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Retrospective Study

Are laparoscopic cholecystectomy and NOTES gallbladder preserving cholecystolithotomy truly comparable? A propensity matched study for symptomatic gallstones

Laparoscopic cholecystectomy vs. NOTES gallbladder preserving cholecystolithotomy

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Abstract

BACKGROUND

Cholecystectomy is the preferred option for symptomatic gallstones. However, gallbladder preserving cholecystolithotomy has been proposed in order to preserve the normal physiological function of the gallbladder and to satisfy patients desiring to avoid surgical resection.

AIM

To compare the feasibility, safety and effectiveness of pure natural orifice transluminal endoscopic surgery (NOTES) gallbladder-preserving cholecystolithotomy *vs* laparoscopic cholecystectomy (LC) for symptomatic gallstones.

METHODS

We adopted propensity score matching (1:1) to compare transrectal NOTES cholecystolithotomy and LC patients with symptomatic gallstones from December 2017 to December 2020. We reviewed a total of 2511 patients with symptomatic gallstones, of whom 517 patients met the matching criteria (NOTES, 110; LC, 407), yielding 86 pairs of patient.

RESULTS

The technical success rate for NOTES group *vs*. LC was 98.9% *vs*. 100%. The median procedure time was 119 minutes (IQRs, 95-175) with NOTES group *vs*. 60 minutes (IQRs, 48-90) in LC ($p < 0.001$). Post-operative pain was similar between NOTES and LC: 4.7% (4/85) *vs*. 5.8% (5/95) ($P = 0.740$). The median duration of fasting was less with NOTES 1 day (IQRs, 1-2) *vs* 2 days with LC (IQRs, 1-3) (difference, 1 day; $p < 0.001$). The median post-operative hospital stay for NOTES was 4 days (IQRs, 3-6) *vs*. 4 days with LC (IQRs, 3-5), ($P = .092$). During the follow-up, diarrhea was significantly less with NOTES 5.8% compared to LC, 18.6% ($p = .011$). The recurrence rate of stones and cholecystitis within median 12 mo (range: 6-40 mo) following NOTES was 10.5%

and 3.5% respectively. Concerns about the presence of abdominal wall scars were present in 17.4% ($n = 15/86$) patients following LC (mainly women).

CONCLUSION

NOTES provides a feasible new alternative scar-free treatment for patients who are unwilling or unable to undergo cholecystectomy. This minimally invasive organ-sparing procedure both relieved the gallstones and preserved the physiological function of the gallbladder. Reducing the recurrence is potentially essential to achieve widespread clinical adoption.

Key Words: Gallstones; Trans-rectal; Natural orifice transluminal endoscopic surgery; Minimally invasive surgery; Gallbladder preservation; Cholecystolithotomy; Laparoscopic cholecystectomy

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Core Tip: Cholelithiasis is a common with over 10% morbidity that is increasing significantly with the ageing of the population. Laparoscopic cholecystectomy (LC) is the gold standard for treating gallstones. However, long term complications of LC largely remain unreported/unstudied and listed as follows: duodenogastric reflux, post cholecystectomy syndrome, bile duct injuries and an increase in colonic cancer. Additionally, with a deep understanding of the function of the gallbladder, surgeons now realize that the gallbladder not only concentrates and stores bile but also regulates the flow of bile. Some experts advocated simple gallstone extraction with gallbladder preservation (cholecystolithotomy) in order to preserve the normal physiological function of the gallbladder, avoid post-cholecystectomy syndromes, bile duct injury,

complications from abdominal wall incisions, bile reflux gastritis, and its association of colon cancer. In response to the clinical desires and importance of gallbladder retention to a large number of patients, author's developed pure NOTES trans-rectal gallbladder preserving cholecystolithotomy as an ultra-minimally invasive technique for removal of gallbladder stones, and in this study compared it with traditional LC. Although, this procedure is unlikely to replace the LC, it proved useful for patients desiring to avoid surgical resection and are unfit for surgery.

INTRODUCTION

About 25 million people in the United States have gallstones, resulting in more than one million hospitalizations each year [1-4]. Cholecystectomy is the gold standard treatment for symptomatic gallstones [5]. For the past three decades, laparoscopic cholecystectomy (LC) has been the treatment of choice [5-8] as it is minimally invasive. However, the ultra-minimally invasive technique of natural orifice transluminal endoscopic surgery (NOTES) cholecystectomy is evolving since Rao and Reddy's description of the first human NOTES transgastric appendectomy in 2004[9]. Some experts now advocate cholecystolithotomy without gallbladder excision in order to preserve gallbladder function and to avoid gallbladder resection-related complications[10-13]. In addition, cholecystectomy is associated with post-cholecystectomy syndromes, surgical incision complications, and bile duct injury[14-16]. Among the reasons given for gallbladder preservation include that cholecystectomy has also been reported to be associated with colon cancer and, functional gastrointestinal and psychological conditions[12-17].

8 Experimental studies of flexible endoscopic trans-rectal NOTES have suggested this approach as an attractive alternative options for intra-abdominal procedures[18-21]. However, the concern about peritoneal contamination with trans-rectal NOTES have limited adoption of trans-rectal NOTES as a routine clinical practice. The problem of peritoneal contamination during trans-rectal NOTES has now been largely overcome with the use of a detachable obstructive colonic balloon which prevents distal colonic contamination (Figure 1)[22-24].

Until now, no comparison of NOTES and LC for symptomatic gallstones has been reported. Therefore, we performed a comparative study of pure NOTES gallbladder preservation cholecystolithotomy and laparoscopic cholecystectomy that examined effectiveness as well as differences in post-operative pain, infection, time to normal diet intake, hospital stay duration, short and long term complications.

MATERIALS AND METHODS

Study design

The study protocol was approved by the independent ethics committee of the Second Affiliated Hospital of Harbin University. Written informed consent was obtained from all patients before the procedure. All NOTES procedures were performed by an expert gastroenterologist with an experience of more than 150 NOTES procedures. The research was carried out in accordance with the Helsinki Declaration. All authors had access to the study data and reviewed and approved the final manuscript.

Patients selections for NOTES

We extracted data of patients from the inpatient database of the first affiliated hospital of Zhengzhou university who were treated for gallbladder disease from December 2017 to December 2020. The inclusion criteria were: 1) patients over the age of 18 years and less than of 80 years of age, 2) Patients with symptomatic cholelithiasis confirmed by B-ultrasound or other imaging examination (CT/MRI), 3) patients with no history of major upper abdominal surgery, 4) a strong desire to retain the gallbladder, 5) no absolute surgical contraindications, including severe hepatic, renal, cardiac and pulmonary insufficiency, history of cerebral coma and allergy to anesthesia *etc.* Exclusion criteria included: 1) patients younger than 18 years, older than 80 years of age 2) patients with acute cholecystitis, chronic atrophic cholecystitis, atrophy of gallbladder due to any reason and suspicion of gallbladder cancer, 4) unable to undergo endoscopic surgery for various reasons such as associated other diseases or age factor, 5) could not be contacted or loss of information.

Interventions

Description of trans-rectal NOTES technique: After routine bowel preparation, all procedures were performed under general anesthesia. With the patients in the lithotomy position, a colonoscope (EVIS GIF-Q260J, Olympus, Tokyo, Japan) was advanced into the transverse colon for colonic cleansing. A detachable colonic exclusion balloon was placed into the transverse colon with help of the colonoscope and inflated to 3.0-3.5 cm in diameter by injecting 120 to 140 mL of air into the balloon to occlude the transverse colonic lumen (Figure 3A). Cleansing and disinfection of the distal colonic and rectal lumen was then completed with a 0.1% povidone-iodine solution. A disinfected (a low temperature ethylene oxide processed) gastroscope with a transparent cap attached on the tip of endoscope was inserted and an incision was made on the right anterior wall of the rectum 15 to 20 cm from the anal verge using Hook and IT knives (Figure 3B). The endoscope was advanced upward through the inter-bowel space into the upper peritoneal cavity where the liver and gallbladder were identified. A full-thickness longitudinal incision was created in the gallbladder wall using the Hook and IT knives (Figure 3C). The tip of endoscope was inserted into the gallbladder cavity and the bile was aspirated. The lumen was then cleansed with normal saline and the gallstones were extracted from the gallbladder using a biliary stone extractor (E151186, GMBH FLEX, Germany) and removed *via* the trans-rectal incision (Figure 3D). The gallbladder incision was closed with endoclips (longclip, HX-610-090, Olympus, Tokyo, Japan) (Figure 3E). The endoscope was then withdrawn and the stomal opening in the rectum was closed with endoclips and endoloops (HX-20L-1, Olympus, Tokyo, Japan) (Figure 3F). The colon occlusion balloon was deflated and removed and the colonic mucosa at the site of balloon occlusion was inspected (Video 1 and Supplementary Video 2).

Description of laparoscopic technique: All patients undergone LC were performed by expert gastroenterology surgeons with an experience of more than 500 cholecystectomies. LC was performed using standard laparoscopic approach.

Outcomes

The two methods of therapy were compared with regard to treatment success, procedure time, post-operative pain, time to normal diet intake, duration of hospital stay, and postoperative short and long term complications, and recurrence rate.

Follow up

The median follow-up period was one year (range: 6 - 40 mo). The primary outcome was treatment success. In the NOTES-treated group, treatment success was defined as successful if the procedure was completed using endoscopic surgery without conversion to laparoscopic or open surgery. In the LC group, treatment success was identified as a successful cholecystectomy, if the procedure was done without converting to open surgery.

Secondary measured outcomes included procedure time, postoperative pain, duration of post-operative hospital stay, duration of fasting, and postoperative short term (within 2 wk) and long term complications, and recurrence rate. In the NOTES group, short-term complications included biliary peritonitis, fever, nausea and vomiting, bleeding and systemic complications (pulmonary embolism, stroke, cardiac events, acute renal failure, and sepsis). Long-term complications included recurrent gallstone, recurrent cholecystitis, diarrhea, constipation, and malignant tumor of gallbladder. In the LC group, short-term complications included incisional infection, incisional pain, bile duct injury, anesthesia-related complications, and systemic complications. Long-term complications included abdominal pain, hernia, and digestive symptoms. All enrolled patients were followed up by telephone and/or medical records.

Statistical analysis

We used logistic regression models for the calculation of propensity scores. We used a 1:1 propensity score matching (PSM) with the NOTES and LC groups and the caliper value fixed at 0.1 for the propensity matching score. The study matched clinical baseline indicators including age, sex, bilirubin levels, gallbladder stones, temperature, white

blood cell count, and hemoglobin. An absolute standard difference (ASD) of less than 0.1 was considered negligible between both groups. Categorical variables were expressed as frequency and percentages with 95% CIs, and continuous variables (operative time, post-operative hospital stay, fasting time, and recurrent time) were expressed as medians with interquartile ranges (IQRs). The Pearson χ^2 and Fisher's exact test was used for categorical variables, and the Mann-Whitney test was applied for continuous variables. Gender, age, baseline leukocytes, total bilirubin, and number of gallbladder stones were analyzed by univariate Cox proportional risk regression for the 1-year recurrence-free outcome. PSM and all calculations were conducted with Stata/SE 15.0 (Stata Corp, College Station, TX). A two-sided p-value less than 0.05 were considered significant difference.

RESULTS

Population characteristics before and after propensity score matching

We extracted data of 2511 patients from the inpatient database who were treated for gallbladder disease. Among these patients, we excluded 15 patients younger than 18 years of age, 201 patients older than 80 years of age, 55 patients with malignant gallbladder tumor, 112 patients with open surgery, 1281 patients with chronic atrophic cholecystitis and/or atrophy of gallbladder, 159 patients unable to undergo endoscopic surgery, and 171 patients who could not be contacted (loss the follow-up). Consequently, there were 517 patients eligible for matching (NOTES, 110; LC, 407), and yielded 86 patient pairs (Figure 2). Table 1 shows the characteristics of the patients before and after PSM.

Short-term complications

In the NOTES group, one patient (n=85/86) was referred to open surgery for removal of the gallbladder due to adhesions between the gallbladder and surrounding tissue. The overall success rate was 98.9% (95% CI, 94.3% 99.8%; n=85/86). All the patients in the LC group successfully underwent laparoscopic cholecystectomy with a success rate of

100%, and later pathology confirmed chronic cholecystitis in all. The median operative time was 119 minutes (IQRs, 95-175) in the NOTES group which was longer than the LC group median time of 60 minutes (IQRs, 48-90), (difference, 59 minutes; $p < .001$). The median duration of fasting of the NOTES group was 1 day (IQRs, 1-2) vs 2 days (IQRs, 1-3) with the LC group, (difference, 1 day; $p < 0.001$). The median post-operative hospital stay was 4 days (IQRs, 3-6) in the NOTES group vs 4 days with LC (IQRs, 3-5), ($P = 0.092$).

In NOTES group, 2.3% (95%CI, 0.6%-8.9%; $n = 2/85$) patients developed postoperative biliary peritonitis. All the peritonitis patients recovered with abdominal irrigation (percutaneous flushing the peritoneal cavity with saline solution) and combined antibiotic treatment. In the LC group, 2.3% (95%CI, 0.6-7.4%; $n = 2/86$) patients developed lung infections, 5.8% (95%CI, 2.3%-11.7%; $n = 5/86$) patients had severe abdominal pain, 1 (1%, 95%CI, 0.2-5.7%) patient had a wound infection with fever, and one patient had urinary retention. The mortality rate in both groups was 0%.

Long-term complications (post-cholecystectomy syndrome)

During the follow-up, all patients in the two groups are alive. In the LC group, 18.6% (95%CI, 10.6-25.6%; $n=16/86$) patients developed diarrhea, of which 8 (8.4%, 95%CI, 4.3-15.7%) had frequent diarrhea, 5 (5.3%, 95%CI, 2.3-11.7%) patients were prone to diarrhea after eating fatty foods, 3 (3.3%, 95%CI, 1.1-8.9%) patients had occasional diarrhea, and diarrhea symptoms were not relieved after symptomatic treatment. In comparison, 5.8% (95%CI, 2.3-11.8%; $n=5/85$) of NOTES patients presented with diarrhea, 3 of them after undergoing cholecystectomy which was significantly less frequent than after LC (difference, 11.5 percentage points [95%CI, 2.5-20.8]; $P = 0.011$).

2.3% (95%CI, 0.6-7.4%; $n = 2/85$) NOTES patients presented with constipation vs. 3.5% (95%CI, 1.1-8.9%; $n = 3/86$) with LC (difference, 1.03 percentage points [95%CI, -0.5-7]; $P = 0.663$).

In the LC group, 5.8% (95%CI, 2.3-11.7%; $n = 5/86$) patients had pain in the surgical area with anxiety; 17.4% (95%CI, 9.8-24.4%; $n = 15/86$) patients were concerned about scars

on the abdominal wall (mainly women). 11.6% (95%CI, 5.8-18.3%; $n = 10/86$) patients had decreased appetite and reduced their diet compared to their preoperative status. Only 2.3% ($n = 2/85$) of NOTES patients had decreased appetite (difference, 8.4 percentage points [95%CI, 1.3-16.3]; $P = 0.018$). Two (2.3%, 95%CI, 0.6%-7.4%) patients had back pain after exertion, and one (1.06%, 95%CI, 0.2-5.7%) patient had chest tightness. One (1.06%, 95%CI, 0.2-5.7%) patient developed renal calculi (Table 2).

Risk factors for patients with recurrent gallbladder stones

Nine NOTES patients had recurrence of gallbladder stones suggested by abdominal ultrasound. The recurrent gallbladder stones were all mud-like stones with a median recurrence time of 210 days (IQRs, 165-255). The recurrence rate was 10.5% (95%CI, 5.1-17.2%; $n = 9/85$), among which 5 underwent cholecystectomy; 4 patients were asymptomatic and they did not wish to undergo further therapy with either NOTES or LC. We recommended re-NOTES or LC for recurrence cases. The postoperative pathology revealed chronic cholecystitis; 3.5% (95%CI, 1.1-9%; $n = 3/85$) of patients had pain in the right upper abdomen and the diagnosis of cholecystitis recurrence was made by ultrasound and CT examination, among which 1 (1.1%, 95%CI, 0.2-5.8%) patient had gallbladder stones combined with cholecystitis. In patients with recurrence who did not receive surgical treatment, symptoms were significantly reduced after antibiotic treatment. Figure 4 shows the cumulative incidence of recurrent gallbladder stones and recurrent cholecystitis in the NOTES patients. To identify risk factors for recurrence of gallbladder stones, we performed univariate Cox regression analysis for gender, baseline leukocytes, number of gallstones, and age, and no factor was statistically significant for recurrence of gallbladder stones.

DISCUSSION

Symptomatic gallstones are common and cholecystectomy remains the 'gold standard' for their management^[25-26]. In 1987, the first laparoscopic cholecystectomy was conducted which ushered in the age of cholecystectomy with minimal trauma and

rapid recovery. This approach demonstrated superiority and created a precedent for minimally invasive operations. Subsequently, with improved technology, many patients with cholelithiasis worldwide have undergone laparoscopic cholecystectomy and this technique has become the standard treatment for cholelithiasis. However, simple gallstone extraction with gallbladder preservation (cholecystolithotomy) has been proposed in order to preserve the normal physiological function of the gallbladder, avoid post-cholecystectomy syndromes, bile duct injury, complications from abdominal wall incisions, bile reflux gastritis, and reduce the incidence of gastrointestinal cancer^[27-29]. The justification for this practice includes considerations regarding safety, reduced short and long term complications as well as cosmetic results and patient satisfaction. Besides this, in clinical practice, we have found that many patients express a strong desire for preservation of their organ (gallbladder). In response to the clinical desires and importance of gallbladder retention to a large number of patients, we developed pure NOTES trans-rectal gallbladder preserving cholecystolithotomy as an ultra-minimally invasive technique for removal of gallbladder stones and gallbladder preservation.

Both LC and NOTES approaches have advantages and disadvantages. The advantages of NOTES cholecystolithotomy include: 1) Organ retention and preserved its biological function, 2) no incision on the body surface, 3) early diet intake (e.g., 6 h after the procedure patient are able to take a liquid diet), and, 4) reduced post-operative pain. 5) less long term complications compared to LC.

The problem with this approach is at current longer procedure time than that of LC and the recurrence of gallstones. Long operative time is expected during early clinical stage. In the beginning of laparoscopic surgery, 2-3 h' operation was common. ¹² With experience and improved techniques, the operative time for NOTES cholecystolithotomy is expected to decrease.

The gallstone recurrence remains a concern. A recent report showed the average recurrence risk for percutaneous cholecystolithotomy was 3% in 4 years and 10% in 15 years^[30]. ² In China, a long-term analysis of the gallstone recurrence rate after laproscopic

cholecystolithotomy over more than 15 years reported a rate of 10.11% within both 10 and 15 years^[31]. In our study, the recurrence risk of gallstones was 9.8 % (9/94) between 6 to 40 mo of follow up. Widespread use of NOTES cholecystolithotomy may require development of a reliable method to prevent recurrence of gallstones. A randomized, double-blind placebo-controlled multicenter clinical trial reported that ursodeoxycholic acid is a safe and effective drug for the prevention of gallstone recurrence^[32]. In another meta-analysis Li *et al'* noted that not taking oral ursodeoxycholic acid after gallbladder preserving therapy increased the rate of stone recurrence^[33]. Therefore, we recommend that patients who undergo cholecystolithotomy take ursodeoxycholic acid orally to prevent the recurrence of stones. However, further studies are needed to explore the mechanism and then prevent recurrence of gallstones before the final recommendations are made.

The advantage of LC is a shorter procedure time than with NOTES. Disadvantages includes: 1). The organ is resected so the loss of its biological function which may result in long term complications, 2) a scar on the body surface, 3) diet intake is delayed (e.g. on day 2), 4) risk of incision related complications, and 5) more short and long term complications than that with NOTES (abdominal pain, nausea, diarrhea, constipation, fatty food intolerance, indigestion, association with colon cancer, functional gastrointestinal and psychological conditions)^[14-22].

There was no significant difference for duration of hospital stay between two groups. Initially, we admitted patients after undergoing NOTES procedure for longer than usual time as this was a preliminary study with a limited sample size. Post-operative stay ranged between 3 to 5 days vs. same day surgery for laparoscopic cholecystectomy in USA and western world might raises questions. The explanation for that is in China the standard of post-operative care is different, and after all kinds of abdominal surgeries (laparoscopic or open surgery) patients are being kept in hospital under observation for 3-5 days.

In our study, the most significant differences between these groups were long term complications and no wound infections. Although, LC seem to be a 50 minutes'

procedure with a good outcome, its long time complications remain largely unstudied included post cholecystectomy syndrome and a possible association with colon cancer. On the other hand, only long term reported (between 10-15 years of follow-up) complication of percutaneous cholecystolithotomy is gallstones recurrence. And the main reported factors associated with the recurrence of gallstones were a family history of cholelithiasis, a preference for greasy food and gallbladder dysfunction prior to cholecystolithotomy^[29-33].

Compared with LC, NOTES is more than a cosmetic way to perform surgery as it also has the potential to reduce ¹⁰ anesthesia requirements, accelerate patient recovery, and, above all, provide minimally invasive access to organs that are otherwise difficult to access with conventional open or laparoscopic approaches. In addition, sometimes few patients refuse surgery and some older patients are not compatible for surgical procedure. NOTES provides an alternative option to treat gallstones disease. Though we found some short term complications and recurrences overall, the safety and efficacy were good with NOTES. With time and improved technology these complications rate will likely be reduced.

⁴ This study has some limitations, including characterization of the new technique, retrospective design, small cohort, and absence of a control group which makes the study prone to attrition and possible loss of clinical data. The same limits the generalizability of the study. Additional studies especially larger multi-center trials are needed to confirm the advantages shown here, and ⁴ to understand the future for this innovative new approach to the treatment of symptomatic gallstones.

CONCLUSION

In conclusion, NOTES appears to be minimally invasive and feasible alternative technique for management of patients with symptomatic gallstones. In our study more than 85% of the patients showed good results without any complications. Its advantages include no skin wound, organ retention, quick recovery, fewer postoperative complications, and patient satisfaction. Although, this procedure is unlikely to replace

the LC, it proved useful for patients desiring to avoid surgical resection, and have good results with NOTES. Reducing the recurrence is potentially essential to achieve widespread clinical adoption.

ARTICLE HIGHLIGHTS

Research background

Laparoscopic cholecystectomy (LC) remains the preferred option for symptomatic gallstones. However, gallbladder has an indispensable function in regulating the bile flow and storing bile, while cholecystectomy may disrupt the whole biliary system and induce subsequent complications. Simple gallstone extraction with gallbladder preservation (cholecystolithotomy) has been proposed in order to preserve gallbladder function and to avoid gallbladder resection-related complications.

Research motivation

In response to the clinical desires and importance of gallbladder retention to a large number of patients, we developed pure natural orifice transluminal endoscopic surgery (NOTES) trans-rectal gallbladder preserving cholecystolithotomy as an ultra-minimally invasive technique for removal of gallbladder stones and gallbladder preservation.

Research objectives

To compare the feasibility, safety and effectiveness of pure NOTES gallbladder-preserving cholecystolithotomy *vs* LC for symptomatic gallstones.

Research methods

We extracted data of patients from the inpatient database and adopted propensity score matching (1:1) to compare transrectal NOTES cholecystolithotomy and LC for patients with symptomatic gallstones.

Research results

The technical success rate for NOTES group vs. LC was 98.9% vs. 100%. Post-operative pain was similar between NOTES and LC, however, the median duration of fasting was less with NOTES group patients. During the follow-up, diarrhea was significantly less with NOTES 5.8% compared to LC, 18.6%. The recurrence rate of stones and cholecystitis within median 12 mo (range: 6-40 mo) following NOTES was 10.5% and 3.5% respectively. Concerns about the presence of abdominal wall scars were present in patients following LC.

Research conclusions

NOTES appears to be minimally invasive and feasible alternative scar-free technique for management of patients with symptomatic gallstones. Reducing the recurrence is potentially essential to achieve widespread clinical adoption.

Research perspectives

Although cholecystectomy remains the mainstay for gallstones treatment due to its unique merits, it may be frustrated in surgical patients with high-risks or biliary deformity. In addition, since postoperative adverse events after removal of gallbladder are inevitable in some patients, more and more endoscopists become interested in preservation of gallbladder function during management of gallstone. So, in our opinion NOTES cholecystolithotomy could be an alternative choice for symptomatic gallstones, as it proved useful especially for patients desiring to avoid surgical resection.

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REFERENCES

- 1 **Zeng Q**, He Y, Qiang DC, Wu LX. Prevalence and epidemiological pattern of gallstones in urban residents in China. *Eur J Gastroenterol Hepatol* 2012; **24**: 1459-1460 [PMID: 23111386 DOI: 10.1097/MEG.0b013e3283583d13]
- 2 **Bar-Meir S**. Gallstones: prevalence, diagnosis and treatment. *Isr Med Assoc J* 2001; **3**: 111-113 [PMID: 11344819]
- 3 **Festi D**, Dormi A, Capodicasa S, Staniscia T, Attili AF, Loria P, Pazzi P, Mazzella G, Sama C, Roda E, Colecchia A. Incidence of gallstone disease in Italy: results from a multicenter, population-based Italian study (the MICOL project). *World J Gastroenterol* 2008; **14**: 5282-5289 [PMID: 18785280 DOI: 10.3748/wjg.14.5282]
- 4 **Duncan CB**, Riall TS. Evidence-based current surgical practice: calculous gallbladder disease. *J Gastrointest Surg* 2012; **16**: 2011-2025 [PMID: 22986769 DOI: 10.1007/s11605-012-2024-1]
- 5 **Litynski GS**. **Highlights in the History of Laparoscopy**. Frankfurt, Germany: Barbara BernertVerlag, 1996;165-168. [DOI:10.1080/110241598750005336]
- 6 **Reynolds W Jr**. The first laparoscopic cholecystectomy. *JLS* 2001; **5**: 89-94 [PMID: 11304004]
- 7 **Zanghì G**, Leanza V, Vecchio R, Malaguarnera M, Romano G, Rinzivillo NM, Catania V, Basile F. Single-Incision Laparoscopic Cholecystectomy: our experience and review of literature. *G Chir* 2015; **36**: 243-246 [PMID: 26888698 DOI: 10.11138/gchir/2015.36.6.243]
- 8 **Talseth A**, Lydersen S, Skjedlestad F, Hveem K, Edna TH. Trends in cholecystectomy rates in a defined population during and after the period of transition from open to laparoscopic surgery. *Scand J Gastroenterol* 2014; **49**: 92-98 [PMID: 24354967 DOI: 10.3109/00365521.2013.853828]
- 9 **Rao GV**, Reddy DN, Banerjee R. NOTES: human experience. *Gastrointest Endosc Clin N Am* 2008; **18**: 361-70; x [PMID: 18381176 DOI: 10.1016/j.giec.2008.01.007]
- 10 **Akiyama H**, Nagusa Y, Fujita T, Shirane N, Sasao T, Iwamori S, Hidaka T, Okuhara T. A new method for nonsurgical cholecystolithotomy. *Surg Gynecol Obstet* 1985; **161**: 72-74 [PMID: 4012547]

- 11 **Kerlan RK Jr**, LaBerge JM, Ring EJ. Percutaneous cholecystolithotomy: preliminary experience. *Radiology* 1985; **157**: 653-656 [PMID: 4059554 DOI: 10.1148/radiology.157.3.4059554]
- 12 **Pai RD**, Fong DG, Bundga ME, Odze RD, Rattner DW, Thompson CC. Transcolonic endoscopic cholecystectomy: a NOTES survival study in a porcine model (with video). *Gastrointest Endosc* 2006; **64**: 428-434 [PMID: 16923495 DOI: 10.1016/j.gie.2006.06.079]
- 13 **Ye L**, Liu J, Tang Y, Yan J, Tao K, Wan C, Wang G. Endoscopic minimal invasive cholecystolithotomy vs laparoscopic cholecystectomy in treatment of cholecystolithiasis in China: a meta-analysis. *Int J Surg* 2015; **13**: 227-238 [PMID: 25527194 DOI: 10.1016/j.ijssu.2014.12.014]
- 14 **Jaunoo SS**, Mohandas S, Almond LM. Postcholecystectomy syndrome (PCS). *Int J Surg* 2010; **8**: 15-17 [PMID: 19857610 DOI: 10.1016/j.ijssu.2009.10.008]
- 15 **Barrett M**, Asbun HJ, Chien HL, Brunt LM, Telem DA. Bile duct injury and morbidity following cholecystectomy: a need for improvement. *Surg Endosc* 2018; **32**: 1683-1688 [PMID: 28916877 DOI: 10.1007/s00464-017-5847-8]
- 16 **Lum YW**, House MG, Hayanga AJ, Schweitzer M. Postcholecystectomy syndrome in the laparoscopic era. *J Laparoendosc Adv Surg Tech A* 2006; **16**: 482-485 [PMID: 17004873 DOI: 10.1089/Lap.2006.16.482]
- 17 **Zhang Y**, Peng J, Li X, Liao M. Endoscopic-Laparoscopic Cholecystolithotomy in Treatment of Cholecystolithiasis Compared With Traditional Laparoscopic Cholecystectomy. *Surg Laparosc Endosc Percutan Tech* 2016; **26**: 377-380 [PMID: 27579981 DOI: 10.1097/SLE.0000000000000305]
- 18 **Tsai MC**, Chen CH, Lee HC, Lin HC, Lee CZ. Increased Risk of Depressive Disorder following Cholecystectomy for Gallstones. *PLoS One* 2015; **10**: e0129962 [PMID: 26053886 DOI: 10.1371/journal.pone.0129962]
- 19 **Renz BW**, Bösch F, Angele MK. Bile Duct Injury after Cholecystectomy: Surgical Therapy. *Visc Med* 2017; **33**: 184-190 [PMID: 28785565 DOI: 10.1159/000471818]
- 20 **Abbasoğlu O**, Tekant Y, Alper A, Aydın Ü, Balık A, Bostancı B, Coker A, Doğanay M, Gündoğdu H, Hamaloğlu E, Kapan M, Karademir S, Karayalçın K, Kılıçturgay S,

Şare M, Tümer AR, Yağcı G. Prevention and acute management of biliary injuries during laparoscopic cholecystectomy: Expert consensus statement. *Ulus Cerrahi Derg* 2016; **32**: 300-305 [PMID: 28149133 DOI: 10.5152/UCD.2016.3683]

21 **Zha Y**, Chen XR, Luo D, Jin Y. The prevention of major bile duct injuries in laparoscopic cholecystectomy: the experience with 13,000 patients in a single center. *Surg Laparosc Endosc Percutan Tech* 2010; **20**: 378-383 [PMID: 21150413 DOI: 10.1097/SLE.0b013e3182008efb]

22 **Liu B**, Du B, Pan Y. Video of the Month: Transrectal Gallbladder-Preserving Cholecystolithotomy *via* Pure Natural Orifice Transluminal Endoscopic Surgery: First Time in Humans. *Am J Gastroenterol* 2015; **110**: 1655 [PMID: 26673494 DOI: 10.1038/ajg.2015.266]

23 **Du B**, Fan YJ, Zhao LX, Geng XY, Li L, Wu XW, Zhang K, Liu BR. A reliable detachable balloon that prevents abdominal cavity contamination during transrectal natural orifice transluminal endoscopic surgery. *J Dig Dis* 2019; **20**: 383-390 [PMID: 31069947 DOI: 10.1111/1751-2980.12757]

24 **Zhao LX**, Liu ZZ, Ullah S, Liu D, Yang HY, Liu BR. The detachable balloon: A novel device for safe trans-rectal natural orifice transluminal endoscopic surgery. *Dig Liver Dis* 2021; **53**: 931-934 [PMID: 33994130 DOI: 10.1016/j.dld.2021.04.019]

25 **Lammert F**, Gurusamy K, Ko CW, Miquel JF, Méndez-Sánchez N, Portincasa P, van Erpecum KJ, van Laarhoven CJ, Wang DQ. Gallstones. *Nat Rev Dis Primers* 2016; **2**: 16024 [PMID: 27121416 DOI: 10.1038/nrdp.2016.24]

26 **Qu Q**, Chen W, Liu X, Wang W, Hong T, Liu W, He X. Role of gallbladder-preserving surgery in the treatment of gallstone diseases in young and middle-aged patients in China: results of a 10-year prospective study. *Surgery* 2020; **167**: 283-289 [PMID: 31606197 DOI: 10.1016/j.surg.2019.09.001]

27 **Du S**, Zhu L, Sang X, Mao Y, Lu X, Zhong S, Huang J. Gallbladder carcinoma post gallbladder-preserving cholecystolithotomy: a case report. *Hepatobiliary Surg Nutr* 2012; **1**: 61-63 [PMID: 24570906 DOI: 10.3978/j.issn.2304-3881.2012.07.01]

- 28 **Tan YY**, Zhao G, Wang D, Wang JM, Tang JR, Ji ZL. A new strategy of minimally invasive surgery for cholecystolithiasis: calculi removal and gallbladder preservation. *Dig Surg* 2013; **30**: 466-471 [PMID: 24481280 DOI: 10.1159/000357823]
- 29 **Zhu X**, Liu J, Wang F, Zhao Q, Zhang X, Gu J. Influence of traditional Chinese culture on the choice of patients concerning the technique for treatment of cholelithiasis: Cultural background and historical origins of gallbladder-preserving surgery. *Surgery* 2020; **167**: 279-282 [PMID: 31590916 DOI: 10.1016/j.surg.2019.05.037]
- 30 **Gao DK**, Wei SH, Li W, Ren J, Ma XM, Gu CW, Wu HR. Totally laparoscopic gallbladder-preserving surgery: A minimally invasive and favorable approach for cholelithiasis. *Exp Ther Med* 2015; **9**: 395-398 [PMID: 25574204 DOI: 10.3892/etm.2014.2107]
- 31 **Liu J**, Li J, Zhao Q. The analyses of the results of 612 cases with gallbladder stones who underwent fibrocholedoscope cholecystectomy for removal of caculas and preservation of gallbladder (Chinese Article). *Mag Chin Surg* 2009; **47**:279-281 [DOI:10.1007/978-981-15-6010-1_28]
- 32 **Kosters A**, Jirsa M, Groen AK. Genetic background of cholesterol gallstone disease. *Biochim Biophys Acta* 2003; **1637**: 1-19 [PMID: 12527402 DOI: 10.1016/s0925-4439(02)00173-4]
- 33 **Li W**, Huang P, Lei P, Luo H, Yao Z, Xiong Z, Liu B, Hu K. Risk factors for the recurrence of stones after endoscopic minimally invasive cholecystolithotomy in China: a meta-analysis. *Surg Endosc* 2019; **33**: 1802-1810 [PMID: 30701362 DOI: 10.1007/s00464-018-6455-y]

Footnotes

5

Institutional review board statement: This study was reviewed and approved by the Independent ethics committee of the Second Affiliated Hospital of Harbin University and the First Affiliated Hospital of Zhengzhou University.

Institutional animal care and use committee statement: N/A

Clinical trial registration statement: N/A

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-
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