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Over-the-scope-clip applications for perforated peptic ulcer

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Abstract

Aim To investigate the effectiveness of over-the-scope-clip (OTSC)-based endoscopic closure in patients with perforated peptic ulcer (PPU).

Methods One hundred six patients diagnosed with PPU were treated with either OTSC ($n=26$) or conservative treatments ($n=80$), respectively. The outcome assessments included technical success rate, clinical success rate, post-treatment complications after 1 month, mortality rate, time to resume oral feeding, length of hospital stay, and the administration of antibiotics.

Results In the OTSC group, technical and clinical success was achieved in 100% of patients without any complications, including death, incomplete closure, duodenal obstruction, and gastrointestinal bleeding, with a median operation time of 10 min. All patients in the OTSC group were discharged, while the mortality rate in the control group was 13.8%. Subsequent surgeries were required in 30% of patients in the control group. The median times to resume oral feeding were 3.5 (interquartile range [IQR] 2.0–5.25) days in the OTSC group and 7.0 (IQR 5.0–9.0) days in the control group ($p<0.001$). One month post-procedure, 30% (24/80) of patients in the control group and 0 (0/26) in the OTSC group required additional operations ($p<0.001$). No significant difference was found in the length of the hospital stay and the administration of antibiotics between the two groups ($p>0.05$).

Conclusions OTSC-based endoscopic technique, with a high clinical success rate and a shorter time to resume oral feeding, was effective in achieving closure of PPU with a diameter < 15 mm.

Keywords Over-the-scope system · Perforated peptic ulcer · Endoscopic closure · Oral feeding

Perforated peptic ulcer (PPU) has been traditionally treated with surgery. However, with the rapid development of the techniques, in addition to their use as a diagnostic tool, endoscopic procedures are beginning to be recognized as a suitable first-line treatment option in selected population of patients with perforation [1, 2]. In clinical practice, over-the-scope clip (OTSC) has been used as a treatment for acute iatrogenic gastrointestinal perforation. The system can be attached to the tip of the endoscope and is easy to maneuver with reported success rates as high as 90% in animal studies and in a clinical case series [3, 4]. The median operation time for an experienced endoscopist ranged from 3 to 12 min [5]. However, the practicability of OTSC-based endoscopic closure in patients with PPU is unclear.

Gas insufflation during endoscopic procedures was thought to aggravate symptoms in PPU patients. However, the presence of endoscopic procedure with CO_2 supply has largely eliminated this concern. OTSC is relatively safe, as there are no pulmonary adverse events related to CO_2 insufflation during the endoscopic procedure observed in a clinical study of OTSC [6]. CO_2 use leads to faster recovery times (decreased postprocedural pain, flatus, and bowel distention) [7], which could contribute to the decrease of the overall rate of decompression of tension pneumoperitoneum [8].

Sepsis, a leading cause of mortality, can be caused by rupture of the gastrointestinal wall, which in turn leads to infection and resultant multiple organ failure. The estimated mortality rate was 16.7% in patients with perforated

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duodenal ulcer (PDU) which correlated with the presence of septic shock on admission [9]. The Boey score and Mannheim Peritonitis Index (MPI) score are usually used to screen suitable patients for OTSC procedure. For the patients that are older, with complex comorbidities, or averse to undergoing surgery, OTSC could be a treatment option despite the fact that they may not be ideal candidates for the procedure. The current study aims to explore the effectiveness of OTSC as a treatment for patients with PPU in real-world clinical practices.

Materials and methods

Clinical records and patients' information

We searched clinical records of the First Affiliated Hospital of Fujian Medical University from January 2016 to December 2017, which were stored in the database of Zhiye electronic medical record system (V3.0, Zoe soft, Xiamen, China), for PPU cases with the keywords/ICD-10 codes for gastrointestinal perforation (K27.504), gastric perforation (K31.814), and pyloric perforation (K25.501). Written informed consent was collected from all participants in our retrospective study.

OTSC procedure

After the endoscopic evaluation, the endoscope was withdrawn and OTSC device (Ovesco Endoscopy AG, Tuebingen, Germany) loaded, and positioned towards the lesion where the tissue around was invaginated into the applicator cap by suction. When the tissue was trapped adequately, the OTSC was released and technical success was evaluated visually.

Prognostic assessments

Prognoses in patients were evaluated using the Boey score and the MPI score. The Boey score was the sum total of three independent risk factors: (1) concomitant severe medical illness (chronic obstructive pulmonary disease, heart failure, and active cancer), (2) preoperative shock (systolic blood pressure < 90 mmHg), and (3) duration of PPU longer than 24 h (the time interval between the onset of severe acute abdominal pain and arrival time at the hospital) [10]. The MPI score was based on a combination of risk factors including age > 50 years (5), female sex (5), organ failure (7), malignancy (4), preoperative duration of peritonitis > 24 h (4), origin of sepsis not colonic (4), diffuse generalized peritonitis (6), and exudate (clear 0; cloudy, purulent 6; fecal 12) [11].

Outcome measures

The overall technical success rates (TSR), clinical success rates (CSR), procedure times, rate of surgery in 1 month post-treatment, complications, serum albumin levels, time to oral feeding, length of hospital stay, and the duration of antibiotics during hospital stay treatment were considered as major outcomes. Complications include death, incomplete closure, duodenal obstruction, and gastrointestinal bleeding. The procedure time was measured from fixing to successful release of OTSC in the lesion. Primary technical success was defined as the adequate deployment of the OTSC on the target lesion. Clinical success was defined as a composition of improvements in abdominal pain and persistent closure of the perforation that was verified by a CT scan. In cases of recurrence, retreatment of a lesion with a second intervention was allowed.

Statistical analysis

Data analysis was performed using SPSS for Windows, Version 17.0 (SPSS Inc, Chicago, Illinois). Kolmogorov–Smirnov test was used to determine if the distributions of continuous variables were normal. Continuous variables are presented as mean ± SD or median (minimum–maximum) unless otherwise noted. Student's t test was used to compare means between groups; Mann–Whitney U test was used to compare the median values. Nominal data were analyzed by Pearson's or Fisher's exact test, where applicable. A p value < 0.05 was considered statistically significant.

Results

A total of 132 consecutive records of patients with gastrointestinal perforation were initially retrieved from the database. Twenty-six patients were excluded from the study due to a diagnosis of lower digestive tract perforation ($n = 12$) or treatment with emergency operations ($n = 14$). Of the 106 patients included in the study, 26 were treated with OTSC (OTSC group) and 80 were treated with pharmacotherapies as the initial choice (control group). The detailed patients' demographic and baseline information are summarized in Table 1. No significant differences in age ($p = 0.073$), gender composition ($p = 0.182$), Boey score ($p = 0.847$), or MPI scores ($p = 0.113$) were noted between the two treatment groups.

The sites and sizes of perforation were assessed by endoscopic examination in all 26 patients treated with OTSC. In our study, the mean lesion size of perforation was 5.0 ± 1.0 mm in this group and were located to duodenal

Table 1 Demographic information and baseline characteristics of the patient population

	OTSC group $N=26$	Control group $N=80$	p value
Median age (years)	60.5 (IQR 1.25–78.25)	55 (IQR 27.25–67.0)	0.073
Male/female (n/n)	17/9	64/16	0.182
Boey score	1 (IQR 0–2)	1 (IQR 0–2)	0.847
MPI	5.0 (IQR 4.75–15.5)	11 (IQR 6.0–18.5)	0.113
Location of lesions			
Stomach	7 (26.9%)	7 (8.8%)	N/A
Ulcer	2 (7.7%)	7 (8.8%)	
Iatrogenic	5 (19.2%)	0/80	
Duodenum	18 (69.2%)	17 (21.2%)	
Gastro-jejunal anastomotic lesion	1 (3.8%)	0/80	
Unknown	0/26	56 (70.0%)	

($n=18$), gastric ($n=7$), and anastomotic ($n=1$) regions. In the control group, radiological examination and abdominal laparotomy were used for clinical diagnosis and treatment-response assessments. The sites of perforation were unlocated in up to 70% patients in those who were examined radiologically. The sites of perforation were located to duodenal bulb ($n=17$) and stomach ($n=7$) in patients who underwent laparotomy.

The TSR in the OTSC group was 100% (26/26) (Fig. 1). Successful closure of the lesion was mainly achieved by deploying an OTSC 12/6t (76.9%, 20/26), but OTSC 12/6gc (15.4%, 4/26), OTSC 11/6t (3.8%, 1/26), and OTSC 14/6t (3.8%, 1/26) were also used. None of the patients experienced any complications associated with OTSC placement in our study. The mean procedure time was 10.0 ± 2.5 min.

The CSR was 100% (26/26) in the OTSC group and 57.5% (46/80) in the control group. Subsequent operations for diagnosis and/or treatment of recurrent ulcer after discharge from the hospital including abdominal laparotomy and peritoneal lavage were not required for any of the patients in the OTSC group but were required for 30.0% (24/80) of patients in the control group ($p<0.001$, Fisher's exact test). All patients in the OTSC group were discharged from the hospital. However, the mortality rate was 13.8% (11/80) in the control group, higher than the OTSC group ($p=0.062$). The causes of death were uncontrolled sepsis followed by advanced multiple organ failure (8/11), heart failure (2/11), and gastrointestinal bleeding (1/11). A subgroup analysis found that the patients who died ($n=11$) scored 2 (interquartile range [IQR] 1–2) on the Boey scale and 26 (IQR 11–31) on the MPI scale, the patients who required subsequent surgeries ($n=23$) scored 1 (IQR 0–2) on the Boey scale and 17 (IQR 12–26) on the MPI scale, and the patients who achieved clinical success ($n=46$) scored 1 (IQR 0–2) on the Boey scale and 9 (IQR 4–13) on the MPI scale.

Other key outcome measures are summarized in Table 2. The time to oral feeding was significantly shorter in the OTSC group (3.5 days, IQR 2.0–5.25) compared with the control group (7.0 days, IQR 5.0–9.0; $p<0.001$). However, no significant difference was noted in the length of hospital stay ($p=0.439$) or antibiotic use ($p=0.237$). The serum albumin levels were 34.2 ± 7.3 g/L in the OTSC group and 32.7 ± 6.8 g/L in the control group.

Discussion

The endoscopic procedure OTSC has not been routinely used as a treatment option for PPU, despite the benefits the procedure offers. In our study, we noted a lower mortality rate in the OTSC group and all the patients were discharged without additional surgical procedures, which could be attributed to the fact that the procedure enables clear location of the perforation, accurate evaluation of lesion sizes, and reliable assessment of the patients' response to therapy.

The operation time of OTSC is less than 10 min, substantially shorter than laparotomy (70 min) and laparoscopy (82 min) reported in an earlier study [12]. However, two patients in the OTSC group underwent a second OTSC procedure, which was due to early detachment of the clip and an unhealed perforation which might be related to malnutrition. Some studies hypothesized that hypoalbuminemia (< 37 g/L) was the strongest single predictor of mortality in PPU patients [13]. Poor nutritional conditions also could reduce the combination and transport of antibiotics and associated effects. The serum albumin levels in our two patients were 31.1 g/L and 32 g/L, respectively, which was lower than the average level. Early oral intake helps mucosal healing and shortens the time needed for recovery. Theoretically, OTSC procedure does not affect the motility of the patients and allows the patients the option to take food orally as soon as the procedure is completed. However, we did not observe oral food intake in the clinical setting, which might be because the patients preferred avoiding expected abdominal pain after eating, and therefore were non-compliant with doctor's recommendation.

The MPI and the Boey score system could be used to predict outcomes. Muller et al. considered an MPI of > 21 as one of predictive factors for septic complications [14]. A Boey score of 3 was considered contraindicative for laparoscopic intervention, as it is associated with high mortality and morbidity rates [15]. No death occurred in the OTSC group when the mean Boey score was 1 and the mean MPI score was 5. In the control group, the mean

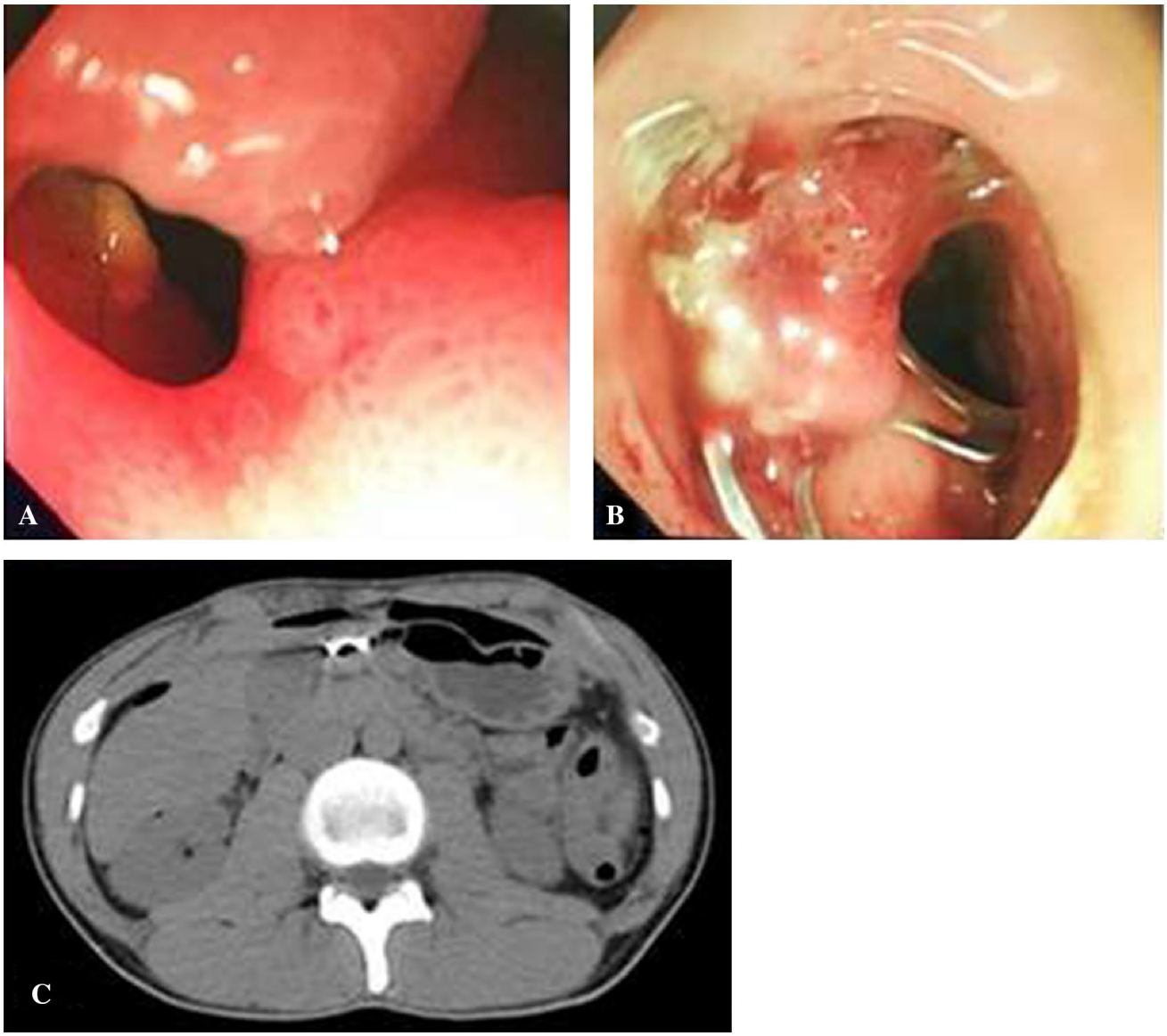

Fig. 1 **A** A perforated peptic ulcer was found in the greater curvature of the duodenal bulb through endoscopic examination; **B** the perforation was successfully closed by OTSC; **C** post-operative CT scan revealed the location of OTSC

Table 2 The main outcomes

Outcome Index	OTSC group $N=26$	Control group $N=80$	p value
Hospital stay (day)[a]	8.5 (IQR 6.75–11.25)	9.0 (IQR 8.0-12.75)	0.439
Antibiotic use (day)[a]	8.5 (IQR 4.0–11.0)	9.0 (IQR 7.0–12.0)	0.237
Time to resuming oral feeding (day)[a]	3.5 (IQR 2.0-5.25)	7.0 (IQR 5.0–9.0)	0.000
Surgery needed (n, %)[b]	0/26	24 (30.0%)	0.000
Death (n, %)[b]	0/26	11 (13.8%)	0.062

[a]Data were analyzed by non-parameter test

[b]Data were analyzed by Fisher's exact test

Boey score was 2 and MPI score was 26 in the patients who died, and the mean Boey score was 1 and the mean MPI score was 17 in the patients who required subsequent surgeries. This observation was consistent with the report by Tas et al. [16] and Guadagni et al. [17].

Identifying risk factors for infections requires peritoneal lavage that would inform treatment selection. The OTSC procedure does not offer the benefits of therapeutic lavage that could prevent sepsis associated with abdominal contamination. However, lesion closure by OTSC is not inferior to those who are only treated with non-intervention approach. Our study found that the MPI score and Boey score are predictive factors in therapeutic decision making. Furthermore, an important direction for future study is to identify additional predictive factors for sepsis which would facilitate selecting the most appropriate treatment approach.

Our study has several limitations. Firstly, the study is retrospective, where the predictors for the outcome of OTSC in PPU need further investigation. The diameter of the perforation and the severity of abdominal contamination that contribute to the prognosis should be considered when the treatment choice is made. One of the identified predictors for OTSC closure outcome is that the size of the perforation should be smaller than 15 mm within the workable limitation as it is difficult to completely close perforation with a diameter of > 30 mm according to previous studies [18, 19]. For patients with severe peritoneal infection and/or inflammation, further evaluation of indicators for the use of percutaneous catheter drainage, such as the Boey and MPI scale, is needed. Additionally, there were 5 cases with delayed gastric perforation as complication of endoscopic submucosal dissection in the OTSC group. However, the perforation of these patients has not been repaired immediately and the baseline severity of illness in the OTSC group showed no significant difference when compared to that in the control group; this limitation may not confuse the results. Future study will examine the efficacy of OTSC for perforation results from different causes. Another limitation of the study is the relatively short follow-up period (1 month), as all patients in the OTSC group recovered and were discharged in 1 month. Long-term outcomes, including the time of OTSC detachment, long-term complications, and risk factors for recurrent leakage at the repair site, among others, should be further explored.

Our experience demonstrated the clinical success of OTSC as a treatment of mild to moderate PPU with a diameter of less than 15 mm. The procedure is well tolerated with the benefits of early oral feeding after closure. Further studies in a large population will be needed to confirm its effectiveness and safety.

Compliance with ethical standards

Disclosure Dr. Jing-Jing Wei, Xue-Ping Xie, Ting-Ting Lian, Zhi-Yong Yang, Yu-Feng Pan, Zhen-Lv Lin, Guang-Wei Zheng, and Ze-Hao Zhuang have no conflicts of interest or financial ties to disclose.

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