

# Direct endoscopic necrosectomy at the time of transmural stent placement results in earlier resolution of complex walled-off pancreatic necrosis: Results from a large multicenter United States trial

Linda Yan, Andrew Dargan, Jose Nieto<sup>1</sup>, Reem Z. Shariha<sup>2</sup>, Kenneth F. Binmoeller<sup>3</sup>, Douglas G. Adler<sup>4</sup>, Michael DeSimone<sup>5</sup>, Tyler Berzin<sup>5</sup>, Mandeep Swahney<sup>5</sup>, Peter V. Draganov<sup>6</sup>, Dennis J. Yang<sup>6</sup>, David L. Diehl<sup>7</sup>, Lillian Wang<sup>7</sup>, Asma Ghulab, Nausharwan Butt, Ali A. Siddiqui

Division of Gastroenterology, Department of Internal Medicine, Thomas Jefferson University, Philadelphia, <sup>7</sup>Division of Gastroenterology, Department of Internal Medicine, Geisinger Health System, Danville, PA, <sup>1</sup>Division of Gastroenterology, Borland Groover Clinic, Jacksonville, <sup>6</sup>Division of Gastroenterology, Department of Internal Medicine, University of Florida, Gainesville, FL, <sup>2</sup>Division of Gastroenterology, Department of Internal Medicine, Weill Cornell Medical Center, New York City, NY, <sup>3</sup>Division of Gastroenterology, Department of Internal Medicine, California Pacific Medical Center, San Francisco, CA, <sup>4</sup>Division of Gastroenterology, Department of Internal Medicine, University of Utah, Salt Lake City, UT, <sup>5</sup>Division of Gastroenterology, Department of Internal Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

## ABSTRACT

**Background and Objectives:** EUS-guided drainage, and direct endoscopic necrosectomy (DEN) of walled-off necrosis (WON) using a lumen-apposing metal stent (LAMS) is safe and effective. Early debridement of WON may improve overall clinical outcomes. The aim of this study is to perform a multicenter retrospective study to compare the clinical outcomes and predictors of success for endoscopic drainage of WON with LAMS followed by immediate or delayed DEN performed at standard intervals. **Methods:** Patients with WON managed by EUS-guided drainage with LAMS were divided into 2 groups: (1) those that underwent immediate DEN at the time of stent placement and (2) those that underwent delayed DEN 1 week after stent placement. DEN was subsequently performed every 1–2 week (s). Technical success (successful placement of LAMS), adverse events (AEs), and clinical success (complete resolution of the WON) were evaluated. **Results:** Totally, 271 patients underwent WON drainage with LAMS: 69 who underwent immediate DEN and 202 who underwent delayed DEN. The technical success for LAMS placement was 100% in both groups. There was no significant difference in the overall procedural AEs between the immediate and delayed DEN groups ( $P = 7.2\%$  vs.  $9.4\%$ ;  $P = 0.81$ ). Stent dislodgement during index endoscopy occurred in three patients in the immediate DEN group compared to zero in the delayed DEN group ( $P = 0.016$ ); all three dislodgements occurred during necrosectomy. Clinical success for WON resolution in the immediate DEN group was 91.3% compared to 86.1% in the delayed DEN group ( $P = 0.3$ ). The mean number of necrosectomy sessions for WON resolution was

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com

**How to cite this article:** Yan L, Dargan A, Nieto J, Shariha RZ, Binmoeller KF, Adler DG, *et al.* Direct endoscopic necrosectomy at the time of transmural stent placement results in earlier resolution of complex walled-off pancreatic necrosis: Results from a large multicenter United States trial. *Endosc Ultrasound* 2019;8:172-9.

### Access this article online

#### Quick Response Code:



#### Website:

www.eusjournal.com

#### DOI:

10.4103/eus.eus\_108\_17

### Address for correspondence

Dr. Ali A. Siddiqui, Thomas Jefferson University Hospital, 132 S. 10<sup>th</sup> Street, Main Building, Suite 585, Philadelphia, PA 19107, United States. E-mail: asiddiqu2004@gmail.com

**Received:** 2017-08-10; **Accepted:** 2017-10-24; **Published online:** 2018-06-06

significantly lower in the immediate DEN group compared to the delayed DEN group (3.1 vs. 3.9,  $P < 0.001$ ). Performing DEN at the time of stent placement was an independent predictor for resolution of WON with lesser number of DEN sessions (odds ratio 2.3;  $P = 0.004$ ). **Conclusions:** DEN at the time of initial stent placement reduces the number of necrosectomy sessions required for successful clinical resolution of WON.

**Key words:** Direct endoscopic necrosectomy, EUS, pancreatic walled-off necrosis

## INTRODUCTION

EUS-guided drainage of symptomatic pancreatic fluid collections (PFCs) through transmural stents has been established as the first-line therapy.<sup>[1,2]</sup> PFCs most commonly occur as a complication of acute pancreatitis, and clinically significant PFCs include pancreatic pseudocysts (PC) and walled-off necrosis (WON). The key difference between the types of PFCs is that PCs contain predominately fluid whereas WON collections have varying degrees of solid debris. EUS-guided drainage of PFCs is as clinically effective as surgical and percutaneous approaches, but it also has lower morbidity and cost.<sup>[3]</sup> PC can be adequately drained with stents because the contents can flow easily whereas the debris in WON can occlude the stent or the surrounding cystoenteric fistulous opening, leading to impaired drainage.<sup>[4]</sup> Hence, for WON, transmural drainage alone is often inadequate, and direct endoscopic necrosectomy (DEN) is frequently required.<sup>[5]</sup>

Transmural DEN involves the passage of the endoscope through the cystenterostomy tract into the WON followed by debridement of the necrotic debris within the WON cavity.<sup>[6]</sup> Several studies have demonstrated this approach to be superior to surgical necrosectomy and percutaneous catheter drainage (PCD) in regard to improved clinical outcomes, lower adverse events (AEs), and decreased health-care costs.<sup>[7-9]</sup>

The novel lumen apposing metal stent (LAMS) with both proximal and distal anchor flanges has been designed specifically for the treatment of WON. These metal stents are now commonly used because they have a larger caliber lumen that is more likely to maintain patency, and LAMS has been shown to have high technical (89%–100%) and treatment success rates (93%–100%) for the management of WON.<sup>[10-16]</sup> When a LAMS is inserted for WON drainage, it is easy to both drain and directly gain access to the WON cavity using an endoscope without further balloon dilatation of the cyst-enterostomy tract. DEN is usually

not performed at the time of initial stent placement. DEN is typically delayed because it allows time for the cyst-enterostomy tract formed by the stent to mature and decreases the potential for stent dislodgement and may avoid unnecessary interventions because some WON can resolve with stent drainage alone.<sup>[8]</sup>

There is currently no consensus about the timing of DEN after stent placement in patients with symptomatic WON. Early mobilization and debridement of solid debris by DEN within the WON may improve overall clinical outcomes. The aim of our study was to perform a large multicenter retrospective study to compare the clinical outcomes, AEs, and predictors of success for endoscopic drainage of WON with LAMS with immediate *versus* delayed DEN performed at standard intervals.

## METHODS

### *Patients*

The endoscopy databases at eight tertiary centers were queried for all patients who had undergone EUS-guided drainage/debridement of a pancreatic WON using LAMS between 2012 and 2016. Only patients who underwent DEN after LAMS placement and had a 6-month or greater follow-up were included in the study. A pancreatic WON was defined as a mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that had developed a well-defined inflammatory wall (as per the Revised Atlanta Classification).<sup>[17]</sup>

All WON were characterized by computed tomography or magnetic resonance imaging. The indications for drainage of WON included the following: (1) refractory abdominal pain, (2) gastric outlet or biliary obstruction, (3) ongoing systemic illness, anorexia, and weight loss, (4) rapidly enlarging WONs, and/or (5) infected WONs.<sup>[11]</sup> Patients who had PC, neoplastic cystic lesions, coagulopathy (INR >1.5), thrombocytopenia (platelets <50,000/mm<sup>3</sup>), disconnected pancreatic duct syndrome, and imaging

showing that the WON wall was not in close contiguity (>2 cm) to the EUS probe were excluded from the study. Data on procedural details and overall clinical course of the patient were collected from outpatient and hospital records.

### *Procedure technique*

#### Initial endoscopic drainage of the WON cavity

All patients underwent endoscopy using a linear array echoendoscope under monitored anesthesia care or general anesthesia. Sedation type was decided by the treating physician. Patients were administered broad-spectrum antibiotics before and after the procedure. The site of the WON was examined by the echoendoscope. EUS imaging under Doppler flow guidance was used to assess local vasculature and determine the cyst puncture site (either trans-gastric or trans-duodenal). A 19-gauge needle (Cook Medical, Winston-Salem, NC, USA) was utilized to perform the primary puncture into the WON cyst cavity. Aspiration of contents was then performed to confirm location and send the aspirate for microbiology. A 0.025" or 0.035" guide-wire was inserted through the needle and then coiled into the WON. The needle was then withdrawn while the guide-wire was left in the cyst. In certain cases, needle knife coagulation was used to dilate the cystenterostomy tract. An 8F-10F Soehendra Dilator (Cook Medical, Winston Salem, NC, USA) or a 4 mm or 6 mm wire-guided balloon (Hurricane, Boston Scientific, Natick, MA, USA) was used to dilate the cyst-enterostomy fistula tract based on the preference of the endoscopist. After dilation, the LAMS stent delivery catheter was advanced over the wire and into the WON cavity. The distal flange was deployed under EUS guidance followed by positioning of this flange against the WON wall. Deployment of the proximal flange was then performed under endoscopic guidance. The selection of stent diameter (10 mm or 15 mm) was at the discretion of the endoscopist. The deployed stent lumen was then dilated up to the selected stent diameter with a controlled radial expansion balloon to allow for optimal stent luminal expansion.

#### *Patient follow-up after procedure*

Intravenous antibiotics were administered at time of procedure and were subsequently changed to oral form. In selected patients with persistent or new-onset symptoms after the procedure, a noncontrast CT was done to assess response to treatment and exclude any procedure-related AEs. Patients who remained symptomatic without clinical improvement after 72 h

underwent endoscopic assessment to evaluate for stent malfunction or infection in the WON cavity.

Procedure-related AEs such as perforation, bleeding, hypotension or respiratory distress, and delayed AEs were carefully documented using the electronic medical records of hospital admissions and ambulatory office visits.

Patients in the immediate DEN group underwent a necrosectomy using an upper endoscope advanced through the LAMS and into the WON cavity at the time of the initial stent placement. Patients in the delayed DEN group underwent DEN 1 week after stent placement. DEN was subsequently performed in both groups every 1–2 weeks until the complete resolution of the necrotic cavity as confirmed endoscopically and by cross-sectional imaging.

All patients underwent imaging with a contrast-enhanced CT of the abdomen 4 weeks after initial stent placement to evaluate the size of the WON. The stent was removed if complete WON decompression was achieved, defined as complete resolution of the WON without any residual fluid component. Patients were then followed at regular intervals in an ambulatory setting for at least 6 months after stent removal and repeat imaging was performed if there was any clinical suspicion of WON recurrence.

### *Outcomes measures*

The primary outcome of this study was to evaluate the clinical success rate of endoscopic WON drainage, defined as complete resolution of WON cavity and resolution of patient's symptoms without need for additional intervention at 6-month follow-up, in the immediate and delayed DEN groups.

The secondary treatment outcome measures assessed were as follows: (1) technical success (ability to access and drain a WON by placement of transmural stents), (2) procedure-related AEs, (3) delayed AEs, (4) the need for endoscopic reintervention after the initial procedure, (5) total number of endoscopic sessions needed to achieve WON resolution, (6) the need for additional concomitant PCD, and (7) WON recurrence rates after stent removal.

Procedural AEs were defined as complications that occurred within 7 days after the procedure, and late AEs were those that occurred more than 7 days after

the initial procedure. Reinterventions were defined as the need for repeat WON debridement as a result of stent occlusion/migration, WON cavity infection, or enlarging WON size leading to symptoms.

### Statistical analysis

This was a retrospective cohort study. We divided the participants into two groups: (1) those that underwent immediate DEN at the time of stent placement and (2) those that underwent delayed DEN 1 week after stent placement. Chi-square tests of independence and generalized linear modeling (GLM) were performed on categorical and continuous variables, respectively, to assess the impact of DEN timing. All initial GLMs are univariate, with DEN timing as the only predictor. A multivariate GLM was also run to assess the impact of when DEN was performed in the presence of age, sex, WON size, and short-term AEs indicator on the odds of a successful WON resolution. The Akaike information criterion was used to determine the most appropriate link function in the GLMs for each outcome. Statistical significance was determined *a priori* at  $P \leq 0.05$ .

## RESULTS

### Baseline characteristics

We evaluated 271 patients with symptomatic pancreatic WONS in whom EUS-guided drainage

using LAMS was performed. The mean age of the patients was 54.3 years, and 54% were female. The overall etiologies of the patients' pancreatitis were as follows: gallstones (40.2%), alcohol (24.4%), idiopathic (17.7%), trauma (5.5%), hypertriglyceridemia (4.8%), and other causes (4.8%). WON were located in the pancreatic head (16.6%) and body/tail (83.4%). The patient and WON characteristics of the two groups are summarized in Table 1. There were 69 patients who underwent immediate DEN and 202 who underwent delayed DEN. Patients in the delayed DEN group had significantly larger WON as compared to the immediate DEN group (111 *vs.* 96 mm;  $P = 0.025$ ).

### Procedure characteristics of initial EUS-guided WON drainage procedure

Transgastric drainage was performed in 156 patients (57.6%) while 114 patients (42.1%) received transduodenal drainage. Simultaneous ERCP was performed in 9/271 (3.3%) of patients, of which all but one patient was in the immediate DEN group. Pancreatic duct stents were placed in five of the eight patients who underwent immediate DEN. Only one patient in the delayed DEN group underwent a concomitant ERCP during or immediately after the drainage procedure and had a pancreatic duct stent placed.

**Table 1. Patient demographics and pancreatic fluid collection characteristics**

	Initial DEN (n=69)	Late DEN (n=202)	P
Gender			
Female	17	129	0.001
Male	51	73	
Mean age (years)	54.79	54	0.52
Race			
White	53	158	0.86
Black	8	21	
Hispanic	1	6	
Other	7	15	
Pancreatitis etiology			
Gallstone	26	83	0.67
Alcohol	17	49	
Idiopathic	10	38	
Trauma	4	11	
Autoimmune	1	1	
High triglycerides	4	9	
Drug related	6	5	
Mean WON long-axis measurement (mm)	96	111	0.025
Site of WON			
Pancreatic head	13	32	0.33
Pancreatic body/tail	56	170	

DEN: Direct endoscopic necrosectomy, WON: Walled-off necrosis



**Technical success**

The technical success for LAMS placement was 100% in both groups. In the immediate DEN group, the diameters of the stents were 15 mm in 67 patients (97%) and 10 mm in 2 (3%) patients. In the delayed DEN group, the diameters of the stents were 15 mm in 198 patients (98%) and 10 mm in 4 (2%) patients.

**Procedural adverse events**

There were no significant differences in the overall procedural AEs between the immediate and delayed DEN groups (7.2% *vs.* 9.4%, respectively; *P* = 0.81).

In the immediate DEN group, procedure-related AEs occurred in five patients (7.2%). Two patients developed super-infection requiring intravenous antibiotics. Three (4.3%) patients in the immediate DEN group were found to have LAMS dislodgement and all of which occurred during immediate necrosectomy. The LAMS was repositioned successfully into the WON using grasping forceps in all three patients, patients were treated with intravenous antibiotics, and none of the patients required surgical intervention.

In the delayed DEN group, procedure-related AEs occurred in 19 patients (9.4%). Eight patients had postprocedural self-limited bleeding at the site of LAMS placement. Super-infection requiring intravenous antibiotics occurred in eight patients. Three patients developed perforation during the cyst-enterostomy as a result of stent maldeployment by the endoscopist. There was no LAMS dislodgement in the delayed DEN group at the time of initial placement.

Stent dislodgement during the index endoscopy was significantly higher in the immediate DEN group (*n* = 3) compared to the delayed DEN group (*n* = 0) (*P* = 0.016).

**Delayed adverse events**

There were no significant differences in the delayed AEs between the immediate and delayed DEN groups (7.2% *vs.* 12.9%, respectively).

In the immediate DEN group, delayed AEs occurred in five patients (7.2%). Three (4.3%) patients developed infection of the WON cavity that was effectively treated with intravenous antibiotics. One (1.4%) patient developed stent occlusion and one (1.4%) patient had LAMS migration.

In the delayed DEN group, delayed AEs occurred in 26 patients (12.9%). Seven (3.5%) patients developed infection of the WON cavity requiring intravenous antibiotics. Nine (4.4%) patients developed stent occlusion, and ten (4.9%) patients had LAMS migration.

There was no significant difference in the stent migration rate in the immediate DEN and delayed DEN groups (1.4% *vs.* 4.9%, respectively, *P* = 0.296). Stent migrations in both groups occurred spontaneously and the stent passed without incidence. The procedural characteristics and AEs are summarized in Table 2.

There was no significant difference in stent occlusion rates between the immediate and delayed DEN groups (1.4% *vs.* 4.4%, respectively; *P* = 0.46).

**Direct endoscopic necrosectomy**

In the immediate DEN group, 38 patients had one necrosectomy session, 11 patients had 2 necrosectomy sessions, 10 patients had 3 necrosectomy sessions, and 10 had four or more necrosectomy sessions to achieve WON resolution. Hydrogen peroxide-assisted necrosectomy was performed in six patients (8.7%). Nine patients (13%) required nasocystic tube (NCT) placement with irrigation, which was maintained for 3–7 days. Seven patients (10.1%) with mild adherent debris required placement of a plastic pigtail stent within the LAMS.

In the delayed DEN group, 33 patients underwent one necrosectomy session, 51 patients underwent

**Table 2. Procedural characteristics and adverse events**

	Initial DEN (n=69)	Late DEN (n=202)	<i>P</i>
Site of cystenterostomy			
Stomach	56	100	0.001
Duodenal bulb	13	101	
Procedural technical success (%)	100	100	1
Procedural adverse events			
None	65	176	0.12
Bleeding	0	8	0.20
Suprainfection	2	13	0.36
Perforation	0	3	0.57
Other	2	1	0.16
Late adverse events			
None	64	174	0.2
Infection	3	7	0.71
Stent occlusion	1	9	0.46
Stent migration	1	10	0.29

DEN: Direct endoscopic necrosectomy

2 necrosectomy session, 49 patients had 3 necrosectomy sessions, and 69 patients had 4 or more necrosectomy sessions to achieve WON resolution. Hydrogen peroxide-assisted necrosectomy was not performed in any of these patients. 48 patients (23.8%) required nasocystic tube (NCT) placement with irrigation. Five patients (2.5%) with adherent debris to the LAMS after placement which required placement of a concomitant plastic pigtail stent within the LAMS.

### Clinical success

While the clinical success for WON resolution in the immediate DEN group was higher compared to the delayed DEN group, this was not a significantly different (91.3% *vs.* 86.1%, respectively;  $P = 0.3$ ). Patients whose WON did not resolve with endoscopic therapy required additional interventions in the form of percutaneous or surgical drainage. Seven patients (10.1%) in the immediate DEN group and 28 patients (13.9%) in the delayed DEN group required additional interventions for complete WON drainage ( $P = 0.53$ ).

The mean number of necrosectomy sessions required for WON resolution after initial LAMS placement was significantly lower in the immediate DEN group compared to the delayed DEN group (3.1 *vs.* 3.9, respectively;  $P < 0.001$ ). Nearly 34% of patients in the delayed DEN group required four or more endoscopic sessions for DEN following LAMS placement in comparison to only 14.5% of patients in the immediate DEN group.

On multivariable analysis, the sole positive predictor for earlier resolution of WON was performing DEN at the time of initial stent placement (OR = 2.3, 95% CI: 1.06-4.73;  $P = 0.004$ ), even after adjusting for age, sex, WON size, and AEs [Table 3].

**Table 3. Multivariate data outcomes in patients who underwent successful walled-off necrosis drainage**

Characteristic	OR	95% CI	P
Delayed DEN	Reference (1.00)	-	-
Immediate DEN	2.3	1.06-4.73	0.004
Age	1.04	0.06-0.97	0.41
Sex	0.51	0.23-2.1	0.46
Size of WON	0.98	0.97-1.02	0.73
Procedural adverse events	1.67	0.66-3.76	0.52

DEN: Direct endoscopic necrosectomy, WON: Walled-off necrosis, CI: Confidence interval, OR: Odds ratio

### Patient follow-up

Symptomatic PFC recurrence after stent removal occurred in one patient in the immediate DEN group as compared to 5 patients in the delayed DEN group ( $P = 1.0$ ). The endoscopic session and success rates of the two groups are summarized in Table 4.

## DISCUSSION

EUS-guided drainage through transmural stents has been firmly established as the preferred, first-line therapy in the management of pancreatic WON.<sup>[1-3]</sup> In comparison studies to surgical and percutaneous approaches of PFC management, endoscopic therapy has been shown to have equal clinical effectiveness to the traditional approaches, but with lower complication rates and significantly lower morbidity and mortality rates as compared to surgery. Previously, double-pigtail plastic stents (DPT) were utilized as the first-line endoscopic accessory to achieve drainage of contents from PFCs. DPTs were inexpensive and had low complication risks; however, their small diameter (7–10 Fr), risk of migration, high rates of stent occlusion, and need for multiple stent placements to obtain adequate drainage, and debridement were major, inherent disadvantages of their use in the management of WON that limited their use overall.<sup>[18-20]</sup>

Limitations in the conventional accessories used to manage WON led to the development of LAMSS which have been shown to have high technical and treatment success rates for the drainage/debridement of WON.<sup>[13,15,16]</sup> These stents are now widely used because the large inner diameter of these stents is more likely to maintain patency. Furthermore, the design allows DEN of WONs after stent deployment by passage of the standard endoscope through the stent lumen and into the WON cavity without stent removal and without further balloon dilation; in addition, the anchoring flanges prevent stent dislodgement while performing the debridement.<sup>[5]</sup>

DEN is frequently required in the management of symptomatic WONs because the solid debris in WON can occlude the stent, leading to inadequate drainage, infection of the WON, and incomplete resolution of the WON.<sup>[4,5]</sup> Comparative studies have demonstrated that for infected WON with significant solid debris, endoscopic drainage by insertion of transmural stents alone was inadequate because the solid debris had to be physically removed; the success rate of

**Table 4. Results of EUS-guided drainage/debridement of walled-off necrosis**

	Initial DEN (n=69)	Late DEN (n=202)	P
Mean number of endoscopic sessions for complete WON resolution	3.09	3.95	<0.01
Total number of DEN sessions after stent placement			
1	38	33	<0.001
2	11	51	0.14
3	10	49	0.09
4 or more	10	69	0.002
Success rate for endoscopic drainage of WON (%)	91.3	86.1	0.3
Patients that required radiological and/or surgery for final WON therapy (%)	10.1	13.8	0.53
Recurrence of WON after endoscopic stent removal (%)	1.4	2.4	1

DEN: Direct endoscopic necrosectomy, WON: Walled-off necrosis

endoscopic drainage in such patients could be as low as 25%.<sup>[8,9]</sup> A retrospective study which compared DEN with conventional endoscopic transmural drainage for the treatment of WON found that successful resolution was accomplished in 88% of patients who underwent DEN *versus* 45% of those who received standard transenteric drainage ( $P < 0.01$ ).<sup>[8]</sup> Endoscopic transmural stent placement with DEN for WON with large amount of debris continues to be preferred over surgical necrosectomy and PCD because studies have demonstrated that DEN for WONs has superior outcomes and fewer AEs.<sup>[8,9]</sup>

There is still much debate about the timing of DEN after stent placement. Currently, most endoscopists delay performing DEN until at least a week after LAMS placement so as to allow the formation of a fully mature cystenterostomy tract and to reduce the risk of stent dislodgement and to allow fluid, which could obscure visualization, to drain. Conversely, some endoscopist's hypothesize that performing DEN at the time of stent placement allows for early mobilization and debridement of solid debris within the WON, which may contribute to improved overall clinical outcomes.

Our study is the first to compare the clinical efficacy and safety of immediate DEN at the time of LAMS placement to delayed DEN in patients with WON. In the present study, we found excellent technical success rates (100%) in patients in both groups. There were no significant differences in the procedure-related AEs between the immediate and delayed DEN groups (7.5% *vs.* 9.4%, respectively;  $P = 0.81$ ). While the clinical success for WON resolution trended toward being higher in the immediate DEN group compared to the delayed DEN group, this difference was not statistically significant (91.3% *vs.* 86.1%, respectively;  $P = 0.3$ ). On

long-term follow-up, there was no statistical difference in the percentage of patients who required additional therapy in the form of surgical debridement or PCD due to the failure of endotherapy (10.1% in immediate DEN *vs.* 13.9% in delayed DEN).

The most frequent AEs associated with endoscopic drainage and DEN of WON are bleeding perforation, or postprocedure infection.<sup>[21]</sup> Although the anchoring design of LAMS is meant to achieve firm anchorage, there have been reports of stent migration and dislodgement.<sup>[22]</sup> A significantly higher rate of stent dislodgement and migration was found in the immediate DEN group, all of which occurred at the time of stent placement (4.3% in immediate DEN *vs.* 0% in delayed DEN,  $P = 0.016$ ). However, the stent was successfully repositioned with grasping forceps in all patients, and none of the patients required further intervention as a result of stent migration during necrosectomy. This suggests delaying DEN reduces the risk of stent dislodgement; however, there were neither further complications as a result of stent dislodgement nor was the clinical success for WON resolution impaired by the stent dislodgement.

The mean number of procedures required for WON resolution was significantly higher in the delayed DEN group compared to the immediate DEN group (3.95 *vs.* 3.09, respectively,  $P < 0.0001$ ) although this essentially amounted to only one additional procedure. It can thus be hypothesized that early DEN at the time of stent placement may decrease the need for further interventions to achieve successful WON drainage by early mobilization and removal of solid debris in the WON cavity. These findings were further validated by MVA which showed that patients who underwent immediate DEN at the time of stent placement were two times more likely to have earlier resolution of

their WON (odds ratio 95% confidence interval 2.3; 1.06–4.73;  $P = 0.004$ ).

This is the first study that directly evaluates the role of performing DEN at the time of stent placement in comparison to the previously traditional method of delayed DEN for endoscopic WON therapy. Strengths of this study are that it is a multicenter study, the large number of patients evaluated, and clearly defined primary and secondary outcomes.

The main limitation of our study is the retrospective nature of the study with its inherent limitations, such as variable follow-up of patients, quality of cross-sectional imaging at different centers, and variability in the technique of the endoscopist. However, as the participants in each group were not from the same representative sample, our population consisted of a heterogeneous group of patients with WONs who had considerable follow-up postprocedure.

In this study, we have demonstrated that DEN at the time of initial stent placement is safe and effective treatment for patients with walled off necrosis. Early intervention may improve clinical outcomes and expedite resolution of walled-off necrosis, without increasing the risk of immediate complications and while reducing the need for additional procedures. Due to its clinical efficacy, this method of immediate DEN at the time of stent placement may find a role in the management of symptomatic WON. Further, larger scale randomized controlled studies are needed to confirm these results and investigate the AEs related to performing immediate DEN.

#### *Financial support and sponsorship*

This study was funded entirely by existing intramural funds and salary support from the authors' respective institutions.

#### *Conflicts of interest*

There are no conflicts of interest.

## REFERENCES

- Panamonta N, Ngamruengphong S, Kijisrichareanchai K, *et al.* Endoscopic ultrasound-guided versus conventional transmural techniques have comparable treatment outcomes in draining pancreatic pseudocysts. *Eur J Gastroenterol Hepatol* 2012;24:1355-62.
- Johnson MD, Walsh RM, Henderson JM, *et al.* Surgical versus nonsurgical management of pancreatic pseudocysts. *J Clin Gastroenterol* 2009;43:586-90.
- Teoh AY, Dhir V, Jin ZD, *et al.* Systematic review comparing endoscopic, percutaneous and surgical pancreatic pseudocyst drainage. *World J Gastrointest Endosc* 2016;8:310-8.
- Baron TH, Harewood GC, Morgan DE, *et al.* Outcome differences after endoscopic drainage of pancreatic necrosis, acute pancreatic pseudocysts, and chronic pancreatic pseudocysts. *Gastrointest Endosc* 2002;56:7-17.
- Gardner TB, Coelho-Prabhu N, Gordon SR, *et al.* Direct endoscopic necrosectomy for the treatment of walled-off pancreatic necrosis: Results from a multicenter U.S. Series. *Gastrointest Endosc* 2011;73:718-26.
- Li JW, Ang TL. Is endoscopic necrosectomy the way to go? *Gastrointest Intero* 2016;5:193-8.
- Baron TH, Thaggard WG, Morgan DE, *et al.* Endoscopic therapy for organized pancreatic necrosis. *Gastroenterology* 1996;111:755-64.
- Gardner TB, Chahal P, Papachristou GI, *et al.* A comparison of direct endoscopic necrosectomy with transmural endoscopic drainage for the treatment of walled-off pancreatic necrosis. *Gastrointest Endosc* 2009;69:1085-94.
- Seewald S, Groth S, Omar S, *et al.* Aggressive endoscopic therapy for pancreatic necrosis and pancreatic abscess: A new safe and effective treatment algorithm (videos). *Gastrointest Endosc* 2005;62:92-100.
- Bapaye A, Itoi T, Kongkam P, *et al.* New fully covered large-bore wide-flare removable metal stent for drainage of pancreatic fluid collections: Results of a multicenter study. *Dig Endosc* 2015;27:499-504.
- Chandran S, Efthymiou M, Kaffes A, *et al.* Management of pancreatic collections with a novel endoscopically placed fully covered self-expandable metal stent: A national experience (with videos). *Gastrointest Endosc* 2015;81:127-35.
- Gornals JB, De la Serna-Higuera C, Sánchez-Yague A, *et al.* Endosonography-guided drainage of pancreatic fluid collections with a novel lumen-apposing stent. *Surg Endosc* 2013;27:1428-34.
- Itoi T, Nageshwar Reddy D, Yasuda I. New fully-covered self-expandable metal stent for endoscopic ultrasonography-guided intervention in infectious walled-off pancreatic necrosis (with video). *J Hepatobiliary Pancreat Sci* 2013;20:403-6.
- Mukai S, Itoi T, Sofuni A, *et al.* Clinical evaluation of endoscopic ultrasonography-guided drainage using a novel flared-type biflanged metal stent for pancreatic fluid collection. *Endosc Ultrasound* 2015;4:120-5.
- Sharaiha RZ, Tyberg A, Khashab MA, *et al.* Endoscopic therapy with lumen-apposing metal stents is safe and effective for patients with pancreatic walled-off necrosis. *Clin Gastroenterol Hepatol* 2016;14:1797-803.
- Siddiqui AA, Adler DG, Nieto J, *et al.* EUS-guided drainage of peripancreatic fluid collections and necrosis by using a novel lumen-apposing stent: A large retrospective, multicenter U.S. Experience (with videos). *Gastrointest Endosc* 2016;83:699-707.
- Banks PA, Bollen TL, Dervenis C, *et al.* Classification of acute pancreatitis–2012: Revision of the Atlanta classification and definitions by international consensus. *Gut* 2013;62:102-11.
- Krüger M, Schneider AS, Manns MP, *et al.* Endoscopic management of pancreatic pseudocysts or abscesses after an EUS-guided 1-step procedure for initial access. *Gastrointest Endosc* 2006;63:409-16.
- Lopes CV, Pesenti C, Bories E, *et al.* Endoscopic-ultrasound-guided endoscopic transmural drainage of pancreatic pseudocysts and abscesses. *Scand J Gastroenterol* 2007;42:524-9.
- Varadarajulu S, Tamhane A, Blakely J. Graded dilation technique for EUS-guided drainage of peripancreatic fluid collections: An assessment of outcomes and complications and technical proficiency (with video). *Gastrointest Endosc* 2008;68:656-66.
- Ruiz-Clavijo D, de la Higuera BG, Vila JJ. Advances in the endoscopic management of pancreatic collections. *World J Gastrointest Endosc* 2015;7:381-8.
- Shah RJ, Shah JN, Waxman I, *et al.* Safety and efficacy of endoscopic ultrasound-guided drainage of pancreatic fluid collections with lumen-apposing covered self-expanding metal stents. *Clin Gastroenterol Hepatol* 2015;13:747-52.