Technology Brief: Update

Natural orifice transluminal endoscopic surgery (NOTES): cholecystectomy

February 2012
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TECHNOLOGY BRIEF UPDATE 2012

REGISTER ID
WP073

NAME OF TECHNOLOGY
NATURAL ORIFICE TRANSLUMINAL ENDOSCOPIC SURGERY (NOTES): TRANSVAGINAL CHOLECYSTECTOMY

PURPOSE AND TARGET GROUP
PATIENTS WITH SYMPTOMATIC CHOLELITHIASIS

STAGE OF DEVELOPMENT IN AUSTRALIA
☐ Yet to emerge
☐ Experimental
☐ Investigational
☐ Nearly established
☐ Established
☐ Established but changed indication or modification of technique
☐ Should be taken out of use

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL
☐ Yes
☐ No
☒ Not applicable

INTERNATIONAL UTILISATION

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2012 SAFETY AND EFFECTIVENESS ISSUES

Study description

NOTES: Transvaginal cholecystectomy: Update February 2012
A total of three studies, including two comparative studies (Zornig et al 2011 and Niu et al 2011) and one case series study (Hensel et al 2011), were included in this update.

One matched-pair analysis study compared 100 patients who underwent transvaginal cholecystectomy (TVC) with 100 patients who underwent conventional laparoscopic cholecystectomy (CLC) (level III-2 intervention evidence) (Zornig et al 2011). The TVC was not a pure NOTES technique, but rather a hybrid technique that used laparoscopic instruments (optic, dissector and clipping device) inserted via the umbilicus. The CLC was performed using an umbilicus optic and 2–3 abdominal trocars. All surgeries took place between June 2007 and February 2009 and were performed by the head of the surgical department or by one of three consultants.

TVC was offered to female patients with symptomatic cholecystolithiasis. Initially, only ‘easy’ cases were enrolled (i.e. slim patients who had no previous operations and no signs of acute cholecystitis); however, with growing experience, the technique was offered to all patients. Contraindications to TVC included BMI >35 kg/m², a previous operation in the small pelvis, previous radiation therapy where severe adhesions could be expected, and endometriosis.

For the matched-pair analysis the authors selected a group of 192 female patients who had undergone CLC, although the indication for this procedure was not clearly defined and it was unclear how these patients were selected. The authors created a total of 108 pairs by matching patients from each group according to the degree of gallbladder inflammation (acute and chronic cholecystitis or no cholecystitis) and age (± 10 years).

The mean age was 49 years (range 16–76 years) in the TVC group and 50 years (range 18–76 years) in the CLC group (no statistical analysis reported). The average age difference between the pairs was 1.1 years ($P$>0.05). The average BMI per group was 26 kg/m² (TVC range 16–35 kg/m²; CLC range 18–40 kg/m²) (no statistical analysis reported). Twelve per cent of patients in each group had acute or chronic inflammation of the gallbladder. A total of 35 TVC patients (35%) had undergone a previous operation, compared with 54 CLC patients (54%) (no statistical analysis provided).

One week after the operation the TVC patients were examined by a gynaecologist, and after at least three months all patients were interviewed regarding late complications in the abdomen or vagina. The follow-up interviews were conducted at a mean of five months after surgery (range 3–10 months). Patients were asked about sexual intercourse since the operation and any possible negative experiences, via a structured questionnaire delivered over the telephone. A total of 208 patients (96%) could be contacted for a follow-up interview; however, it was unclear which
treatment group these patients belonged to. The final study analyses were performed with 100 complete pairs.

Niu et al (2011) compared a series of 43 patients who underwent TVC with a series of 48 patients who underwent CLC (level III-2 intervention evidence). The TVC was not a pure NOTES technique, but rather a hybrid technique that used laparoscopic instruments (optic, clips and scissors) inserted via the umbilicus. No operative details were provided for the CLC technique. All surgeries took place between May 2009 and April 2010 but it was unclear who performed the surgeries.

Female patients who presented with symptomatic cholelithiasis or enlarged gallbladder polyps (>1 cm) and no severe pelvic adhesions derived from previous operations were offered the option of transvaginal endoscopic cholecystectomy. Patients were required to have had mild clinical symptoms and a short duration of disease (<2 years). Initially, relatively simple cases were selected. Excluded patients were those younger than 20 years or older than 65 years, with a BMI >30 kg/m², an increased risk for common bile duct stones, of an unmarried status or preparation for pregnancy, with severe medical comorbidities or bleeding or clotting disorders. After the first 12 NOTES procedures had been successfully performed without intra- or postoperative complications, patient eligibility was extended to patients with inflammation of the gallbladder, previous surgery or obesity. Two TVC patients presented after hysterectomy, and 12 patients had undergone previous lower abdominal surgeries such as caesarean section and appendectomy. For CLC patients the indication for surgery and inclusion criteria was not clearly defined and it was unclear how these patients had been selected.

No demographic data were provided for the CLC group, preventing comparison with TVC patients. TVC patients had a mean age of 47.2 ± 9.6 years and a mean BMI of 21.5 ± 6.2 kg/m². Twenty-nine patients were American Society of Anesthesiology (ASA) physical class 1 and the remaining 14 patients were class 2. Thirty-one patients presented with gallbladder stones and 12 presented with gallbladder polyps.

Follow-up was performed between 2 and 11 months, and it appears that all patients were available at follow-up. The comparative outcomes assessed included pain, operative time, blood loss, length of hospital stay and associated costs. Data on complications were only reported for TVC patients.

Hensel et al (2011) reported on a series of 80 patients who underwent TVC for symptomatic cholelithiasis (level IV intervention evidence). The TVC was not a pure NOTES technique, but rather a hybrid technique that used laparoscopic instruments (optic, clip device and dissector) inserted via the umbilicus.

All female patients with symptomatic cholelithiasis admitted to the Park-Klinik Weissensee teaching hospital in Berlin were informed about the two surgical
techniques available for the removal of the gallbladder (CLC and TVC). Based on written informed consent, all patients who decided to undergo TVC were consecutively enrolled in the study. All surgeries took place between February 2009 and April 2010 and were performed by two experienced surgeons, although gynaecological support was only provided for the first 10 operations. These patients had a mean age of 52 years (range 19–77 years), a mean BMI of 29 kg/m² (range 18–42 kg/m²) and a mean ASA score of 2 (range 1–3).

Prospective data were collected for symptoms, operation, complications and postoperative course. Operative complications were defined as injuries to the bowel, bile duct, bladder, or ureter; vascular injuries; significant bleeding; and vaginal or urinary tract infections. A gynaecological follow-up examination was performed three weeks after surgery, which involved external genital, speculum, bimanual and rectal examination, and urine screening to diagnose urinary tract infections and transvaginal ultrasonography if necessary. Additionally, an interview was performed three months after surgery, although the nature of this interview was unclear. Hensel et al (2011) also reported data relating to a ‘numeric rating scale’; however, no details were provided regarding this scale or to what outcomes it related.

2012 Safety
Zornig et al (2011) reported that there were no intraoperative complications in either group. There was one major postoperative complication that occurred after TVC (1%) which required reoperation, where a patient was readmitted three weeks post-surgery with a Douglas pouch abscess that required laparoscopic drainage. Two CLC patients (2%) required reoperation (both on the second postoperative day), one for bleeding and one for bile leakage from an accessory duct. Wound infection occurred in one TVC patient (1%) (the patient who suffered the Douglas pouch abscess) and in three CLC patients (3%) (p=0.625). There were no trocar hernias in either group. Pain in the upper abdomen was mentioned by 14 TVC (14%) and 16 CLC (16%) patients (p>0.05). Three patients (3%) in each group complained of lower abdominal pain. Significantly more TVC patients were entirely free of abdominal symptoms (81% of TVC versus 60% of CLC patients) (p=0.007), although it was unclear what was defined as an abdominal symptom.

In the study by Niu et al (2011), there were no intraoperative complications in either group. In addition, no bile leakage, haemorrhage or colpotomy-related problems occurred after TVC, and none of the patients reported abdominal or vaginal pain. There were no reported complications during the 2- to 11-month follow-up period.

Hensel et al (2011) reported that one urinary bladder injury (1.3%) occurred in a 63-year-old obese patient who had pre-existing pelvic adhesions from a previous hysterectomy. This injury was detected intraoperatively and was repaired.
laparoscopically with sutures, and the patient recovered without any additional postoperative problems. One patient suffered delayed bleeding from the colpotomy wound (1.3%), which ceased after resuturing. The gynaecological follow-up examination found no infections of the surgical wound or any other complications. After a follow-up of three months, eight patients (10%) reported vaginal pain (5 ‘sometimes’ and 3 ‘frequently’). Five patients were reported to have suffered from vaginal pain preoperatively, although it was unclear whether these same patients also reported postoperative vaginal pain.

2012 Effectiveness

In the study by Zornig et al (2011) all 200 cholecystectomies were performed successfully using the chosen technique without conversion. Four cases (4%) in the TVC group required an additional abdominal trocar. The average operative time was significantly longer in the TVC group (52 minutes, range 23–100) than the CLC group (35 minutes, range 17–75) ($P<0.001$). Patients in both groups received 3.3 single doses of analgesics, and the mean postoperative hospital stay was 2.1 days in the TVC group and 2.3 days in the CLC group ($P>0.05$). When analysed in 51 pairs that excluded pensioners, 29% of patients were immediately able to work after TVC, compared with 20% after CLC ($P>0.05$), while TVC patients required 7.1 days of sick leave compared with 6.7 days for CLC patients ($P>0.05$).

Ten CLC patients (10%) spontaneously volunteered that they were not satisfied with their scars, while no similar complaints were received from the TVC group. Ninety-six TVC patients (96%) and 99 CLC patients (99%) said they would recommend the cholecystectomy technique that they had experienced ($P>0.05$). With regard to sexual intercourse post-surgery, 75 TVC (75%) and 73 CLC (73%) patients reported that this had occurred, 22 TVC (22%) and 24 CLC (24%) patients reported that this had not occurred, and three patients (3%) in each group did not answer this question. No noticeable change compared to the pre-operative state was reported, and there were no complaints about dyspareunia.

Niu et al (2011) reported that TVCs were successfully performed for all patients without conversions to either CLC or open surgery. TVC was also successful in the two patients who presented after hysterectomy, and in the 12 patients who had undergone previous lower abdominal surgeries such as caesarean section and appendectomy.

Comparative data for TVC and CLC patients were provided for selected outcomes. The operative time was significantly longer in TVC patients (87.1 ± 26.1 minutes) than in CLC patients (60.6 ± 13.1 minutes) ($P<0.05$). In addition, for TVC there appeared to be a learning curve, as surgery required more than three hours in the first case and less than two hours in the subsequent cases. There was no significant
difference between groups for the amount of blood lost (TVC 21.6 ± 9.9 mL; CLC 20.6 ± 7.8 mL) (P>0.05). Postoperative pain measured using the VAS was significantly lower in TVC patients (2.0 ± 0.7) than in CLC patients (4.6 ± 1.2) (P<0.05).

The length of hospital stay was significantly shorter in TVC patients (2.7 ± 0.9 days) than in CLC patients (5.9 ± 1.1 days) (P<0.05). For TVC patients, discharge occurred on postoperative day two for 23 patients, on day three for 15 patients, and on day four for one patient. Four older patients had a postoperative stay of five days. All TVC patients had completely resumed normal activity by 10 days postsurgery. In TVC patients, no scars were visible on the abdominal wall during the 2-to 11-month follow-up period.

In the study by Hensel et al (2011), TVC was performed in all 80 patients without conversion to laparoscopy or open surgery. The mean operative time was 47 minutes (range 25–80) and on average patients spent 43 minutes (range 20–90) in the recovery room. Five patients (6.3%) suffered postoperative nausea and vomiting. Fluid intake commenced at mean of three hours after surgery (range 1–9) and patient mobilisation commenced at mean 4 hours after surgery (range 1–10). The mean length of hospital stay was 3 days (range 2–5).

There was a change in the sexual behaviour of nine patients (11.3%) during the first three postsurgical months. Two of the 55 women (3.6%) who had sexual intercourse occasionally or regularly after the operation suffered from dyspareunia. Six patients (7.5%) reported episodes of unclear lower abdominal pain. In total, four per cent of the patients aged under 50 years reported slight and temporary problems after TVC, whereas these were reported in approximately nine per cent of women aged over 50 years (P<0.05). A 33-year-old woman who had initial sexual intercourse three weeks post-surgery became pregnant and gave birth to a healthy child.

**2012 Cost Impact**

Niu et al (2011) reported that the cost of hospitalisation was significantly lower in TVC patients (1.2 ± 0.2 x10³ ¥) compared with CLC patients (1.5 ± 0.3 x10³ ¥) (P<0.05). No other studies evaluating the cost-effectiveness or cost impact of NOTES transvaginal cholecystectomy were identified from the retrieved material.

**2012 Ethical, Cultural or Religious Considerations**

No issues were identified from the retrieved material.
2012 OTHER ISSUES

The studies by Zornig et al (2011) and Niu et al (2011) reported that none of the authors had any conflicts of interest or financial ties to disclose. Similarly, Hensel et al (2011) reported that there were no competing financial interests to disclose.

A recent Australian study surveyed women’s views on the transvaginal NOTES procedure (Strickland et al 2010). A total of 300 women were surveyed using a questionnaire that was designed to determine their opinions on NOTES compared with standard laparoscopic procedures. The study reported that three-quarters of the women surveyed indicated that they were neutral or unhappy about the prospect of a NOTES procedure. In addition, the potential negative effect of NOTES on sexual function was of most concern to younger women, who were also more concerned about surgical scars than older women; however, only a minority of all women surveyed were concerned about the cosmetic effect of surgery. This study indicated that Australian women remain to be convinced of the potential benefits of NOTES technologies.

Searches of clinical trial registers indicate that there are currently 11 ongoing clinical trials evaluating NOTES transvaginal cholecystectomy (Table 1).
Table 1  Ongoing and currently recruiting clinical trials involving NOTES

<table>
<thead>
<tr>
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<th>Description</th>
<th>Estimated date of completion</th>
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<td>NCT00710502 (recruiting)</td>
<td>UK</td>
<td>Non-randomised comparative study comparing clinical results between transvaginal cholecystectomy and laparoscopic cholecystectomy in patients with biliary colic. Two year follow-up period.</td>
<td>August 2012</td>
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<td>NCT00940264 (recruiting)</td>
<td>Switzerland</td>
<td>Prospective case series of estimated 200 patients undergoing laparoscopic transvaginal hybrid cholecystectomy. Three year follow-up period.</td>
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<td>NCT01039129 (recruiting)</td>
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<td>Case series of 20 patients undergoing hybrid transvaginal-transabdominal endoscopic surgery. One year follow-up period.</td>
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<td>NCT00910325 (recruiting)</td>
<td>USA</td>
<td>Case series of patients undergoing laparoscopic-assisted transvaginal cholecystectomy. One year follow-up period.</td>
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<td>NCT00530998 (recruiting)</td>
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<td>Case series of estimated 30 patients undergoing transvaginal cholecystectomy. One month follow-up period.</td>
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<td>NCT01232959 (recruiting)</td>
<td>USA</td>
<td>Case series of estimated 10 patients undergoing laparoscopic-assisted transvaginal cholecystectomy. One year follow-up period.</td>
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<td>NCT01171027 (recruiting)</td>
<td>USA</td>
<td>Randomised controlled trial comparing clinical results between transvaginal (n=35) and transgastric (n=35) cholecystectomy with those of laparoscopic cholecystectomy (n=22) in patients with gall bladder diseases. Four week follow-up period.</td>
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<td>NCT00984100 (recruiting)</td>
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<td>Case series of estimated 3 patients undergoing NOTES transvaginal cholecystectomy. One year follow-up period.</td>
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<td>NCT00835250 (recruiting)</td>
<td>Spain</td>
<td>Prospective randomised clinical trial comparing clinical results between transvaginal hybrid NOTES cholecystectomy and laparoscopic cholecystectomy (total n=60) One year follow-up period.</td>
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<td>NCT00552162 (recruiting)</td>
<td>Israel</td>
<td>Case series of estimated 40 patients undergoing NOTES transvaginal cholecystectomy. Follow-up period not defined.</td>
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<td>NCT0095735 (recruiting)</td>
<td>Brazil</td>
<td>Prospective case series of patients undergoing NOTES transvaginal cholecystectomy. Follow-up period not defined.</td>
<td>August 2009</td>
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2012 Summary of Findings

TVC may lead to an improved cosmetic result (i.e. no visible scar). Two comparative studies assessing TVC and CLC indicated that TVC is associated with significantly less postoperative pain and may lead to a shorter length of hospital stay (and associated hospitalisation costs); however, no other advantages were reported in the comparative evidence.
It is difficult to assess the potential long-term effects or complications of the transvaginal access route, as the maximum available length of follow-up was 11 months. Two comparative studies reported that TVC requires a significantly longer operative time than CLC. This difference may be less pronounced in high-volume centres. It is unclear whether complications such as bladder injuries and postoperative vaginal infections are specific to transvaginal procedures, as these were exclusively reported in large case series. The presence of adhesions may lead to intraoperative damage of surrounding structures. TVC may be associated with a change in sexual behaviour and with vaginal pain, particularly in women aged over 50 years.

2012 HealthPACT Assessment

Based on the evidence presented in this brief, the advantages of TVC compared with CLC are limited to a reduction in postoperative pain and length of hospital stay. In addition, research suggests that patients remain to be convinced of the potential benefits of NOTES technologies, which is likely to limit the diffusion of this procedure into clinical practice in Australia. Therefore, HealthPACT have recommended that no further assessment of this technology is warranted.

2012 Included Studies

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the following link on the HealthPACT web site.

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2012 References


PRIORITISING SUMMARY UPDATE 2010

NAME OF TECHNOLOGY  NATURAL ORIFICE TRANSLUMINAL ENDOSCOPIC SURGERY (NOTES): TRANSVAGINAL CHOLECYSTECTOMY

PURPOSE AND TARGET GROUP  PATIENTS WITH SYMPTOMATIC CHOLELITHIASIS

2010 SAFETY AND EFFECTIVENESS ISSUES

Study description

Three studies were selected for inclusion in this update based on study quality and cohort size. The first of these studies, published by Navarra et al (2010), reported outcomes in a small cohort of patients undergoing NOTES and compared these outcomes with those of patients undergoing two commonly used cholecystectomy alternatives. The second study (Lehman et al 2010) analysed data gathered through the German NOTES Registry (GNR), and has some overlap with the data presented in the original summary (Zornig et al (2008) submitted NOTES data to the GNR). The third study (Zorron et al 2010) analysed data gathered through the International Prospective Multicenter Trial on Clinical NOTES (IMTN) Registry.

The comparative study by Navarra et al (2010) compared the safety and efficacy of NOTES with both traditional laparoscopy and single incision laparoscopic surgery (SILS) to perform cholecystectomy. One hundred patients were diagnosed with symptomatic cholelithiasis, with surgical removal of their gallbladder proposed. Transvaginal NOTES was offered to women over 40 years of age and with no previous pelvic surgery or history of inflammatory pelvic disease (9/100). Of the nine patients who fulfilled these inclusion criteria, six selected to undergo cholecystectomy via the NOTES approach over traditional laparoscopy and SILS. Of the remaining patients, 20 opted for SILS and the remaining 74 underwent traditional laparoscopy. Mean age and BMI statistics were not included for traditional laparoscopic patients; however, these two factors differed slightly between NOTES and SILS patients. The mean age of NOTES and SILS patients was 52 years (range: 46-65) and 45 years (range: 28-65), respectively, and the mean BMI of NOTES and SILS patients was 31 kg/m² (range: 29-37 kg/m²) and 27 kg/m² (range: 23-36 kg/m²), respectively. The authors noted that statistical comparisons were not applicable due to the difference in the number of cases treated. NOTES and SILS patients were followed up for a minimum of 45 days (the follow-up period for traditional laparoscopy patients was not reported).
Lehmann et al (2010) analysed the results of 551 patients subject to transvaginal NOTES between March 2008 and April 2009 as compiled by the voluntary German NOTES Registry (GNR). Of interest to this summary, 486 procedures were transvaginal cholecystectomies (with a further two cholecystectomies in which no access route were specified). The mean ± Standard Deviation (SD) age of all patients undergoing transvaginal cholecystectomies was 48.9 ± SD14.6 years (range: 16-84) and mean BMI was 27.0 kg/m\(^2\) ± SD5.4 (range: 16.3-48.9). For each of the transvaginal cholecystectomies performed the hybrid NOTES procedure was utilised, with between one and four trocars used (mean: 1.2 ± SD0.5). A further 7 NOTES procedures were planned but not carried out due to technical problems with transvaginal access. No specific patient selection criteria or surgical methodology was detailed, and presumably individual institutions involved in this study applied their own criteria relating to the exclusion of putative patients and execution of surgical procedures. No mention is made regarding the absence or presence of follow up complications, nor were any controls involving comparators included. Furthermore, as the analysis was based on an anonymous and voluntary registry, there is no guarantee of the completeness and validity of data.

In similar fashion to Lehmann et al (2010), Zorrón et al (2010) presents data published from the International Prospective Multicenter Trial on Clinical NOTES (IMTN) Registry, which involved 362 NOTES cases from sixteen centers in 9 different countries, all prospectively documented between July 2007 and June 2009. Of these 362 patients, 240 patients were subject to transvaginal cholecystectomies (66.3%). No consensus was reached as to the methodology used for TV cholecystectomies, although each institution submitted their own procedures, resulting in four different operational variants used in this study. Unlike the majority of studies published to date, no age or BMR statistics were included. No controls using comparators were included, and no mention was made regarding postoperative follow up periods.

**2010 Safety and Effectiveness**

Navarra et al (2010) reported no complications related to the culdotomy, trocar or stay suture placements in any of the NOTES, SILS or traditional laparoscopic procedures, however one patient with acute cholecystitis undergoing traditional laparoscopy required conversion to an open procedure due to massive adhesions. Mean operative time was 65 minutes (range: 45-75 min) for NOTES, 53 minutes (range: 25-75 mins) for SILS, and 40 minutes (range: 25-60) for traditional laparoscopy. The majority of patients were discharged the day after surgery, with the exception of 1 patient (16.7%) in the NOTES group, 4 patients (20%) in the SILS group and 20 patients (27%) in the traditional laparoscopy group. No complications or readmissions were reported in the 45 day postoperative period in NOTES and SILS.
patients, nor were any complications or readmissions reported for traditional laparoscopic patients.

Lehmann et al (2010) noted that of the 488 patients who received transvaginal cholecystectomies, 3.3% (16/488) and 4.6% (23/488) of patients experienced complications or required conversion to a laparoscopic/open procedure, respectively. Of those patients experiencing complications, seven were intraoperative, comprising of rectal injury (n=2), small bowel injury (n=1), and bladder injury (n=4), and nine were postoperative, consisting of postoperative/vaginal bleeding (n=3), infection (n=4), emesis (n=1), abscess in the Pouch of Douglas (n=1), and abdominal pain (n=1). One patient had both intraoperative and postoperative complications (serosa injury of the rectum and postoperative bleeding). Of those patients requiring conversions, 20 converted to conventional laparoscopy and 3 to open surgery, resulting from gallbladder inaccessibility (n=7) or intraoperative complications (n=4) (reason for conversion was not reported for 12 patients). Of interest, patients ≥ 65 years experienced conversion levels 3.6 times higher than patients < 65 years (P = 0.001). Furthermore, in older patients the number of trocars used and length of hospital stay were significantly increased; however, there was no subsequent increase in complication rate in older patients. There was also no difference in complication (P = 0.461) or conversion (P = 0.490) rate for transvaginal cholecystectomies whether an assisting gynaecologist was present or absent.

The mean length of operation was 61.9 ± SD26.5 minutes (range: 20-211 min), however a statistically significant variation was observed in length of operation between overweight/obese patients (BMI ≥ 25.0 kg/m²) and normal weight patients (BMI = 18.5-24.9 kg/m²), with such operations requiring 66.3 ± SD27.9 minutes and 59.4 ± SD28.5 minutes (P = 0.006) to complete, respectively. Institutional case volume had a significant effect on the length of operations, with high volume centres (those which performed more than 30 NOTES procedures each) requiring 56.7 ± SD22.8 minutes compared with 67.0 ± 30.9 minutes (P = 0.009) for low volume centres. This suggests that a correlation may exist between increased efficacy and experience/case volume, although the authors have no knowledge as to whether one or more surgeons were involved at each institution. The overall duration of hospitalisation following transvaginal cholecystectomy was 3.2 ± SD2.1 days (range: 1-19 days).

In the study presented by Zorron et al (2010), conversion to traditional laparoscopy was required in six patients due to difficult exposure, bleeding of appendiceal or cystic vessels, or adhesions from previous surgery, however these data include all entries in the registry and are thus not specific to transvaginal cholecystectomy.
procedures. From all 240 transvaginal cholecystectomies, 11 intraoperative and 5 postoperative complications were experienced. Intraoperative complications resulted from cystic artery bleeding (n=5), gastric wall perforation due to inflammatory adhesions (n=1), bowel serosal laceration (n=1), vaginal lacerations (n=3) and intra-abdominal hypertension (n=1), and postoperative complications were as a result of biliary leak (n=2), Dyspareunia (n=1), Vaginal granuloma (n=1), and Urinary tract infection (n=1). Zorron et al (2010) categorised(rated) complications according to the classifications presented in Dindo et al (2004). According to their definitions, transvaginal cholecystectomy patients experienced 17 (5.33%) Grade I-II complications and 5 (1.57%) Grade III-IV complications (see Table 1).

Table 1. Classification of Surgical Complications (adapted from Dindo et al 2004)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Any derivation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also included wound infections opened at the bedside.</td>
</tr>
<tr>
<td>Grade II</td>
<td>Requiring pharmacological treatment with drugs other than such allowed from grade I complications. Blood transfusions and total parenteral nutrition are also included.</td>
</tr>
<tr>
<td>Grade III</td>
<td>Requiring surgical, endoscopic or radiological intervention.</td>
</tr>
<tr>
<td>Grade IIIa</td>
<td>Intervention not under general anaesthesia.</td>
</tr>
<tr>
<td>Grade IVb</td>
<td>Intervention under general anaesthesia.</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Life-threatening complication requiring ICU/ICU management.</td>
</tr>
<tr>
<td>Grade IVa</td>
<td>Single organ dysfunction (including dialysis).</td>
</tr>
<tr>
<td>Grade IVb</td>
<td>Multiorgan dysfunction.</td>
</tr>
<tr>
<td>Grade V</td>
<td>Death of a patient.</td>
</tr>
</tbody>
</table>

Mean operation time was 96.08 ± SD57.815 minutes, however this time was significantly decreased when one or more trocars for retraction or dissection were used. Operative bleeding was minimal (12.41 ± SD22.424 ml) (mean was higher because of intra-operative haemorrhage during dissection or direct arterial lesions, which occurred in 5 cases). Mean post operative stay was 46.04 ± SD32.167 days (P < .05) however this figure includes data from centres who adopted a minimum postoperative stay of 3 days as required by local study protocols.

2010 SUMMARY OF FINDINGS

Current evidence suggests that there are minimal differences in the safety and efficacy between transvaginal NOTES and other commonly used and newly developed alternatives. In the study published by Navarra et al (2010), NOTES procedures took longer to perform than both traditional laparoscopic and SILS.
procedures. However, data published by the GNR showed a decrease in time taken to perform transvaginal NOTES between high volume and low volume institutions, suggesting that increased experience in performing the operation may reduce this time difference.

Although transvaginal cholecystectomy NOTES is a viable alternative to more conventional procedures, further information is required before any definitive conclusions can be drawn. For example, more comprehensive studies comparing NOTES to common alternatives are necessary to determine whether NOTES presents any significant advantage with regards to safety and efficacy over comparators. Several such trials are in the planning and recruitment stage (see original summary), and one randomised controlled trial has recently been completed (ClinicalTrials.gov ref: NCT00710502, data not published).

Furthermore, considerable research is taking place in the field of NOTES-specific tool development, and the trade-off between increased efficiency, safety and ease of use compared with a potential increase in operational cost may be the deciding factor in whether NOTES becomes the preferred methodology of transvaginal cholecystectomies.

2010 HealthPACT action

There remains a strong interest in the development and usage of transvaginal NOTES, however additional studies are required before transvaginal NOTES can be performed routinely. Based on the high probability of further data becoming available as a result of one or more randomly controlled trials, and increased development and possible consensus reached on the widespread adoption of NOTES-specific tools, it is recommended that transvaginal choleystectomy NOTES be monitored and reassessed in 12 months.

2010 Studies included

| Total Number of Studies: | 3 |
| Level III-3 interventional evidence: | 1 |
| Level IV interventional evidence: | 2 |

2010 References


PRIORITISING SUMMARY 2009

REGISTER ID S000101

NAME OF TECHNOLOGY NATURAL ORIFICE TRANSLUMINAL ENDOSCOPIC SURGERY (NOTES): TRANSVAGINAL CHOLECYSTECTOMY

PURPOSE AND TARGET GROUP PATIENTS WITH SYMPTOMATIC CHOLELITHIASIS

STAGE OF DEVELOPMENT (IN AUSTRALIA)

- ✔ Yet to emerge
- ☐ Established
- ☐ Experimental
- ☐ Established but changed indication or modification of technique
- ☐ Investigational
- ☐ Should be taken out of use
- ☐ Nearly established

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- ☐ Yes
- ✔ No
- ☐ Not applicable

INTERNATIONAL UTILISATION

<table>
<thead>
<tr>
<th>Country</th>
<th>Level of Use</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Trials Underway or Completed</td>
</tr>
<tr>
<td>United States</td>
<td>✔</td>
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<tr>
<td>United Kingdom</td>
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<td>India</td>
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<td>Germany</td>
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</tbody>
</table>

2009 IMPACT SUMMARY

Natural orifice transluminal endoscopic surgery (NOTES) is an emerging surgical procedure which may potentially be less invasive than laparoscopic surgery.

2009 BACKGROUND

In the last few years, minimally invasive surgical access techniques have garnered substantial interest among patients and the medical community, due to the promise of less pain, shorter hospital stays, lower complication rates and better cosmetic
results. It is not surprising therefore that there has been substantial research into the development of new techniques to further reduce the invasiveness of surgery. NOTES represents a new approach to access the peritoneum that is being evaluated as a complement to, or even a replacement for, laparoscopic and open abdominal procedures. Recently, NOTES has attracted widespread interest and in some cases has been claimed to be a defining paradigm shift in modern surgery (McGee et al 2006). The procedure was first described in 2005, where a flexible endoscope is passed through a natural orifice, such as the mouth, vagina or rectum to perform intra-abdominal procedures. The technique has been touted as less invasive than laparoscopic surgery by virtually eliminating incision-related complications such as scars, hernias, pain, adhesions and surgical site infections (McGee et al, Merrifield et al 2006). To date, the best portal for access is not yet determined, but all have been evaluated in various animal studies (Box et al 2009). However, despite the enthusiasm among its proponents, there are major concerns with regards to transgastric approaches to NOTES as improper gastric closure may lead to postoperative leakage and peritonitis. Currently, there are substantial efforts to develop a safe closure device to improve the safety profile of transgastric NOTES.

In contrast to transgastric NOTES, transvaginal NOTES has the potential advantages of easy access and closure under direct vision. The experience gained from experimental settings has suggested that with current available technology, procedures involving in the upper part of the abdomen are better undertaken via natural orifices located in the pelvis (Pearl and Ponsky 2008). Furthermore, transvaginal access to the abdominal cavity is not a new concept to surgeons, as it has been used occasionally by general surgeons to extract large specimens and by gynaecologists to perform diagnostic and therapeutic procedures. At the time of writing, one of the most common applications of transvaginal NOTES is cholecystectomy, which will be discussed further in this summary.

The first transvaginal cholecystectomy in a human being was carried out in 2003 at the Mount Sinai Hospital by Dr. Tsin, utilising rigid laparoscopic instruments and minimal abdominal assistance. From 2007, several research groups have described different techniques for transvaginal cholecystectomy using flexible endoscopes with minimal laparoscopic assistance (Pugliese 2009). In virtually all human trials to date, a hybrid procedure was adopted where the operators utilised a fusion of minilaparoscopy and NOTES (Noguera et al 2009).

**2009 Clinical Need and Burden of Disease**

Cholecystectomy is one of the most common hospital procedures in Australia, with a total of 46,816 cholecystectomy procedures performed between 2005 and 2006 (all
hospitals). Of these, laparoscopic cholecystectomy accounted for 40,557 procedures (Australian Institute of Health and Welfare 2008). The Medicare Benefits Schedule claims for services that are performed by a registered provider, but not including services provided by hospital doctors to public patients in public hospitals, indicated that laparoscopic procedures were performed more commonly than open procedures, with 19207 claims for laparoscopic cholecystectomy (item number 30445) and 1026 claims for open cholecystectomy (item number 1026) between 2007 and 2008 (Medicare Australia 2009). The average length of hospital stay for public or private hospital patients undergoing laparoscopic cholecystectomy (without closed common duct exploration or catastrophic or severe complications or comorbidities) was 1.8 days (Australian Institute of Health and Welfare 2008).

2009 DIFFUSION

Transvaginal cholecystectomy is currently at the investigational stage and has been conducted on a few patients in different centres, including Spain, the United States, Germany and Italy. In practically all of these cases, the operation was performed with the help of at least one abdominal trocar. The German Society of General and Visceral Surgery has registered over 300 NOTES operations, almost all are transvaginal cholecystectomies (Zornig et al 2009). There is no indication that this procedure is being performed in Australia or New Zealand.

Our searches revealed 8 planned/ongoing clinical trials on transvaginal cholecystectomy. Brief details of these trials are provided below:

- Transvaginal cholecystectomy versus laparoscopic cholecystectomy in patients with biliary colic (ClinicalTrials.gov identifier: NCT00963950). Enrolling participants by invitation only, estimated completion date: August 2012.
- Natural orifice transluminal endoscopic surgery (NOTES) transvaginal cholecystectomy (ClinicalTrials.gov identifier: NCT00984100). Currently recruiting patients, estimated completion date: January 2011.
- Natural orifice transluminal endoscopic surgery: Laparoscopic-assisted transvaginal cholecystectomy (ClinicalTrials.gov identifier: NCT00910325). Currently recruiting patients, estimated completion date: December 2009.
- NOTES transvaginal cholecystectomy and appendectomy (ClinicalTrials.gov identifier: NCT00552162). Not yet open for patient recruitment, estimated completion date: July 2009.
- Trial comparing laparoscopic cholecystectomy and hybrid natural orifice transluminal surgery (ClinicalTrials.gov identifier: NCT00835250). Currently recruiting patients, estimated completion date: June 2010.
Laparoscopic transvaginal hybrid cholecystectomy: a prospective data collection (ClinicalTrials.gov identifier: NCT00940264). Currently recruiting patients, estimated completion date: not stated.

A trial to evaluate natural orifice transvaginal endoscopic cholecystectomy with laparoscopic assistance (NOTES) (ClinicalTrials.gov identifier: NCT00889928). Currently recruiting patients, estimated completion date: January 2010.

2009 Comparators

The comparative procedures for transvaginal cholecystectomy are:

- open cholecystectomy (now reserved for special situations only);
- small-incision open cholecystectomy;
- conventional laparoscopic cholecystectomy;
- single incision laparoscopic cholecystectomy.

2009 Safety and Effectiveness Issues

Study description

Three case series studies have been selected for inclusion in this summary based on cohort size and quality of the study.

The retrospective case series study by Zornig et al (2009) reported on the safety and effectiveness of transvaginal NOTES in 68 patients treated for symptomatic cholecystolithiasis from June 2007 to June 2008. Eleven of these patients had acute or chronic inflammation of the bladder. The mean age was 50 years (range: 16-76 years) and mean BMI was 25.4 kg/m² (range: 16-35 kg/m²). A total of 26 patients (38%) have had previous abdominal operations. Patients were interviewed 3 to 10 months after surgery (mean: 5 months). It is important to note that a hybrid NOTES procedure was utilised, as an abdominal trocar was used during the operation.

The second case series study was performed by Pugliese et al (2009) between July 2007 and May 2009 and involved 18 patients (mean age: 54 years; range: 32-67 years) with symptomatic cholelithiasis. Mean BMI was 28 kg/m², however four patients had BMIs >30 kg/m². Unlike Zornig et al (2009), patients with previous major abdominal surgery were excluded. In addition, patients had to be free of gynaecologic disease, not pregnant and have no intention to plan a pregnancy in the early postoperative period. Patients with ultrasonographic features of cholecystitis were also excluded. As with Zornig et al (2009), a hybrid procedure was utilised (Pugliese et al 2009). It is unclear if patients were enrolled in a consecutive manner. Dissection was conducted in the first 4 cases by a round tip unipolar electrode introduced through an endoscope from the vagina. The last 14 cases underwent dissection with an ultrasonic scalpel introduced via the 5mm abdominal port. Mean follow up duration was 12 months (Pugliese et al 2009).
The final study was conducted by Noguera et al (2009), where a prospective series of 15 consecutive patients underwent a hybrid transvaginal NOTES procedure for symptomatic cholelithiasis. The mean age of patients was 39.7 years (range 22-47 years); no data on BMI was presented. Patients selected for inclusion had to fulfil several criteria: no gynaecological conditions that could complicate the procedure, perforated hymen and agreement to abstain from sex for 2 weeks after the procedure. Patients were followed-up for a mean of 62 days (range: 30-90 days)

2009 Safety and Effectiveness

Zornig et al (2009) noted that three patients had severe adhesions in the lesser pelvis during diagnostic laparoscopy. These patients were converted to conventional laparoscopic cholecystectomy. There were no intraoperative complications, but in three cases (4.4%) an additional abdominal trocar was necessary. The in-hospital postoperative course was uneventful in all patients. The authors reported that patients complained of well-known consequences of pneumoperitoneum, but no specific examples were presented. None of the patients reported pain as a result of vaginal manipulation. At 1-week follow up (n=59), none of the patients had any complaints, and physical examination including vaginal endosonography revealed no pathological findings. However, one patient who did not undergo the 1-week follow up examination presented with an abscess in the pouch of Douglas 3 weeks after surgery. When patients were interviewed 3 to 10 months after surgery (mean: 5 months; n=68), there were no complaints regarding the procedure. A total of 48 patients (70.5%) had sexual intercourse after the operation (mean time not stated) and did not notice any changes (Zornig et al 2009).

Pugliese et al (2009) reported no intraoperative complications and no conversions to open or laparoscopic cholecystectomy. The hybrid transvaginal NOTES technique was successfully employed in four obese patients (BMI>30). However, the performance of colpotomy was difficult in these patients due to the thickness of the properitoneal fat layer. There were no cases of rectal injury or colpotomy-related complications. There was one case of biliary leak (4th patient in series, BMI=45) after dissection with the unipolar electrode. This complication required endoscopic retrograde pancreatocolangiography. Complete healing was achieved in 7 days and the patient was discharged 11 days after surgery. In contrast, there were no biliary complications when dissection was performed with the ultrasonic scalpel. Analysis revealed that patient morbidity was significantly higher for those who underwent unipolar electrode dissection compared with those who received ultrasonic scalpel dissection (p<0.005), however the validity of this was limited by the small patient cohort. No patient referred pain at the vaginal level. Meanwhile, the mean values for abdominal pain were 3 (range: 1-4), 2 (range: 0-3), 1 (range: 0-2) and 0 at 4, 12, 24
and 48 hours after surgery, respectively. Several patients experienced shoulder pain that resolved spontaneously within 12 hours. Oral feeding resumed the evening of the operation and the use of pain relievers was minimal (no data provided). No specific treatment was required for colpotomy and there were no colpotomy-related problems or discomfort during the postoperative period. In addition, there were no complaints of dyspareunia or genital infections after intercourse. At a mean follow up of 12 months (range: 1-22 months), there were no cases of sexual or vaginal discomfort.

Noguera et al (2009) reported that 2 patients (2/15, 13%) had adhesions that needed to be severed, while 2 other patients (13%) had ovarian cysts that were not suspected preoperatively but did not complicate the procedure. The only complication was mild haematuria that resolved spontaneously within 12 hours. No surgical wound infections were observed.

Zornig et al (2009) reported that the overall mean operative time was 51 minutes (range: 30-100 minutes). The mean operative time for the last 40 cases was 47 minutes (range: 30-85 minutes). This did not appear to be substantially different to the investigators’ previous experience with conventional laparoscopic cholecystectomy (mean 43 minutes; n=430). Pugliese et al (2009) reported that the average duration for the whole NOTES procedure was 75 minutes (range: 40-190 minutes). When conducted with unipolar electrode dissection, mean operating time was 148 minutes (range: 140-190 minutes). This was substantially longer compared with patients who underwent ultrasonic scalpel dissection, with a mean operating time of 53 minutes (range: 40-60 minutes) (p<0.01). Overall hospital stay was 2.2 days (range: 1-11 days). Noguera et al (2009) reported that all patients (n=15) were discharged within 36 hours after surgery, with 2 patients returning home on the same day. Mean length of stay was 0.8 days and mean procedure duration was 89.62 minutes (range 48-121 minutes).

**2009 COST IMPACT**

There are no cost effectiveness studies on transvaginal cholecystectomy. However, the evidence to date suggests that the overall operative time can match conventional laparoscopic cholecystectomy (Zornig et al 2009). There are no strict requirements for the use of new devices during the procedure; however, it is likely that new technologies will be introduced to perform NOTES more efficiently as the technique matures, which will add to the overall cost. No clear comparisons with regards to patient recovery and discharge time have been performed.
2009 Ethical, Cultural or Religious Considerations

No issues were identified from the retrieved material.

2009 Other Issues

As NOTES is a rapidly evolving technique, there are no standardised approaches for the procedure. As a result of this, it is difficult to perform valid comparisons between studies.

Surgeons attempting this technique must be experienced with performing biliary laparoscopic surgery and familiar with the use of minilaparoscopic instruments.

2009 Summary of Findings

The overall evidence on NOTES transvaginal cholecystectomy remains limited. The evidence retrieved indicates that the procedure is feasible; however, there is insufficient data to determine if it is comparable to conventional laparoscopic cholecystectomy. In addition, it is important to note that in all three included studies, the investigators performed hybrid NOTES techniques which utilised an abdominal trocar. Transvaginal cholecystectomy appears to be safe and does not appear to affect sexual function after a 2 week recovery period.

Hybrid cholecystectomy is becoming the only viable and safe clinical application at this time for a NOTES approach to the gallbladder. In addition, hybrid techniques also provide a bridge between laparoscopy and pure NOTES, that allows researchers and clinicians to expand their experience before pure transluminal techniques are utilised. Our search indicates that interest in transvaginal NOTES is likely to increase over time and this is reflected by the number of clinical trials due for completion in 2010.

2009 HealthPACT Action

Additional studies are required before transvaginal NOTES can be performed routinely. Considering the interest and the potentially rapid diffusion of this technique, it is recommended that transvaginal cholecystectomy is monitored for 12 months for new evidence.

2009 Number of Studies Included

| Total number of studies | 3 |
| Level IV intervention evidence | 3 |
2009 References


2009 Search Criteria to be used

Natural orifice cholecystectomy, transvaginal OR trans vaginal, NOTES cholecystectomy.