

Endoscopic transgastric pure NOTES cholecystectomy with naso-gallbladder drainage tube placement and injection of a hyaluronic acid mixture (with Video)

Hiroyuki Isayama · Hirofumi Kogure · Kazuhiko Koike

Received: 21 January 2010 / Accepted: 19 April 2010 / Published online: 17 June 2010
© Japanese Society of Hepato-Biliary-Pancreatic Surgery and Springer 2010

Abstract

Background Endoscopic transgastric pure natural orifice transluminal endoscopic surgery (NOTES) cholecystectomy is a difficult procedure, and most human female cases are performed as hybrid NOTES, using a transvaginal route. We tried a transgastric pure NOTES procedure without laparoscopic procedure in an animal study after placing an endoscopic naso-gallbladder drainage (ENGBD) tube and injecting a hyaluronic acid (HA) mixture.

Methods We performed the method in four pigs, using a standard single-channel endoscope. The ENGBD tube was placed first and the HA mixture was injected between the gallbladder (GB) serosa and liver bed.

Results We determined the gastrotomy site using an ENGBD tube, which made the GB approach easy under fluoroscopic guidance. The scope was not retroflexed, but was rotated at the stomach fornix. The connecting tissues between the GB serosa and liver bed expanded following the injection of the HA mixture, facilitating GB removal with a Hook knife. The GB wall, liver, and vessels were observed clearly during the procedure, and there were no incorrect cuts.

Conclusion We successfully performed a transgastric pure NOTES cholecystectomy in pigs. An ENGBD tube

was useful as a guide to the GB, and for recognizing the cystic duct, and injecting the HA mixture facilitated the GB dissection.

Keywords

Endoscopic naso-gallbladder drainage (ENGBD) · Natural orifice transluminal endoscopic surgery (NOTES) · Cholecystectomy · Hyaluronic acid · Transgastric surgery

Abbreviations

CD	Cystic duct
ENGBD	Endoscopic naso-gallbladder drainage
ESD	Endoscopic submucosal dissection
GB	Gallbladder
HA	Hyaluronic acid
NOTES	Natural orifice transluminal endoscopic surgery

Introduction

Natural orifice transluminal endoscopic surgery (NOTES) is an effective, minimally invasive procedure that does not produce a scar [1]. In an initial trial, a peroral transgastric route was used to access the peritoneal cavity for NOTES [1–4]. However, the use of a transgastric route to perform a cholecystectomy is considered difficult because of the retroflexed scope position.

Conversely, the gallbladder (GB) can be approached directly with the transvaginal insertion of the endoscope without using a retroflexed position. Some authors have reported their clinical experience with human cases and the advantages of this approach when performing a cholecystectomy; this procedure was performed with laparoscopic

Electronic supplementary material The online version of this article (doi:10.1007/s00534-010-0295-z) contains supplementary material, which is available to authorized users.

H. Isayama (✉) · H. Kogure · K. Koike
Department of Gastroenterology,
Graduate School of Medicine, University of Tokyo,
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
e-mail: isayama-ky@umin.ac.jp

assistance [5–6]. This approach is available only for females, and a NOTES cholecystectomy procedure for males should be established.

However, transgastric cholecystectomy as a pure NOTES technique using only a flexible endoscope has some technical problems [2, 4, 7–8], including difficulty reaching the GB from the stomach with the endoscope because of the limited spatial orientation and retroflexed position of the endoscope, difficulty removing the GB from the liver bed because it is impossible to use a traction technique, and difficulty recognizing and resecting the cystic duct (CD). Recently, this type of surgery has been combined with a laparoscopic technique as the hybrid NOTES technique. Hybrid NOTES enables a wide field of view, the use of many instruments for laparoscopic assistance, and grasping and retracting the GB [8–11].

We considered new strategies to overcome these problems and conducted an animal study. The pure NOTES procedure is performed under fluoroscopic guidance using a previously placed endoscopic naso-gallbladder drainage (ENGBD) tube [12]. We surmised that it might be possible to determine the spatial orientation of the GB fluoroscopically and identify the optimal portal site on the gastric wall for direct access by placing a transnasal tube into the GB preoperatively. To facilitate the dissection procedure in early gastric cancer, Fujishiro et al. [13] suggested injecting a mixture of hyaluronic acid (HA), indigo carmine, and epinephrine into the submucosal layer. This technique has become standard for endoscopic submucosal dissection (ESD), and we introduced it for endoscopic transgastric cholecystectomy. Injecting this HA mixture between the liver bed and GB serosa may make the dissection for a NOTES cholecystectomy easier and safer. We report the results of endoscopic transgastric cholecystectomy using this new technique in an exploratory animal study as a very preliminary pilot study.

Materials and methods

Animal preparations

A transgastric cholecystectomy was performed in four pigs (body weights: 60, 65, 35, and 30 kg), which were subsequently euthanized. The pigs were fasted for 24 h before the NOTES cholecystectomy. The experiments were conducted under general anesthesia with tracheal intubation. All experiments abided by the institutional guidelines for animal experiments and were performed after the animals had been used for other experiments in the animal laboratory of the Research and Development Center of Zeon Medical (Tokyo, Japan).

Endoscopic placement of the naso-gallbladder drainage tube

We used a standard flexible forward-viewing endoscope with a single accessory channel (GIF-XQ230; external diameter, 9.1 mm; full length, 1.35 m; single 3.5-mm accessory channel; Olympus Medical Systems, Tokyo, Japan) and a duodenoscope (JF-230; Olympus Medical Systems). First, we introduced an overtube into the esophagus, orally, along a standard, flexible forward-viewing endoscope. Then, endoscopic retrograde cholangiopancreatography (ERCP) was performed. A pigtail type of endoscopic naso-gallbladder drainage tube (ENGBD; Zeon Medical) was used in this study. The ENGBD tube was inserted into the gallbladder endoscopically along a guidewire via the CD, and the bile juice was replaced with saline. Subsequently, we removed the duodenal scope and overtube.

Preparation of HA mixture

The HA mixture consisted of 10 ml of HA (MucoUp; Seikagaku, Tokyo, Japan), 0.5 ml of 1% indigo carmine, and 0.1 ml of 0.1% epinephrine. The mixture was injected into the connecting tissue layer between the GB serosa and the liver bed to lift the GB off the liver bed, which allowed the vessels to be seen clearly. This procedure was more effective if a transparent cap was attached to the endoscope.

Endoscopic cholecystectomy

An overtube was placed beside the ENGBD tube, and a forward-viewing endoscope with a transparent plastic cap was introduced into the stomach. The endoscopic accessories used were a Hook knife (KD-620LR; Olympus Medical Systems), a 23-G injection needle, hemostatic forceps (Coagrasper, FD-410LR; Olympus Medical Systems), a rotatable clip-fixing device (Zeon Medical), endoclips (Zeon Medical), and grasping forceps (FG-47L-1; Olympus Medical Systems). The scope was inserted into the peritoneal cavity at the anterior wall through a submucosal tunnel made according to reported methods [5]. The gastrotomy site was based on the scope position for approaching the GB under fluoroscopic guidance.

Using fluoroscopic guidance, it was easy to search for the GB and to distinguish the CD from the cystic artery. Subsequently, we injected the previously prepared HA mixture between the liver bed and GB serosa from around the CD to the GB body. Using a Hook knife, we dissected the connecting tissue layer carefully to avoid cutting the GB wall, liver, and vessels. Any exposed visible vessels were coagulated with the Coagrasper in soft coagulation

mode (50 W). The cystic artery and CD were clipped twice on the bile duct side and once on the GB side to avoid severe bleeding. The dissection began from the proximal GB, using a Hook knife. After dissecting the GB body from the intrahepatic fossa, we removed the ENGBD tube and grasped the GB neck with grasping forceps. Then, we dissected the cystic artery and duct between the clips. The dissected GB was removed through the overtube with grasping forceps. The submucosal tunneled gastrotomy was closed with standard endoclips.

Evaluation

We evaluated the ease of the GB approach, CD visibility, ease of the removal technique, completion of the cholecystectomy, procedure time (min), and complications. These parameters were evaluated by a single operator (first author).

Results

Effects of ENGBD tube placement

We performed the procedure in four animals, while observing the institutional guidelines for animal experiments, and the details of the procedures are summarized in Table 1; the time required for each step in the procedure is given in Table 3. There were marked differences in the time required to approach the GB between the first two cases (45 and 225 min) and the last two cases (10 and 5 min). For cases 1 and 2, we did not use an ENGBD tube to determine the gastrotomy site; the scope was advanced toward the pelvic cavity after passing through the gastric wall and it was then rotated toward the upper abdomen at the pelvic floor. In case 2, we could not approach the GB despite replacing the scope with a standard endoscope used for colonoscopy (CF Q200; Olympus Medical Systems), because the approach route was too long. In cases 3 and 4, the endoscope was able to reach the GB directly after

passing through the gastric wall; subsequently, the endoscope was rotated at the stomach fornix and directed toward the GB without retroflexion (Fig. 1).

The CD was readily visible using the transparent ENGBD tube (Fig. 2), and we clipped the cystic artery and CD bundle. The CD bundle was cut after removing the GB from the liver bed with a Hook knife, using grasping forceps. We replaced the bile juice with saline during the procedure to prevent leakage of bile juice.

Effects of injecting the HA mixture

In cases 3 and 4, we removed the GB after injecting a mixture of HA, indigo carmine, and epinephrine between the GB serosa and the liver bed. The connecting tissue expanded and was stained after the injection (Fig. 3), and the removal using a Hook knife was easier than in case 1 without the injection. The GB wall, liver, and vessels were observed clearly during the procedure, which prevented incorrect cutting. Any vessels detected in the expanded, stained connecting tissues were coagulated using a Coagrasper in soft coagulation mode to avoid massive bleeding.

Operating time and complications

The operative results and the time required for each step of the procedure are shown in Tables 2 and 3. Complete resection of the GB was achieved only in cases 1 and 4. The time required for GB removal in case 4 (210 min) was shorter than that for case 1 (260 min). The removal procedure in case 4 was also much easier than that in case 1.

We stopped the procedure in case 3 while dissecting the GB body due to unexpected severe bleeding in the area. We could not detect the source of the bleeding; it might have been in the cavity or on the peritoneal side of the submucosal gastrotomy tunnel. There were no major complications during the procedure in the other cases, except that saline leaked through the incision in the GB wall in case 1.

Table 1 Details of the animal study

	Sex	BW (kg)	ENGBD			
			Placement	Decision on gastrotomy site	Approach to GB	HA injection ^a
1	Male	60	+	–	+	–
2	Male	65	+	–	+	–
3	Female	35	+	+	+	+
4	Female	30	+	+	+	+

ENGBD endoscopic naso-gallbladder drainage, GB gallbladder, BW body weight

^a Injection of a mixture of hyaluronic acid (HA), indigo carmine, and epinephrine

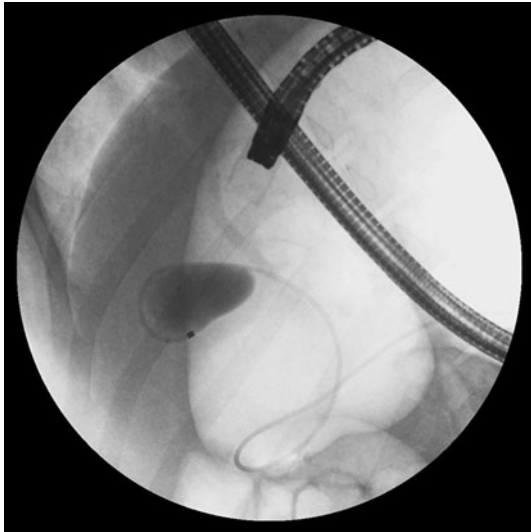


Fig. 1 Placing an endoscopic naso-gallbladder drainage tube to determine the gastrotomy site and for fluoroscopic guidance to reach the gallbladder (GB). The endoscope was rotated at the stomach fornix and directed toward the GB without retroflexion

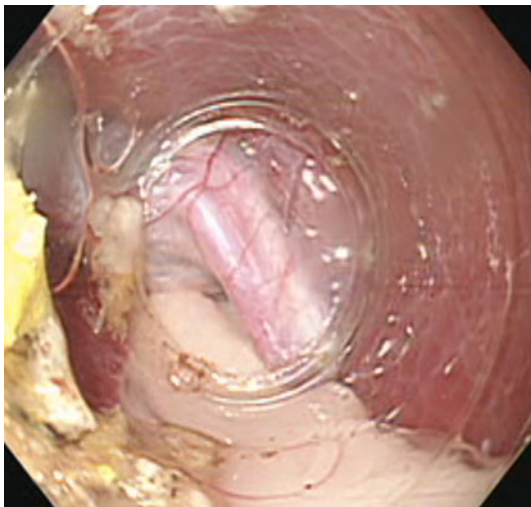


Fig. 2 The cystic duct is clearly seen using the transparent naso-gallbladder drainage tube

Discussion

Our new techniques were effective and seemed to overcome some of the disadvantages of endoscopic transgastric cholecystectomy. We successfully performed pure NOTES with only a standard single-channel scope. The current status of NOTES cholecystectomy may favor a hybrid style and is performed mainly in females using a transvaginal route [5–6]. However, we should establish a method for male NOTES cholecystectomy, and an ideal procedure might be transgastric pure NOTES. In our animal study using the above new techniques, we

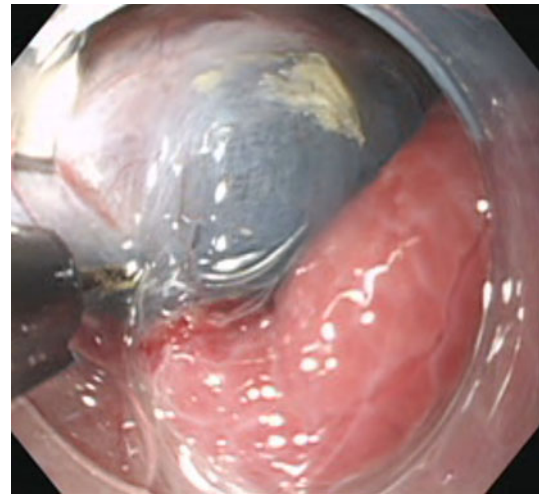


Fig. 3 Injecting the mixture of hyaluronic acid, indigo carmine, and epinephrine between the gallbladder serosa and liver bed. The connecting tissue expanded and was stained after the injection

performed endoscopic transgastric cholecystectomy as a pure NOTES technique.

In the present study, placing the ENGBD tube was effective for determining the gastrotomy site and for reaching the GB under fluoroscopic guidance. In most cases of NOTES cholecystectomy, there is a blind access route at the anterior gastric wall because of the established safety of endoscopic gastrotomy placement. The time required to approach the GB was shortened in cases 3 and 4 compared with the two earlier cases (Table 2). The importance of a procedure-specific access route was described in the article by the American Society for Gastrointestinal Endoscopy, SAGES [14], and some authors have reported several alternative sites. Elmunzer et al. [15] reported on the safety of making an access site using endoscopic ultrasound (EUS) guidance. We think that EUS is another strong modality to determine the access site that makes reaching the target organ easy; however, Elmunzer et al. did not consider the issue of reaching the target organ in their study.

Initially, we used only ENGBD when searching for the GB in the intraperitoneal cavity under fluoroscopic guidance with a blind access route, with the scope advanced toward the pelvic cavity and rotated at the pelvic floor. In this situation, a very long endoscope was needed, and we could not approach the GB, as in our second case, using this approach. Another important factor may be scope position; such as rotating the endoscope at the fornix (Fig. 1). Subsequently, the endoscope was advanced towards the GB. This scope position made it possible to reach the GB directly under fluoroscopic guidance without using a retroflexed scope position. In cases 3 and 4, we used the ENGBD tube to identify the access site under

Table 2 Time required for each step in the procedure

	Placement of ENGBD	Approach to GB	Removal of GB	Total time (min)
1	10	45	260	315
2	15	225 ^a	–	240
3	10	10	115 ^b	135
4	15	5	210	230

ENGBD endoscopic naso-gallbladder drainage, GB gallbladder

^a Impossible to approach the gallbladder

^b Stopped the procedure because of massive bleeding from an unknown site

Table 3 Results of the animal study

	Approach to GB	Visibility of CD	Removal technique	Cholecystectomy
1	Difficult	Clear	Difficult	Completed
2	Failed ^a	–	–	–
3	Easy	Clear	Easy	Not completed ^b
4	Easy	Clear	Easy	Completed

GB gallbladder, CD cystic duct

^a Impossible to approach the gallbladder

^b Stopped the procedure because of massive bleeding from an unknown site

fluoroscopic guidance, and it was easy to reach the GB. We hope that this method may be as useful in human NOTES cholecystectomy as it was in this animal experimental study.

Other advantages of an ENGBD tube were in searching for the GB in the intraperitoneal cavity and clear visualization of the transparent CD. Toyota et al. [12] reported that the placement of an ENGBD tube was useful for recognizing the CD and avoiding bile duct injury during laparoscopic cholecystectomy. The placement of an ENGBD tube was also useful for NOTES cholecystectomy. Recognizing the CD was also important for dissecting it from the connecting tissues, and for clipping and cutting. We exchanged the bile juice using the ENGBD tube to avoid chemical peritonitis due to bile leakage. However, a disadvantage of this procedure is the possibility of post-ERCP pancreatitis and radiation exposure, so a safer alternative procedure is needed.

We found that the ESD technique and injection of the HA mixture was safe and effective and made it possible to perform pure NOTES. In the cases using these techniques, the GB removal procedure was easier and the time was markedly shorter. Dissecting the expanded connecting tissues between the GB wall and liver was easy with a Hook knife, and the GB wall and liver could be observed clearly with the indigo carmine. Endoscopic hemostasis using a Coagrasper was effective for avoiding hemorrhage. In this study, we used a transparent plastic cap to approach the

dissected lesions. This procedure was very effective and made it easy to remove lesions without counter-traction.

In case 1, bile juice leaked though an incision in the GB wall. This complication occurs more frequently when using electronic cutting devices than when using a dissection technique with unsharpened forceps. The injected HA mixture acts as a cushion to prevent this complication. Liver injury is another complication of the use of electronic cutting devices. In this study, we used a Hook knife, but an IT knife (Olympus Medical Systems) with an insulated ball tip knife may be safer.

In the present study, the operating time was longer than in reported cases, because we are endoscopists rather than surgeons, and we could use only a standard single-channel endoscope in the animal study. However, the operating times in cases 3 and 4, using the technique of placing an ENGBD tube and injecting an HA mixture, were shorter than those in the other animals in which these techniques were not used. Another limitation of this study was the very small number of animals included, because this study was exploratory. This article demonstrated only the feasibility of the techniques as a very preliminary pilot study. We should plan a new animal study based on this study.

In summary, we successfully performed a transgastric pure NOTES cholecystectomy, using a standard single-channel endoscope, in pigs. Placing an ENGBD tube and injecting an HA mixture were effective and safe for NOTES cholecystectomy. The ENGBD tube was useful as

a guide to reach the GB and for visualizing the CD. In addition, ENGBD may also be useful to determine the gastrotomy site in human NOTES cholecystectomy, as it was in this animal experimental study. The ESD technique with the injection of the HA mixture facilitated the GB dissection, while it prevented hemorrhage. We believe that an endoscopic transgastric pure NOTES cholecystectomy technique, using many new techniques and devices, might become a standard procedure in humans in the near future.

Acknowledgments We appreciate the materials supplied by Zeon Medical Inc. and the help provided by Mr. Kouta Inoue, Mr. Chimyon Gon, Mr. Yoshihide Toyokawa, and Mr. Nobukazu Nishimura in preparing the animals. We are also grateful to Dr. Yousuke Nakai, Dr. Takashi Sasaki, and Dr. Takeshi Tsujino of Tokyo University Hospital for assistance with the endoscopic procedures.

References

1. Kalloo AN, Singh VK, Jagannath SB, Niiyama H, Hill SL, Vaughn CA, et al. Flexible transgastric peritoneoscopy: a novel approach to diagnostic and therapeutic interventions in the peritoneal cavity. *Gastrointest Endosc.* 2004;60(1):114–7.
2. Abe N, Takeuchi H, Ueki H, Matsuoka H, Yanagida O, Masaki T, et al. Cholecystectomy by a combined transgastric and transperitoneal approach using two flexible endoscopes. *J Hepatobiliary Pancreat Surg.* 2009;16:25–30.
3. Sumiyama K, Gostout CJ, Rajan E, Bakken TA, Deters JL, Knipschild MA, et al. Pilot study of the porcine uterine horn as an in vivo appendicitis model for development of endoscopic transgastric appendectomy. *Gastrointest Endosc.* 2006;64:808–12.
4. Park PO, Bergström M, Ikeda K, Fritscher-Ravens A, Swain P. Experimental studies of transgastric gallbladder surgery: cholecystectomy and cholecystogastric anastomosis (videos). *Gastrointest Endosc.* 2005;61:601–6.
5. Bessler M, Stevens PD, Milone L, Parikh M, Fowler D. Transvaginal laparoscopically assisted endoscopic cholecystectomy: a hybrid approach to natural orifice surgery. *Gastrointest Endosc.* 2007;66:1243–5.
6. Zornig C, Mofid H, Siemssen L, Emmermann A, Alm M, von Waldenfels HA, et al. Transvaginal NOTES hybrid cholecystectomy: feasibility results in 68 cases with mid-term follow-up. *Endoscopy.* 2009;41:391–4.
7. Sumiyama K, Gostout CJ, Rajan E, et al. Transgastric cholecystectomy: transgastric accessibility to the gallbladder improved with the SEMF method and a novel multibending therapeutic endoscope. *Gastrointest Endosc.* 2007;65:1028–34.
8. Astudillo JA, Sporn E, Bachman S, Miedema B, Thaler K. Transgastric cholecystectomy using a prototype endoscope with 2 deflecting working channels (with video). *Gastrointest Endosc.* 2009;69:297–302.
9. Shih SP, Kantsevov SV, Kalloo AN, Magano P, Giday SA, Ko CW, et al. Hybrid minimally invasive surgery—a bridge between laparoscopic and transluminal surgery. *Surg Endosc.* 2007;21:1450–3.
10. Auyang ED, Hungness ES, Vaziri K, Martin JA, Soper NJ. Human NOTES cholecystectomy: transgastric hybrid technique. *J Gastrointest Surg.* 2009;13:1149–50.
11. Dallemagne B, Perretta S, Allemann P, Asakuma M, Marescaux J. Transgastric hybrid cholecystectomy. *Br J Surg.* 2009;96:1162–6.
12. Toyota N, Takada T, Amano H, Yoshida M, Miura F, Wada K. Endoscopic naso-gallbladder drainage in the treatment of acute cholecystitis: alleviates inflammation and fixes operator's aim during early laparoscopic cholecystectomy. *J Hepatobiliary Pancreat Surg.* 2006;13(2):80–5.
13. Fujishiro M, Yahagi N, Nakamura M, Kakushima N, Kodashima S, Ono S, et al. Successful outcomes of a novel endoscopic treatment for GI tumors: endoscopic submucosal dissection with a mixture of high-molecular-weight hyaluronic acid, glycerin, and sugar. *Gastrointest Endosc.* 2006;63:243–9.
14. American Society for Gastrointestinal Endoscopy, SAGES. ASGE/SAGES Working Group on Natural Orifice Transluminal Endoscopic Surgery White Paper, October 2005. *Gastrointest Endosc* 2006;63:199–203.
15. Elmunzer BJ, Schomisch SJ, Trunzo JA, Poulouse BK, Delaney CP, McGee MF, et al. EUS in localizing safe alternate access sites for natural orifice transluminal endoscopic surgery: initial experience in a porcine model. *Gastrointest Endosc.* 2009;69:108–14.