHODS:** The specific problems and benefits of TVC were reviewed using a registry analysis, a comparative cohort study and a randomized clinical trial. At first, feasibility, safety and specific complications of the TVC were analyzed based on the first 488 data sets of the German NOTES Registry (GNR). Hereafter, we compared the early postoperative results of our first 50 TVC-patients with those of 50 female LC-patients matched by age, BMI and ASA classification. The same cohort was contacted an average of two years later to evaluate long-term results concerning pain and satisfaction with the aesthetic results and the overall postoperative results as well as sexual intercourse by means of two domains of the German version of the Female Sexual Function Index (FSFI-d). Consequently, we performed a randomized clinical trial comparing 20 TVC-patients with 20 needlescopic/3-trocar cholecystectomies (NC) also concerning the early postoperative results as well as pain, satisfaction and quality of life by means of the Eypasch Gastrointestinal Quality of Life Index (GIQLI) in the later course. Finally,

we discussed the results in accordance with other published studies.

**RESULTS:** The complication (3.5%) and conversion rates (4.1%) for TVC were low in the GNR and comparable to those of the LC. Access related intraoperative complications included injuries to the bladder ( $n = 4$ ; 0.8%) and bowel ( $n = 3$ ; 0.6%). The study cohort revealed less postoperative pain after TVC comparing to the LC-patients on the day of surgery (NRS, 1.5/10 *vs* 3.1/10,  $P = 0.003$ ), in the morning (NRS, 1.9/10 *vs* 2.8/10,  $P = 0.047$ ) and in the evening (NRS, 1.1/10 *vs* 1.8/10,  $P = 0.025$ ) of postoperative day (POD) one. The randomized clinical trial consistently found less cumulative pain until POD 2 (NRS, 8/40 *vs* 14/40,  $P = 0.043$ ), as well as until POD 10 (NRS, 22/190 *vs* 41/190,  $P = 0.010$ ). Furthermore, the TVC-patients had a better quality of life on POD 10 than did the LC-patients (GIQLI, 124/144 *vs* 107/144,  $P = 0.028$ ). The complication rates were comparable and no specific problems were detected in the long-term follow-up for sexual intercourse for either group. The TVC-patients were more satisfied with the aesthetic result in the long-term course in the matched cohort analysis (1.00 *vs* 1.88,  $P < 0.001$ ) as well as in the randomized clinical trial (1.00 *vs* 1.70,  $P < 0.001$ ) when compared with the LC-patients.

**CONCLUSION:** TVC is a feasible procedure with a high safety profile and has advantages in regard to postoperative pain and aesthetic results when compared with LC or NC.

**Key words:** NOTES; Cholecystolithiasis; Postoperative complications; Postoperative pain; Transvaginal hybrid-NOTES cholecystectomy

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**Core tip:** Transvaginal hybrid-NOTES cholecystectomy (TVC) increased in popularity after its introduction in 2007. We systematically evaluated this new technique with regards to its specific complications and advantages compared with those of the laparoscopic technique (LC) using a registry analysis, a matched cohort analysis and a randomized clinical trial. TVC had a low conversion rate and complication rate. Injuries to the bladder and urinary tract infections were rare but access-specific complications. TVC-patients showed less postoperative pain and a better quality of life in the short-term course than did the LC-patients. TVC led to an improved satisfaction with the aesthetic results also in long-term course. No specific problems, not even for sexual intercourse, were detected.

Bulian DR, Knuth J, Lehmann KS, Sauerwald A, Heiss MM. Systematic analysis of the safety and benefits of transvaginal hybrid-NOTES cholecystectomy. *World J Gastroenterol* 2015; 21(38): 10915-10925 Available from: URL: <http://www.wjgnet.com>

[com/1007-9327/full/v21/i38/10915.htm](http://dx.doi.org/10.3748/wjg.v21.i38.10915) DOI: <http://dx.doi.org/10.3748/wjg.v21.i38.10915>

## INTRODUCTION

On one hand, operative procedures serve to heal or at least alleviate disease or disease-related complaints. On the other hand, these methods hold general and specific risks and obviously harm the physical integrity of the patient. Operative risks result not only from the actual procedure on the target organ but also from the necessary access. The consequences and risks of long-term common abdominal access, namely laparotomy, are pain at the incision site<sup>[1]</sup>, wound infection<sup>[2,3]</sup>, burst abdomen<sup>[4-6]</sup>, incisional hernias and scarring. They may result in a prolonged hospital stay, increased lethality, and possibly further procedures to correct associated complications<sup>[7-9]</sup>. To avoid or at least reduce the access-related problems mentioned above by reducing the access inherent trauma, laparoscopy was developed<sup>[10,11]</sup>. However, the completely unaccustomed instrument handling demanded new, initially unfamiliar skills. This resulted in an increased initial complication rate, *e.g.*, bile duct injuries during cholecystectomy<sup>[12]</sup>.

For many decades, gynecological intraperitoneal procedures have been performed by avoiding the abdominal wall and instead utilizing a natural orifice, namely the transvaginal access point<sup>[13-15]</sup>. In 2004, Kalloo *et al*<sup>[16]</sup> introduced the NOTES-concept for gastroenterologic disease treatment. As a result, cholecystectomy was performed transvaginally by several groups in 2007<sup>[17-21]</sup>. Even prior to that, the retrieval of larger specimens, such as the spleen<sup>[22]</sup>, and even the gallbladder during cholecystectomies in cases of large stones<sup>[23]</sup>, were performed transvaginally but without attracting much attention in the abdominal surgery field. It was not until the aim of performing an operation completely through a natural orifice with a flexible endoscope became desirable that the development of several techniques and the distribution of the NOTES-concept itself gained momentum. However, intraabdominal procedures are only performed with great difficulty when employing the currently available standard endoscopes. Thus, several clinics<sup>[24]</sup> established transvaginal/transumbilical Hybrid-NOTES cholecystectomy (TVC) using rigid instruments as described by Zornig *et al*<sup>[17]</sup>.

Based on experiences with the clinical implementation of the traditional laparoscopic cholecystectomy (LC) at the end of the 1980's including the already mentioned higher rate of complications, a concomitant evaluation of the clinical implementation of TVC as a new method in surgery seemed obligatory. Apart from its safety, investigations into additional benefits for the patients, such as reduced postoperative pain, required clarification.

**Table 1** Overview of the studies that were included for the analysis

Study	Patients	Study aim
Registry analysis <sup>[24]</sup>	551 (488 TVC)	Technical and clinical feasibility Safety (particularly regarding access related complications)
Cohort study A <sup>[25]</sup> (Early postoperatively)	100 (50 TVC; 50 LC)	Benefit (postoperative pain) Disadvantages (specific complications)
Cohort study B <sup>[26]</sup> (24 mo postoperatively)	88 <sup>1</sup> (46 TVC; 42 LC)	Long-term problems (particularly regarding sexual intercourse) Patient satisfaction
NATCH-study <sup>[29]</sup> (Early postoperatively)	40 (20 TVC; 20 NC)	Benefit (postoperative pain) Disadvantages (specific complications)
NATCH-study <sup>[30]</sup> (3 and 6 mo postoperatively)	40 (20 TVC; 20 NC)	Long-term problems (particularly regarding sexual intercourse) Patient satisfaction

<sup>1</sup>From the collective of cohort study A. TVC: Transvaginal cholecystectomy; LC: Traditional laparoscopic cholecystectomy; NC: Needlescopic 3-trocar-cholecystectomy.

## MATERIALS AND METHODS

The following aspects were evaluated by our study group in different trials/studies and will be discussed in this review: feasibility of TVC in clinical routine, safety of the method, possible access-related complications, potential for less postoperative pain when compared with LC, negative influence on sexual life due to transvaginal access, higher patient satisfaction with the esthetic result compared with LC and evaluation of morphological changes as a result of the transvaginal access.

For clarification of these problems, five analyses were used on three different studies with a different conceptual design (Table 1).

On the basis of a national registry<sup>[24]</sup>, feasibility and safety, including access-related complications, were analyzed.

On the basis of a comparative cohort study for our first 50 TVCs<sup>[25]</sup>, the expected advantage regarding reduced postoperative pain and other early postoperative parameters were evaluated in comparison with LC. To record more than just short-term complications, a two-year follow-up exam of the same patients was conducted in order to detect and compare problems concerning sexual life and satisfaction with the esthetic result<sup>[26]</sup>.

Because there is evidence for the usage of mini-instruments to reduce postoperative pain in LC<sup>[27,28]</sup> and a reduction of the number of trocars should have a similar effect, a prospective/randomized, unblinded, single center trial was initiated to compare TVC with the allegedly least traumatizing technique for the abdominal wall, which is the needlescopic 3-trocar-cholecystectomy (NC)<sup>[29]</sup>.

Apart from short-term advantages, long-term safety was also assessed in the prospective/randomized trial. Thus, parameters regarding sexual life and patient satisfaction were also registered at three and six months postoperatively<sup>[30]</sup>.

### Step 1: Registry analysis

The German registry for natural orifice transluminal

endoscopic surgery: report of the first 551 patients<sup>[24]</sup>.

The German NOTES Registry (GNR) was implemented in March 2008. All surgical departments in Germany were invited *via* mail, email, and conference participation, to document all NOTES-related procedures in the GNR *via* an online portal that was especially programmed for this purpose. Participation was voluntary, pseudonymized, not linked to any membership and free of charge after creating an account for the respective department. Technical realization was carried out by the DGAV. In our clinic, all NOTES-related procedures were registered in the GNR.

Registered data included general and patient related data, target organ, therapy and postoperative course. The first published analysis after documentation of more than 550 cases was analyzed using SPSS, version 16 (IBM Germany, Ehningen) and SAS, version 9.2 (SAS Institute, United States, North Carolina). Apart from descriptive statistics of all procedures, a sub group analysis was planned for those target organs that made up for more than 15% of the overall procedures or an absolute number of more than 50 procedures. Eventually, this criterion applied to the target organ "gallbladder" only.

### Step 2: Matched cohort analysis; short-term results

Less pain after transvaginal/transumbilical cholecystectomy than after the classical LC: short-term results of a matched-cohort study<sup>[25]</sup>.

In our clinic, the first TVC was performed on December 8, 2008. Since then, for all patients with an indication for elective cholecystectomy (CHE) due to symptomatic cholelithiasis, the following pre-, intra- and postoperative parameters were recorded and documented in a prospective data base: age, body mass index (BMI), comorbidities, previous abdominal surgery, American Society for Anesthesiologists (ASA)-classification, history of cholecystitis or cholestasis, date of the operation, procedural time, amount of percutaneous trocars, conversion, pre- and postoperative leukocytes, CRP and bilirubin, intra- and postoperative complications, histopathological results, pain [in the recovery room and on the morning and

evening of the first postoperative day as measured blindly using the numeric rating scale (NRS-11)<sup>[31]</sup> from 0 (no pain) to 10 (worst imaginable pain) by nurses especially trained for this purpose], analgesic consumption, time of first solid food intake and postoperative hospital stay.

The choice of technique was made by the patients after informed consent about the possible advantages and disadvantages of both TVC and LC was obtained. Additionally, all TVC-patients were preoperatively examined by a gynecologist to exclude contraindications for a transvaginal procedure. Perioperative treatment was the same for both groups. TVC-patients were advised to abstain from penetrating sexual intercourse for two weeks postoperatively. Furthermore, there was a gynecological re-examination after ten to twelve days.

TVC was performed as described by Zornig *et al.*<sup>[17]</sup>. For LC, four trocars were used: two 11 mm- and two 6 mm-trocars. The gallbladder was retrieved through the umbilical trocar access, which was increased in size in cases of multiple or large stones.

A comparative analysis of the first 50 TVC-patients with 50 traditional laparoscopic patients (LC-group) from the same time period matched according to age, BMI and ASA classification, was conducted.

### **Step 3: Matched cohort analysis; long-term results**

Long-term results of transvaginal/transumbilical vs classical laparoscopic cholecystectomy - an analysis of 88 patients<sup>[26]</sup>.

All 100 patients of the previous cohort study<sup>[25]</sup> were contacted *via* telephone after an average of 2.05 years (1.04-3.14) postoperatively. They were asked to answer a questionnaire about the postoperative course and their satisfaction. A standardized questionnaire was sampled *via* telephone. Alternatively, patients were offered to have the questionnaire sent to them with a self-addressed stamped envelope.

All telephone interviews were conducted by the same female interviewer to avoid not only interpersonal variability but also patients' reservations toward a male interviewer especially in regard to items dealing with sexuality. Evaluation was anonymous. The questionnaire was comprised of 48 items including five items about previous abdominal surgery, five items about previous deliveries, 13 items about the postoperative course, three general items about sexual intercourse, three items each of the domains "satisfaction" and "pain" of the German version of the Female Sexual Function Index (FSFI-d; items 14-16 and 17-19)<sup>[32,33]</sup> related to three different points in time (cooperatively, early postoperatively and during the last four weeks before the interview), two items each about satisfaction with the esthetic result and the overall surgical result (very satisfied/satisfied/ambiguous/dissatisfied/very dissatisfied) as well as two items about the patient's choice of technique in the

hypothetical case of a new necessary cholecystectomy and whether or she would recommend the technique to friends or relatives. Data processing and statistical analysis was conducted using SPSS, Version 19 (IBM Germany, Ehningen).

### **Step 4: Randomized clinical trial; short-term results**

Transvaginal/transumbilical hybrid-NOTES vs 3-trocar needlescopic cholecystectomy: short-term results of a randomized clinical trial<sup>[29]</sup>

After preparation of a study protocol, calculation of sample size, approval by the ethics committee and registration of the study, 40 patients were included in a randomized, prospective, single center and unblinded clinical trial between February 2010 and June 2012. Randomization was 1:1 for TVC and NC. All procedures were conducted by the same surgeon in order to avoid not only interindividual differences but also the influence of a learning curve, which was already completed for the performing surgeon at the beginning of the trial.

Postoperative pain medication, return to food intake and dismissal criteria were standardized and identical for both groups. On postoperative day ten, the first post-dismissal examination took place and included a clinical exam and inquiry of the esthetic result both by the study-physician and the patient using a satisfaction-scale (ordinal scale). Until that assessment point, the patients had documented pain intensity, pain localization and analgesic consumption three times daily. All TVC-patients were re-examined by a gynecologist on postoperative day 12-14.

The primary outcome measure was the cumulative early postoperative pain intensity during movement within the first 48 h following surgery and was comprised of four measurements (pain intensity six hours postoperatively, on the morning and the evening of the first postoperative day and the morning of the second postoperative day) measured on the Numeric Rating-Scale (NRS-11)<sup>[31]</sup>. Secondary short-term outcome measures, documented prospectively, were satisfaction of both the patient and the examiner with the esthetic results of the operation regarding the abdominal wall on postoperative day 10, intra- and postoperative complication rates, conversion rate to traditional laparoscopic or conventional technique, procedural time, evaluation of the operative handling (instrument handling, camera handling, dissection and gallbladder retrieval) by the first and the second surgeon, cumulative postoperative pain intensity during movement until postoperative day ten as measured in the morning and in the evening with the NRS-11, cumulative consumption of peripheral and central analgesics during the first ten days, re-operation rate, time to return to daily, professional and leisure activity as well as quality of life, measured on postoperative day 10 using the Eypasch Gastrointestinal Index for Quality of Life (GIQLI)<sup>[34]</sup>. Furthermore, age, BMI,

ASA classification, number of gallstones, size of the largest stone, history of previous cholecystitis, pre- and postoperative lab results (leukocytes, CRP), number of percutaneous trocars, histological result and postoperative hospital stay were prospectively documented.

SPSS, version 19 (IBM Germany, Ehningen) was used for data processing and statistical analysis. An intention-to-treat-analysis was conducted for all calculations.

### **Step 5: Randomized clinical trial; long-term results**

Transvaginal hybrid NOTES cholecystectomy - results of a randomized clinical trial after 6 mo<sup>[30]</sup>.

This prospective/randomized long-term analysis was conducted with the same 40 patients who had been randomized for TVC or NC in the study mentioned above. Satisfaction with the esthetic result and overall satisfaction, abdominal pain during movement according to the NRS-11 and occurrence of trocar hernias were documented according to a structured questionnaire three and six months postoperatively in a telephone. In cases of a positive or unclear answer for the item "trocar hernia", patients were examined clinically and with sonography. Furthermore, three months postoperatively, satisfaction and occurrence of pain during after sexual intercourse were evaluated using the domains "satisfaction" and "pain" from the German FSFI-d. Naturally, only patients who had had sexual intercourse during the mentioned time frame could be questioned about this matter. Both domains were evaluated separately and together. Moreover, there was a gynecological exam six months postoperatively to detect morphological long-term changes at the point of access. Apart from taking the history, the gynecologist performed a palpation and speculum-inspection, especially of the posterior vault of the vagina, and a transvaginal sonography. The gynecologist also documented complaints, whether the patients already had postoperative sexual intercourse, and if a further follow-up examination was necessary.

Data processing and statistical analysis (intention-to-treat-analysis) was conducted using SPSS, version 21 (IBM Germany, Ehningen).

## **RESULTS**

### **Step 1: Registry analysis**

The German registry for natural orifice transluminal endoscopic surgery: report of the first 551 patients<sup>[24]</sup>.

Of the 64 accounts that were generated, 28 were active and resulted in 551 patient data sets with 572 target organs. The most frequent target organ was the gallbladder (85.3%), and the most frequent indication was symptomatic gallstones (73.6%).

Only female patients underwent NOTES procedures. Complications occurred in 3.3% of all cholecystectomies. Hospital stays were significantly longer in

cases with a complication compared with those who did not experience complications (6.7 d vs 2.6 d,  $P < 0.001$ ). All procedures, except two that lacked further specifications, were carried out transvaginally. Nearly all patients (99.3%) were underwent procedures in which the Hybrid-NOTES techniques were applied with one or more percutaneous trocars for cholecystectomies with an average of  $1.2 \pm 0.5$  trocars. Most procedures ( $n = 534$ ) used a rigid laparoscope, and 96.6% of the procedures were performed by a general or abdominal surgeon. Sixty-four percent of the procedures were assisted by a gynecologist.

Intraoperative complications occurred in seven cases, and postoperative complications occurred in ten cases. The most frequent complication was injury to the bladder, which only occurred in obese patients ( $BMI \geq 30.0 \text{ kg/m}^2$ ) and older patients ( $\geq 59$  years). Postoperative complications included bleeding and vaginal or urinary tract infections. Twenty procedures (3.6%) were converted to traditional laparoscopy and seven (1.3%) to laparotomy. In seven cases, a planned NOTES access was not performed due to technical problems with the transvaginal access. No difference was detected with regards to complication and conversion rates in the presence or absence of a gynecologist. All patients studied survived the entire study period.

Multivariate analysis of the cholecystectomies revealed a significant correlation between conversion rate and hospital stay with BMI and age, but not with case load of the operating clinics. Procedural time was dependent on BMI and case load, and the amount of percutaneous trocars was dependent on patient age and case load, and these trends were all significant. In "high-volume"-clinics, procedural time was shorter and the amount of percutaneous trocars lower. The rate of complications showed no significant dependence on any factor.

### **Step 2: Matched cohort analysis; short-term results**

Less pain after transvaginal/transumbilical cholecystectomy than after the classical LC: short-term results of a matched-cohort study<sup>[25]</sup>.

Age, BMI, ASA classification, preoperative leukocytes and CRP did not differ significantly between both groups. Only previous gynecological conditions or previous gynecological procedures were significantly more frequent in the TVC-group (18 x vs 6 x,  $P = 0.009$ ). Average procedural time was identical in both groups (77.8 min). For the first 25 TVC-procedures, the average procedural time was 82.3 min, and for the second group of 25 procedures it was 73.3 min. In the LC-group, the times were 76.9 and 78.6 min, respectively, with no significant differences between the TVC- and LC-groups. In the TVC-group, there was no conversion, and in the LC-group one patient (2%) needed conversion due to a bile duct injury. This was also the only intraoperative complication

in the LC-group (2%). In the TVC-group, there was one intraoperative injury to the urinary bladder (2%) that did not require conversion. On the day of the operation, the TVC-patients had significantly less pain than did the LC-patients (NRS: 1.5 vs 3.1,  $P = 0.003$ ), although at the same time these patients received significantly less analgesic medication in the recovery room than did the LC-patients (19 x vs 32 x,  $P = 0.016$ ). Notably, TVC-patients received significantly less opiates (16 x vs 31 x,  $P = 0.005$ ). Also on the morning and on the evening of the first postoperative day, there was a significant reduction in pain in the TVC-group (NRS: 1.9 vs 2.8,  $P = 0.047$ ; 1.1 vs 1.8,  $P = 0.025$ ). Inflammation, as measured by CRP, was significantly lower during the first two days after TVC when compared with LC (25.5 mg/L vs 39.1 mg/L,  $P = 0.015$ ). Additionally, the individual increase in CRP (difference between pre- and postoperative value) was significantly lower following TVC compared to LC (21.1 mg/L vs 33.1 mg/L,  $P = 0.003$ ). The postoperative leukocyte count was not different between both groups (7.8/nL vs 8.0/nL,  $P = 0.4$ ). After TVC, the postoperative hospital stay was significantly shorter (2.7 instead of 3.4 d,  $P < 0.001$ ). First solid food intake happened significantly earlier in the TVC than in the LC group (1.02 d vs 1.40 d,  $P < 0.001$ ) and took place significantly more often on the first postoperative day (49 x vs 30 x,  $P < 0.001$ ).

### Step 3: Matched cohort analysis; long-term results

Long-term results of transvaginal/transumbilical vs classical laparoscopic cholecystectomy - an analysis of 88 patients<sup>[26]</sup>.

All 88 patients who could be readily reached answered the questionnaire (TVC: 46; LC: 42; return quota 92% and 84%,  $P = 0.357$ ). Those patients, as in the original 100, did not significantly differ in terms of age, BMI, ASA classification, previous abdominal surgery or amount of previous deliveries. The majority (76.1%) of the TVC-patients and 61.0% of the LC-patients had sexual intercourse in the six months before the CHE. After the CHE the same frequencies were 78.3% and 61.0%, respectively ( $P = 0.165$  and  $0.102$ ). Additionally, the point of first sexual intercourse following CHE was not significantly different. Neither the domains of the FSFI-d, nor their sum were significantly different for all three examined time-points. The TVC-patients were significantly more satisfied with the esthetic results of the CHE and with the overall result ( $P < 0.001$  and  $P = 0.001$ ). All TVC-patients would hypothetically opt for the same technique again, and only 80.5% ( $P = 0.002$ ) would do so after LC. Furthermore, all TVC-patients would recommend the technique applied on them to friends or relatives, whereas only 69.2% would do so in the LC-group ( $P < 0.001$ ). Both general postoperative complications as well as wound infections were less frequent after TVC, but not significantly so (17.8% vs 35.7%,  $P = 0.088$  and 2.2% vs 7.1%,  $P = 0.344$ ).

CHE related incisional hernias occurred in two out of the 42 LC-patients, but not in the TVC-group (4.8% and 0%,  $P = 0.225$ ). Significantly less TVC-patients felt impaired by the CHE (6.5% vs 23.8%,  $P = 0.034$ ). Some of the TVC-patients (19.6%) and the LC-patients (28.6%) reported epigastric pain, and 6.5% and 4.8% had had pain in the lower abdomen and/or pubic area, respectively, during the four weeks before the inquiry ( $P = 0.453$  and  $P = 1$ ). Pain intensity was not significantly different between the two groups ( $P = 0.451$  and  $P = 0.700$ ). After the procedure, the TVC-patients could resume everyday life activities (work, school, household, etc.) significantly earlier than could the LC-patients (after 5.4 d vs 14.4 d,  $P < 0.001$ ). In each group, one patient noticed a change in her menstruation after the CHE. Four TVC-patients and no LC-patients noticed vaginal discharge after the CHE outside of the menstruation cycle (8.7% and 0%,  $P = 0.118$ ).

### Step 4: Randomized clinical trial; short-term results

Transvaginal/transumbilical hybrid-NOTES vs 3-trocar needlescopic cholecystectomy: short-term results of a randomized clinical trial<sup>[29]</sup>.

All patients were treated per protocol, and no conversions or additional trocars were necessary. In addition, no intraoperative complications occurred. Patient-derived parameters were comparable between the two groups. One patient from each group did not fill out the pain- and analgesics-documentation log prospectively, so these had to be excluded from the respective analysis. The primary outcome parameter was cumulative pain intensity during movement within the first 48 h following surgery. It was significantly lower in the TVC-group ( $P = 0.043$ ). Furthermore, the cumulative postoperative pain intensity during movement until postoperative day 10 was significantly lower in the TVC-group ( $P = 0.010$ ), although TVC-patients had a significantly lower consumption of analgesics ( $P = 0.019$ ). TVC-patients had a significantly better GIQLI-score ( $P = 0.028$ ) and were significantly more satisfied with the esthetic results of the operation ( $P < 0.001$ ). Both surgeons considered the retrieval of the gallbladder in TVC to be significantly easier ( $P < 0.001$  and  $P = 0.010$ ), whereas instrument handling was found to be significantly more difficult for TVC by the second surgeon ( $P = 0.020$ ). The remaining outcome parameters did not significantly differ between the two groups. All gynecologic follow-up exams had a regular postoperative findings.

### Step 5: Randomized clinical trial; long-term results

Transvaginal hybrid NOTES cholecystectomy - results of a randomized clinical trial after 6 mo<sup>[30]</sup>.

All 20 patients of the TVC-group were "very satisfied" with the postoperative result of the scars both three and six months postoperatively, which was significantly better than results in the TC-group ( $P = 0.004$  and  $P < 0.001$ ). However, the overall

satisfaction with the procedural result was not significantly different between both groups. One TVC-patient complained about lower abdominal pain three months postoperatively with a value of three on the NRS-11, one NC-patient had pain in the right upper quadrant after six months with a value of six on the NRS-11. Hernias were not detected, although two NC-patients were clinically evaluated after three and six months due to respective results in the telephone interview. Because three TVC- and six NC-patients had no penetrating sexual intercourse during the six pre- and postoperative months, only 31 patients could answer the FSFI-d questions. All preoperatively active patients also had postoperative sexual intercourse. The analysis of the FSFI-d-items revealed no significant difference between both techniques, neither for each domain separately, nor for evaluation of both domains together. None of the gynecologic follow-up exams showed pathological findings.

## DISCUSSION

The aim of our studies was to evaluate TVC, a new surgical technique that previously had not been systematically evaluated. After Kalloo *et al.*<sup>[16]</sup> introduced the NOTES-principle in 2004 by description of the perioral, transgastral access, that principle was adopted by several study groups for different intraperitoneal interventions in both experimental settings and clinical implementation. In 2007, a variety of transvaginal techniques for cholecystectomy were published by several study groups<sup>[17-21]</sup>.

First and foremost, the distribution and advancements of the new technique, including possible procedure-related complications, had to be transparent in order to facilitate timely intervention if necessary, bearing in mind the rapid increase of bile duct injuries following the introduction of minimally invasive surgery in form of LC at the end of the 80's<sup>[35,36]</sup>. For this reason, the appropriate scientific surgical society, the DGAV with its political and social responsibility, created a national NOTES-registry (GNR) order to achieve nationwide documentation of respective procedures to facilitate early detection of possible problems.

After 14 mo, the first analysis of the GNR, including 551 patients showed that more than 85% of the documented entirely transvaginal procedures, 99% of which utilized an additional umbilical trocar, (Hybrid-NOTES-technique) were cholecystectomies<sup>[24]</sup>. Furthermore, most cholecystectomies applied the Hybrid-NOTES-technique as described by Zornig *et al.*<sup>[17]</sup> with rigid instruments. Complications occurred in 3.1% of all patients, which is comparable to the results of LC in a large meta-analysis<sup>[37]</sup>. The most frequent intraoperative complication was a urinary bladder injury, which occurred in four patients with previous hysterectomy during establishment of the transvaginal access. This certainly accounts for an access-related complication. Otherwise, three intraoperative bowel

injuries were documented. Postoperatively, there were two cases of vaginal bleeding, one abscess in the Douglas-cavity and two vaginal infections in terms of access related complications. Some patients (3.6%) needed conversion to LC, and 1.3% needed conversion open cholecystectomy. Multivariate analysis of the documented cholecystectomies revealed several significant influences: the case load of the performing clinics on procedural time and the amount of trocars; BMI on conversion rate, procedural time and hospital stay; age on conversion rate, hospital stay and number of trocars. None of the analyzed parameters had a significant influence on the complication rate. Thus, at least for the clinics taking part in the registry, a responsible handling of the clinical implementation of this new technique became evident.

However, these results are based on the analysis of a voluntary registry and strongly depend on the quality of documentation as entered by the participating clinics. The data were not monitored, and neither were there audits. The logistic and financial effort would have necessitated membership fees or industrial sponsors. Furthermore, it is not guaranteed that all clinics that perform NOTES procedures actually took part in the registry. On the other hand, the robust results of the registry analysis might partly be explained by patient selection but also by the fact that the NOTES procedures were only performed by few surgeons with substantial experience and high expertise in the field of minimally invasive surgery. This fact certainly reflects the responsible clinical implementation of the new technique. Therefore, the validity of a comparison with LC-data derived from health services research is limited.

These results were recently confirmed in the latest analysis of the GNR, where 2992 data sets from March 2008 until November 2013 were analyzed<sup>[38]</sup>. With more than 88%, TVC was still the most frequent procedure by far, followed by appendectomy and colon resection. The recent rate of intraoperative complications was 1.6%, and that of postoperative complications was 3.6%. In this analysis, too, the main intraoperative complication was urinary bladder injury, and bowel injuries were still very rare but potentially serious complications. Postoperatively, urinary tract infections were classified as access related. Rarely (1.1%), procedures were converted to LC or the open procedure (0.4%).

Thus, our first analysis of the GNR, representing the worldwide largest analysis of NOTES procedures at that point, was the first step to proving the feasibility of Hybrid-NOTES procedures, particularly TVC.

The next step was the comparative analysis of TVC vs LC in order to prove the advantages of reducing access related trauma in the abdominal wall. For this purpose, the first 50 TVC-patients in our clinic in 2008 were compared to 50 matched LC-patients from the same time frame<sup>[25]</sup>. Here, when compared to LC, TVC significantly decreased not only postoperative

pain on the day of the operation and on the first postoperative day but also the hospital stay. At the same time, the frequency of analgesic consumption in the recovery room, especially of opioids, as well as the postoperative rise in CRP were significantly lower after TVC. Furthermore, TVC-patients had significantly earlier intake of solid food.

The decrease in postoperative pain by the Hybrid-NOTES technique was confirmed in other comparative non-randomized studies. The retrospective case-control-study by Hensel *et al.*<sup>[39]</sup> compared 47 TVC with 46 LC-3-trocar technique patients. Apart from less postoperative pain and less analgesic consumption, there were less nausea and vomiting following TVC. Additionally, TVC-patients could drink earlier, were mobilized quicker and had a shorter hospital stay than did the LC-3-trocar-patients. In a prospective, non-randomized observational study, Kilian *et al.*<sup>[40]</sup> compared 20 LC vs 15 TVC and 16 single-port cholecystectomies. Despite the small case number, postoperative pain and hospital stay were significantly shorter after TVC than after LC. Another study with three branches and a small case number by Solomon *et al.*<sup>[41]</sup> again found less postoperative pain after TVC when compared with LC and single-incision-CHE. Two further studies confirmed the reduced pain intensity after TVC<sup>[42,43]</sup>. However, Zornig *et al.*<sup>[44]</sup>, with their analysis of the highest number of cases comparing 100 TVC with 100 LC, found no difference for the analyzed parameters including analgesic consumption and hospital stay. Both Zornig *et al.*<sup>[44]</sup> and Noguera *et al.*<sup>[45]</sup> reported a significantly longer procedural time for TVC, while Hensel *et al.*<sup>[39]</sup>, Kilian *et al.*<sup>[40]</sup> and our analysis found no significant difference. Notably, in the study by Zornig *et al.*<sup>[44]</sup>, all procedures from both groups were performed by the chief of department or a senior surgeon, whereas in our LC-group, more than half of the procedures were performed by residents under the supervision of a senior surgeon. Thus a bias results, which is due to the fact that LC is generally considered a teaching procedure. Furthermore, with the analysis of procedural times, we found a learning curve for TVC because the second cluster of TVC procedures was nine minutes shorter than the first 25 TVC procedures. None of the mentioned studies found a significant difference in intra- and early postoperative complications between TVC and LC, which strengthens the favorable results of the GNR-analysis. However, one must consider that probably all of the registered centers are clinics with an above-average expertise in minimally invasive surgery. Therefore, a transfer of the result demands caution. We assume that the proven pain reduction is a result of the missing abdominal wall trauma due to retrieval of the gall bladder in TVC because this has the most relevant technical difference of both techniques. Especially in cases with large gallstones, a great amount of gallstones or a thickened organ wall manipulation at the abdominal wall requires a greater traumatization.

Because a benefit of TVC in regard to less early postoperative pain was evident without increased intra- or early postoperative complication rates, a long-term follow-up and the analysis of long-term parameters was the aim of further studies. This was not because mainly young, sexually active women who took part in respective surveys were concerned about long-term impairment of sexual activity following a transvaginal procedure<sup>[46-48]</sup>. Additionally, according to Kobiela *et al.*<sup>[49]</sup>, more than 60% of the male partners of the patients would advise her against a transvaginal CHE, mostly for fear of decreased postoperative sexual content. Of the 100 patients of our short-term analysis<sup>[25]</sup>, a follow up of 24 mo was possible for 46 TVC- and 42 LC-patients<sup>[26]</sup>. However, only 36 patients of the TVC- and 25 patients of the LC-group were sexually active, and only these 61 patients could answer respective questions. The other patients had not been sexually active in the six preoperative months, either, which is why we did not rate postoperative sexual inactivity as a result of the operation. We found no differences in sexual function regarding satisfaction, dyspareunia, menstruation, vaginal discharge and pain, especially not in the lower abdomen. Indeed, TVC-patients were less impaired by the operation, and they could resume everyday activity earlier and were more satisfied with the esthetic result and the overall result. On the other hand, there was no difference in the postoperative long-term complication rate. Most likely as a result of the latter, significantly more TVC-patients would recommend the Hybrid-NOTES technique to friends and relatives. As a result, for the first time we could document the safety of the technique and the improved satisfaction of TVC-patients after a two-year follow-up in a cohort analysis. In addition, we could show that TVC-patients did not have sexual intercourse at a later postoperative point in time than did the LC-group, as suggested to the participants in a survey by Bucher *et al.*<sup>[48]</sup>. Therefore, a respective difference should not be stated in future surveys or consultations regarding TVC. Additionally, our data rebut the fear of negative influences of the transvaginal access on sexual life. The previously frequently reported apprehension regarding the hygienic aspect of transvaginal access with the consequence of an intraperitoneal bacterial contamination could already be disproved in a study by Linke *et al.*<sup>[50]</sup>. This way, our study could confirm earlier studies with a shorter follow up of up to 12 mo that showed no negative influence of TVC on sexual life<sup>[44,51-53]</sup>.

Because all previous results came from non-randomized studies, we initiated a prospective randomized, unblinded, single center trial<sup>[29]</sup>. Because we wanted to compare TVC vs the least invasive laparoscopic multi trocar technique, we chose the needlescopic 3-trocar cholecystectomy as reference group. Here, two 3.9-mm and one 11-mm trocars were used. Based on the results of our cohort study,

the primary end point was postoperative pain until the morning of the second postoperative day, which was significantly less after TVC in this randomized trial. The rate of intra- and postoperative complications was again comparable, while in opposite to the cohort analysis, postoperative hospital stay was not different. Lower analgesic consumption and comparable procedural time for TVC were confirmed, although in this study all procedures from the reference group were performed by the same single surgeon. Additionally, TVC-patients were significantly more satisfied with the early postoperative esthetic result than NC-patients and had a significantly better quality of life on postoperative day ten as measured by the Eypasch GIQLI<sup>[34]</sup>. Meanwhile, two further randomized studies exist that compared TVC with LC. The three armed study by Noguera *et al.*<sup>[54]</sup>, which also included a transumbilical single-incision-CHE, could neither detect any differences between the techniques regarding the primary end-point complication rate, nor with regard to the secondary end-points pain, hospital stay and sick leave. Of note, the study was clearly underpowered according to the given sample-size calculation. The latest published randomized study by Borchert *et al.*<sup>[55]</sup> compared 41 TVC-patients with 51 LC-patients in a double blind study design with a follow up of seven days and found a longer procedural time for TVC and neither a significant difference in complication rate nor in postoperative pain. A closer look reveals postoperative pain after TVC on the VRS (0-10) to be up to 0.8 points lower than after LC. However, despite the larger case number, this result was not significant. Unfortunately, analgesic consumption was not stated, so the respective influence of this factor could not be detected. Additionally, twelve surgeons with an average case load of 4.9 per group took part in the study, which might blur the potential differences by interindividual effects. Additionally, there was a relatively high conversion rate of 10%, possibly also due to the large number of surgeons. Interestingly, the average procedural time for TVC in our randomized trial<sup>[29]</sup>, compared to that of our cohort study<sup>[25]</sup>, namely the first 50 TVC at our clinic, was more than 24 min shorter (53.6 min vs 77.8 min). This fact underlines the assumption of an existing learning curve for TVC.

Following the confirmation of the early postoperative advantages in the cohort analysis<sup>[25]</sup> by the randomized trial<sup>[29]</sup>, the documentation of more secondary end-points three and six months postoperatively could show the high acceptance and the absence of long-term problems also in a randomized study design<sup>[30]</sup>. Sexual function, measured three months postoperatively, again with the domains "satisfaction" and "pain" in the FSFI-d<sup>[32,33]</sup>, was comparable for both groups, as was abdominal pain. The aesthetic results after three and six months were considered significantly better in the TVC-group,

whereas satisfaction with the overall result was not rated differently. The six-month gynecological follow-up of all TVC-patients had no case with a pathological result. Thus, no access related disadvantages were found in this randomized study design. A limitation was that the case-number was calculated for the primary outcome parameter and that small but possibly relevant differences require an extremely high case number. This is especially true for wound infections and trocar hernias. For the latter, the follow up period of our study was certainly too short. The case number for a study that could theoretically prove a statistically significant reduction of trocar hernias by TVC would be 1500 patients per study arm<sup>[56]</sup>. Because this is unfeasible, this theoretical advantage will remain unproven.

Finally, the study aims mentioned in the introduction could be answered by our investigations as follows: Hybrid-NOTES cholecystectomy in clinical practice is feasible and safe, with a low conversion rate. Access related complications are rare and comprised of urinary bladder injury in patients with previous hysterectomy and bowel injury. Following Hybrid-NOTES cholecystectomy, there is less postoperative pain compared with traditional laparoscopic cholecystectomy. Hybrid-NOTES cholecystectomy does not lead to impairment of sexual function by the transvaginal access and results in a higher patient satisfaction with esthetic results. Even in long-term follow up, no local morphological damage can be attributed to the transvaginal access.

## COMMENTS

### Background

Laparoscopic cholecystectomy (LC) leads to less postoperative pain, a shorter length of stay, an earlier everyday life and a better aesthetic result comparing to the conventional technique so that LC becomes the gold standard for gallbladder disease. Nevertheless, the gallbladder has to be removed from the intraperitoneal cavity. This required trauma to the abdominal wall results in wound pain and scar formation as well as a notable risk of infection and incisional hernia. The transvaginal cholecystectomy with rigid instruments (TVC), the assistance of a 5 mm-trocar in the umbilicus and removal of the gallbladder via the transvaginal access is an alternative that eliminates the mentioned risks of removing the specimen via the abdominal wall. The aim of the authors was to evaluate this new technique concomitantly during its clinical establishment in regard to its advantages and specific complications and to compare it with the traditional laparoscopic technique by means of a registry analysis, a matched cohort analysis and a randomized clinical trial. In this review, the authors discuss these results in the context and with the existing literature.

### Research frontiers

During the uncontrolled implementation and distribution of LC in the early 1990s, the benefits of the new procedure were unknown and the rate of bile duct injuries increased. Hence, the implementation of TVC as a new technique needed to be scientifically controlled and critically supervised.

### Innovations and breakthroughs

The authors succeeded in continuously evaluating a new surgical technique by a registry analysis, a matched cohort analysis and a randomized clinical trial. Therefore, they could show the feasibility of TVC with a low conversion rate and a low complication rate. Access specific complications exist with injuries

of the bladder and rectum as well as urinary tract infections. In comparison to LC and needlescopic 3-trocar cholecystectomy, respectively, TVC leads to less postoperative pain despite less postoperative analgesic consumption, better quality of life in short-term and higher satisfaction with the aesthetic result even in long-term. The complication rate is not significantly different and TVC has no significant influence on sexual intercourse regarding to satisfaction and pain.

### Applications

According to the authors' research, TVC is a feasible and safe procedure with benefits most notably in regard to less postoperative pain.

### Terminology

TVC means a laparoscopic Hybrid-NOTES procedure in which the gallbladder is removed by a transvaginal access with the assistance of a transumbilical 5 mm-trocar.

### Peer-review

Congratulations to the authors on a very good paper on this relatively new topic. This paper is for the most part all written with good information. There are certainly limitations to the database data for example, but this is addressed in the manuscript.

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P- Reviewer: Farkas DT S- Editor: Ma YJ L- Editor: A  
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