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# Drainage of pancreatic pseudocysts: endoscopic vs. surgical, a meta-analysis. Is it time for hybridization?

## *Drenaje de los pseudoquistes pancreáticos: endoscópico vs quirúrgico metaanálisis. ¿Es momento de la hibridación?*

Francisco Javier Hernández-Hernández,[*] Lorena Hernández-Guadarrama,[‡] Sergio Hernández-Aguilar,[§] Ricardo Sanabria-Trujillo,[¶] Ricardo Sánchez-Arteaga,[‖] Jesús Serrano-Jaimes[*]

**Keywords:** pancreatic pseudocysts, cystogastrostomy, laparoscopic drainage.

***Palabras clave:*** *pseudoquistes pancreáticos, cistogastrostomía, drenaje laparoscópico.*

**ABSTRACT**

**Introduction:** pancreatic pseudocysts are peripancreatic collections of non-epithelial capsules that, in case of not presenting a spontaneous resolution, need intervention and drainage; different surgical and endoscopic techniques have shown similar efficacy. However, there is no definitive management algorithm since the available evidence is heterogeneous. **Objective:** to compare endoscopic with surgical drainage for treating pancreatic pseudocysts by evaluating the prognostic variables in the existing evidence that directly compares both techniques. **Material and methods:** a systematized search was performed in MedLine databases via PubMed, SCOPUS, LILACS, TRIP DATABASE and by using metadata search and cross-referencing in REFSEEK and CROSSREF of controlled clinical trials and cohort studies over ten years comparing surgical versus endoscopic techniques. Two independent investigators analyzed and compared the information, which a moderator separately audited. A systematic review and meta-analysis were performed. **Results:** six studies were taken to the qualitative and quantitative analysis, with a total of 347 patients, 187 with endoscopic management and 160 with surgical management; therapeutic success was obtained in 95.1% (from 91.1 to 97.7%) of the patients treated with surgery and 87.8% (from 82.2 to 92.1%) of the patients with endoscopy with an OR of 2.41 (95% CI 1.08 to 5.38) in favor of surgical management with statistical significance (p = 0.03) (heterogeneity $I^2$ 0.0%. p = 0.86); 18.3% (from 13.1 to 24.5%) in the surgical group had adverse events, while in only 15.1% (from 10.3 to 21.1) of those treated with endoscopy, there were adverse events, with an OR of 0.90 (95% CI 0.51 to 1.58) (heterogeneity test $I^2$ 12% p = 0.34) no statistically significant difference was found (p = 0.70); 6.07% of those treated with

***RESUMEN***

***Introducción:*** *los pseudoquistes pancreáticos son colecciones peripancreáticas de cápsula no epitelial que en caso de no presentar resolución espontánea, necesitan intervención y drenaje, diferentes técnicas quirúrgicas y endoscópicas han mostrado eficacia similar; sin embargo, no existe un algoritmo de manejo definitivo, ya que la evidencia disponible es heterogénea.* ***Objetivo:*** *comparar el drenaje endoscópico con el quirúrgico para el tratamiento de los pseudoquistes pancreáticos mediante la evaluación de las variables pronósticas contenidas en la evidencia existente que compara directamente ambas técnicas.* ***Material y métodos:*** *se realizó una búsqueda sistematizada en las bases de datos de MedLine Vía PubMed, SCOPUS, LILACS, TRIP DATABASE y mediante el empleo de búsqueda de metadatos y referencias cruzadas en REFSEEK y CROSSREF, de ensayos clínicos controlados y estudios de cohorte en un periodo de 10 años que comparan técnicas quirúrgicas versus endoscópicas, dos investigadores independientes analizaron y compararon la información, la cual fue auditada por separado por un moderador. Se realizó revisión sistemática y metaanálisis.* ***Resultados:*** *seis estudios fueron llevados al análisis cualitativo y cuantitativo, con un total de 347 pacientes, 187 con manejo endoscópico y 160 con manejo quirúrgico, se obtuvo éxito terapéutico en 95.1% (de 91.1 a 97.7) de los pacientes tratados con cirugía y 87.8% (de 82.2 a 92.1) de los pacientes con endoscopia con un OR de 2.41 (IC 95% 1.08 a 5.38) en favor del manejo quirúrgico con significancia estadística (p = 0.03) (heterogeneidad $I^2$ 0.0% p = 0.86); 18.3% (de 13.1 a 24.5) en el grupo quirúrgico presentaron eventos adversos, mientras que en sólo 15.1% (de 10.3 a 21.1) de los tratados con endoscopia sí los hubo, con un OR de 0.90 (IC 95% de 0.51 a 1.58) (test de heterogeneidad $I^2$*

[*] Fourth-year resident of General Surgery.
[‡] Third-year resident of General Surgery.
[§] Chief of the Surgery Division, Head of the General Surgery course.
[¶] Assistant Professor of General Surgery.
[‖] Physician in General Surgery, Endoscopic Surgery, and Bariatric Surgery.

Durango Sanatorium. Mexican School of Medicine. La Salle University of Mexico.

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endoscopy had adverse events, with an OR of 0.90 (95% CI 0.51 to 1.58).70); 6.07% of the cases in the surgery group showed recurrence, 8.12% showed this characteristic in the endoscopy group with an OR of 1.54 (95% CI from 0.48 to 4.98) and a heterogeneity $I^2$ 29% p = 0.24, without statistical significance (p = 0.47). **Conclusion:** surgical techniques are slightly superior to endoscopic techniques in terms of therapeutic success. No statistically significant difference was found in recurrence and adverse events. The arrival of emerging techniques such as Hybrid NOTES and luminal apposition stents present characteristics that promise to solve the problems currently faced by both techniques. However, it is still necessary to carry out studies focusing on risk stratification based on anatomical variables, probability of recurrence, and complications to determine which patient is a candidate for each procedure.

*12% p = 0.34) no se encontró diferencia estadísticamente significativa (p = 0.70); 6.07% de los casos en el grupo de cirugía mostraron recurrencia, 8.12% evidenciaron esta característica en el grupo con endoscopia con un OR de 1.54 (IC 95% de 0.48 a 4.98) y una heterogeneidad $I^2$ 29% p = 0.24, sin significancia estadística (p = 0.47).* ***Conclusión:*** *las técnicas quirúrgicas son ligeramente superiores a las endoscópicas en términos de éxito terapéutico, no se encontró diferencia estadísticamente significativa en la recurrencia y eventos adversos. La llegada de técnicas emergentes como Hybrid NOTES y los stent de aposición luminal presentan características que prometen resolver los problemas que enfrentan actualmente ambas técnicas. Sin embargo, sigue siendo necesario realizar estudios con enfoque en la estratificación de riesgo basado en variables anatómicas, probabilidad de recurrencia y complicaciones que permitan determinar qué paciente es candidato a cada procedimiento.*

## INTRODUCTION

The 2013 Atlanta review defines pancreatic pseudocysts (PP) as encapsulated fluid collections with a well-demarcated non-epithelial fibrous tissue wall outside the pancreas with minimal necrosis, which occurs more than four weeks after the onset of edematous pancreatitis. It manifests during the late phase of the acute episode of moderate to severe pancreatitis.[1] It is the most common cystic lesion of the pancreas, seen in 75-85%.[2] Its pathogenesis is still controversial; however, it is accepted that disruption of the pancreatic duct (PD) allows extra ductal collection of chyme, which is subsequently blocked by detritus, protein plugs, calculi, and inflammatory tissue. Its occurrence has been reported to be related to acute (AP) and chronic pancreatitis, abdominal trauma, or during surgical procedures, being more common in alcoholic pancreatitis.[2] It occurs with an incidence of 1.6-4.5% per year per 100,000 adults, with a prevalence of 10 to 26% of AP, 20 to 40% of chronic pancreatitis (CP), 6 to 15% in idiopathic pancreatitis and 6 to 8% in biliary pancreatitis.[3] It is estimated that 37% of AP cases will develop some acute peripancreatic collection; however, only 7 to 12% will develop PP.[4] There are two traditional management concepts: time to maturity (four to six weeks) refers to the time needed for the fibrous tissue encapsulating the collection to be stable enough to receive treatment without risk of rupture, and time to resolution (four to eight weeks) of treatment needed for spontaneous resolution.[5] They are considered unlikely a spontaneous resolution when they have: 1) > six weeks, 2) chronic pancreatitis (CP), 3) communication with the CP and abnormalities in the pancreaticobiliary junction, 4) cysts surrounded by a thick wall.[6] They are considered susceptible to transpapillary drainage (TD) with the placement of a 5 to 7 Fr stent (ST) directed to the interior of the cyst; when these are smaller than 4 to 6 cm, communicate with the PC and are close to the papilla, this therapeutic approach being beneficial when there is proximal obstruction of the PC due to stenosis or biliary lithiasis. The transluminal approach (cystogastrostomy or cystoduodenostomy) is preferred in patients with larger lesions with symptomatic PP directly adjacent to the gastroduodenal wall (usually less than 1 cm apart).[7] The prevalence of success of the procedure is 97%, with definitive resolution in 80% of the cases. In the long term, it is 65 to 81%, with a recurrence of up to 23% in some series.[8] There are technical aspects that have been evaluated and that have importance in the prognosis. In a randomized clinical trial, mechanical dilatation was compared with

electrocautery (Needle Knife [NK], cystotome, and sphincterotome), finding greater adverse events with the latter technique, the main one is bleeding.[9] Some recent studies have evaluated the use of transluminal fully covered self-expandable metallic ST (FCSEMS); however, no studies evaluate the cost-effectiveness of plastic versus metallic ST in PP. A complete resolution has been reported in 70% of patients with FCSEMS, with 15% adverse events and 15% device migration.[10] The new luminal apposition plastic STs (Axios Xlumina Inc. Mountain View, CA) have been used for cystogastrostomy in a multicenter cohort with 93% complete resolution, 9% adverse events and complications, and 10.5% device migration.[11] A retrospective study in peripancreatic collections evaluated Another self-expandable apposition ST with an electrocautery delivery system (Hot Axios) for drainage. In 52 cases, direct endoscopic necrosectomy (DEN) was performed almost without fluoroscopy assistance, obtaining complete resolution in 92.5% of cases, with no recurrence during follow-up. Treatment failed in six patients due to the persistence of infection, who required surgery.[11] DT and the application of an SP is necessary, especially in patients with CP, lithiasis in the CP, stenosis requiring dilatation + ST, and in the scenario without obstruction but with demonstrable leakage into the cyst from the PD.[12] In case of partial disruption of the PC, an ST is placed to recanalize the area without leakage.[13] It is considered controversial whether the tip of the ST should be placed in the PC or inside the cyst since if it is placed from the PC towards one of the small branches from which the cyst originates, it may prevent it from closing the connection between these two structures, favoring recurrence. The TS is usually removed one to two weeks after its placement via endoscopic retrograde cholangiopancreatography (ERCP). Surgical management is performed for cysts complicated by infection or necrosis, PP associated with pancreatic stenosis, dilated PC, cystic neoplasia, and biliary stenosis refractory to endoscopic treatment. Complications such as stomach compression, duodenum, perforation, and hemorrhage from erosion of arteries and pseudoaneurysms have been reported.[14] The ideal time to perform the procedure is also four to six weeks in search of cystic wall maturation; patients with CP can be treated without delay because wall maturation is already present.[6] Intraluminal drainage is the method of choice for uncomplicated pseudocysts, although it depends on the anatomical topography; in cysts adjacent to the posterior wall of the stomach, cystogastrostomy is performed; in small cysts of less than 4 cm in the head of the pancreas and cysts in the uncinate process, cystoduodenostomy is preferred, while cystojejunostomy is performed in cysts larger than 15 cm. There is considerable controversy about whether cystogastrostomy is superior due to its simplicity, ease, and speed in its performance and a lower tendency to infections; however, it has been related to upper gastrointestinal bleeding.[15,16] Follow-up with magnetic resonance cholangiopancreatography (MRCP) after the cyst's resolution and the transluminal drainage removal is recommended. Evaluating the integrity of the PC is of utmost importance before removing the transluminal ST; the periampullary edema expected due to venous congestion caused by acute pancreatitis can make papillary cannulation difficult.[10] It is recommended that one to two months after the successful procedure perform, an imaging study is suggested to evaluate possible residual collections; if these are not present, it is recommended to remove the ST. In patients with persistence of the pseudocyst, expectant management is adopted for four to six weeks, and in case of persistence, the PC status will be evaluated with MRCP or ERCP. If obstruction, disruption, or residual communication of the cyst is confirmed, an ERCP with transpapillary pancreatic ST placement is recommended. If it persists, empirical ST replacement, dilatation of the transluminal cystostomy, DEN, and endoscopic ultrasound (EUS) guided drainage of the septa are recommended. In case of recurrence, a

surgical approach is considered. According to the literature, complications occur at a frequency of 11 to 37%, including secondary infection, bleeding, perforation, and ST migration.[17,18] The most common complication is an infection, and it is related to the presence of necrosis, so patient individualization and intentional search for necrosis in the pseudocyst is recommended.[18] Bleeding during the procedure is another frequent complication; in one study, balloon dilatation over the guidewire was proposed to omit electrocautery.[19] Perforation has been reported in 3% of cases, occurring mainly when the pseudocyst wall is poorly defined in imaging studies or if it has a distance greater than 1 cm from the intestinal lumen.[20] Although there is no evidence-based recommendation, it is well accepted that those with poor prognostic factors in the cyst anatomy (giant cyst, calcified walls, distance between the cyst and the drainage site) endoscopic management decreases their performance, so they are probably better treated laparoscopically.[21] The surgical approach can be open or laparoscopic; however, it is associated with a morbimortality of 25% in the open procedure versus 5% laparoscopic. In the setting of multiple cysts, gastrointestinal bleeding with distal splenic pseudoaneurysm, duodenal or common bile duct obstruction, painful CP, and cyst in the uncinate process, cyst resection is preferred over internal drainage.[14] Newell et al. found no difference in cyst recurrence concerning morbidity or mortality between cystogastrostomy versus cystojejunostomy.[22]

### Rationale

PPs need more standardization in their management, and there is no universally used treatment algorithm to choose the most appropriate technique given their anatomical characteristics for drainage based on their risk of recurrence and complications. Among the numerous techniques available, endoscopic, and laparoscopic management stand out due to their efficacy, safety profile, and low prevalence of complications; however, current evidence does not allow us to establish a definitive treatment guideline.

Objective: to determine which procedure offers better efficacy and results in the drainage of PP with surgical versus endoscopic techniques by evaluating the prognostic variables contained in the existing evidence that directly compares both techniques.

## MATERIAL AND METHODS

A search of MedLine databases via PubMed, SCOPUS, LILACS, and TRIP DATABASE was performed, limited to clinical trials and cohort studies published from January 2008 to July 2019 with the terms MeSh (pancreatic pseudocyst, peripancreatic collection) (cystogastrostomy, cystoduodenostomy, Roux-en-Y) (drainage, endoscopy, surgical drainage). A search was done using metadata and cross-referencing using the search engines REFSEEK and CROSSREF; articles were reviewed and analyzed with a focus on patient outcomes and prognosis. Data analysis was performed with Cochrane REVMAN 5.3 software using odds ratios with fixed effects and the Cochran-Mantel-Haenszel test. $I^2$ assessed study heterogeneity and reported the results in an effect diagram.

### Selection of studies

Two independent investigators searched studies comparing management with endoscopic and surgical techniques published within the period between January 2008 and July 2019 in material and methods regardless of whether they were prospective or retrospective with several participants greater than 40, with populations older than 18 years and younger than 85. Literature reviews, letters to the editor, case reports, systematic reviews and existing meta-analyses were excluded, by using the Cochrane semaforization tool (Revman 5.3). Studies considered at high risk of bias, studies not published in English or Spanish, and studies with conflicts of interest were eliminated. Ultimately, studies not considered by both investigators were analyzed with a moderator for review.

Data analysis and extraction: 265 publications were obtained by searching

keywords and MeSh terms, 102 by searching metadata and cross-references, obtaining 367 articles for the application of selection criteria and the inclusion and exclusion criteria; 271 articles were eliminated, 96 were included for qualitative analysis of the abstract, excluding 21 duplicate publications, 12 letters to the editor and explanatory notes, 27 case reports, 18 literature reviews and book chapters, three meta-analyses, and four systematic reviews; 10 publications were taken to exhaustive analysis, where three articles were eliminated due to lack of full text, one publication was eliminated due to incomplete data, and six studies were selected for quantitative analysis and synthesis for meta-analysis *(Figure 1)*.

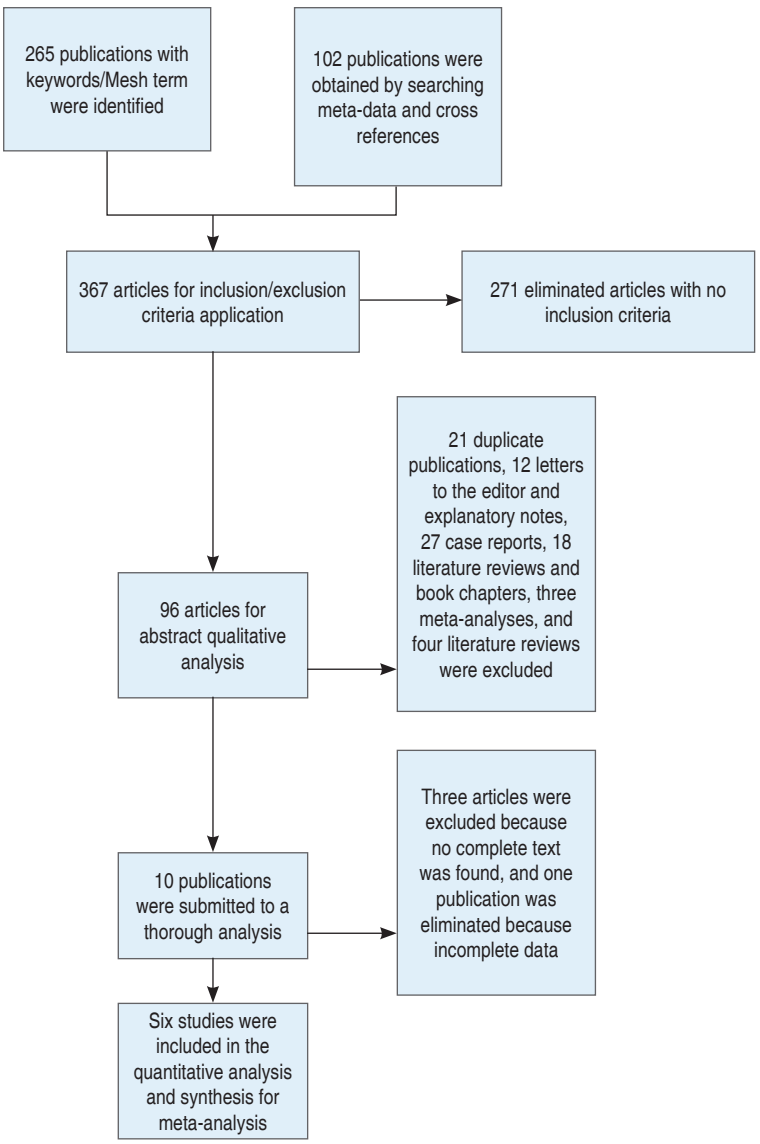



***Figure 1:*** *PRISMA flow chart.*

## RESULTS

No studies directly assessed the laparoscopic versus endoscopic approach with the minimum desired population. Likewise, in different studies, no discrimination was detected between the type of peripancreatic collections, with some frequency of peripancreatic collections with necrosis, among others, observed within the analysis groups. There is wide heterogeneity in the techniques used for both groups and little evaluation of variables identified as important for prognosis, which is not individually analyzed in any articles reviewed about recurrence, therapeutic success, and complications. Likewise, none of the publications considered location, wall, or PD status in the statistical analysis. The risk of bias was evaluated with the Cochrane risk of bias tool, concluding that there was "good" quality evidence in the six included studies. An analysis of the data contained in these studies was performed. A total of 367 patients were evaluated in six publications; only two studies described the follow-up time, and all reported the mean size of the pseudocysts. No uniformity was found in the criteria for surgical drainage used (methodological heterogeneity). Only two studies described the use of pancreatic transpapillary ST in their groups managed with endoscopy. The mean in-hospital stay is reported in only three/six studies; only two studies recorded the mean in-hospital cost. Only in the publication of Saul et al. was performed with a balloon, none of the studies used luminal apposition ST, and all authors used Pigtail. In 2017 Redwan and team published a prospective study conducted from March 2014 to September 2016 with results in a total of 71 patients, with endoscopic management in 35, laparoscopic in 4, and open in 32; 82.9% had immediate success (p = 0.01).

Therapeutic success was obtained in 91.4% of those managed endoscopically, 100% in the laparoscopic group, and 100% in those treated with open techniques. The prevalence of complications after the primary procedure was not significantly different (p = 0.08) between endoscopic 8.6%, laparoscopic 25%, and open 18.8%. No mortality was documented among the three groups; recurrence, reoperation, transoperative time, need for opioids, and in-hospital stay was significantly lower in the endoscopic group. Bleeding was also evaluated, being around 15 ml in the endoscopic procedures and 85 to 100 ml in the surgical drains; no patient required blood transfusions in the three groups. The study is unclear in its choice criteria for one procedure and another. There is an important variability in the number of patients in the different interventions; only four patients were taken to a laparoscopic approach and 35 to endoscopic management.[23] Saluja et al. in 2016 compared a prospective study of cystogastrostomy in 57 patients with PP, they obtained therapeutic success in the endoscopic group in 31 of 35 (89%) patients and 20/20 (100%) in the surgical group; it was associated with the presence of necrosis as the cause of drainage failure. The mean in-hospital stay was 6.4 days in the endoscopic group and 5.9 days in the surgical group. Seventeen percent of the procedures were converted, and complications were reported in 10/35 in the endoscopic group versus 2/20 in the surgical group. The mean size in the endoscopic group was 11 cm, and in the surgical group was 14.2 cm. The study revealed the presence of necrosis in 14/20 in the surgical group and 11/35 in the endoscopic group; it does not specify the techniques used to perform the endoscopic procedures, nor does it specify other variables or poor prognostic factors. It was unclear which techniques were used to select the patients, who would undergo one or the other treatment modality, and did not report the recurrence or the cost of intra-hospital stay.[24] In Mexico, Saul and collaborators carried out a retrospective study in the National Institute of Nutrition, where 64 procedures were evaluated in 61 patients, 21 endoscopic, and 43 with surgical management, and in 16 of the 21 performed endoscopically (76%) drainage was transgastric and in five (24%) it was transduodenal. Therapeutic success was achieved in 90.5% of the patients in the endoscopic group and 90.7% of the surgical patients (p = 0.7) with a prevalence of complications of 23.8 and 25.6% respectively (p = 0.8) and a mortality of zero to 2.3 for each group (p = 0.4). The in-hospital stay was shorter in the endoscopic group, from zero to ten days, compared to the surgical group, from two to 42 days. The cost of the endoscopic group was significantly lower, and recurrence was similar in both groups, 9.5 and 4.5 (p = 0.59). The group of patients treated with endoscopy was associated with ST migration.[25] In a prospective randomized controlled clinical trial in a single institution, 40 patients were evaluated, comparing endoscopic management in 20 patients and surgical management in 20 patients. Therapeutic success was reported in 100% of the patients with surgical management and 95% of the patients with endoscopic management; one of the patients developed pseudocyst recurrence, but this was associated with alcohol abuse; no differences were found in complications and reinterventions. The in-hospital stay was longer in patients with endoscopic management, with a mean of two versus six days in the surgical group (p < 0.001). The mean cost (in American dollars) was lower in patients treated endoscopically at $7,011 versus $15,052 (p = 0.003). The usefulness of this study has been considered limited because the sample was small, and the inclusion data were generated by only one surgeon and two endoscopists at a single institution.[26] Johnson et al. in 2009 published a retrospective study conducted at the *Cleveland Clinic* from December 1998 to October 2005; 49% were treated surgically, 24.39% endoscopically, and 7.11% percutaneously; there was no significant difference in the complication rate, being 20% surgical versus 21% endoscopic.

Pseudocyst resolution was 93.3% in the surgical group and 87.5% in the endoscopic group (p = 0.39). They concluded that both procedures were equivalent in safety and efficacy.[27] In 2009, Melman et al. published a retrospective study from March 1999 to August 2007 at Barnes Jewish Hospital, Washington University Medical Center. Of 83 patients, an endoscopic technique was performed in 45, a laparoscopic in 16, and an open technique in 22. In the endoscopic group, the postoperative in-hospital stay time was 3.9 days, the therapeutic success was 81.2%; 64.4% of the patients with initial endoscopic management did not require further procedures; 13 failed endoscopies were reported, which required an open salvage procedure, and three required percutaneous drainage; major complications within the first 30 days occurred in seven patients (15.6%); of these, three patients, 6.7%, required surgical management. Laparoscopic management was applied in 16 patients; none required conversion to open management. Six of these patients underwent concomitant cholecystectomy; the average in-hospital stay was 6.9 days, the primary success rate was 86.5%, and therapeutic success was obtained in 93.8%; one patient during follow-up developed recurrence. He was treated with endoscopic transgastric drainage; four patients (25%) experienced complications within the first 30 days of the procedure. Open management was performed in 22 patients, six simultaneously with cholecystectomy. The average in-hospital stay was 10.8 days, and therapeutic success was achieved in 90.9%; 22.7% (five patients) developed complications within the first 30 days, which were managed with percutaneous drainage, one patient developed multiple organ failure and required mechanical ventilation and an in-hospital stay of 82 days, 4.5% (one patient) had surgical site infection, 9.1% (two patients) had post incisional hernias. The comparison between the three methods considerably favored the laparoscopic procedure (p < 0.01), the therapeutic success was not significantly different (p > 0.05), and the incidence of late complications at 30 days was not statistically significant (p > 0.05). However, the study analysis did not discriminate between the technique performed, cystogastrostomy versus cystojejunostomy, which entail different complications, recovery time, and success rates, and did not consider the anatomical characteristics of the PP, which implies a higher probability of failure in endoscopic management. The data were collected retrospectively and may be incomplete, particularly concerning follow-up. The evaluation of late complications during follow-up was performed exclusively in a clinical manner, using imaging studies only in those patients with suspicion. The study population was heterogeneous and did not discriminate between etiologies of pancreatitis or comorbidities. The study did not describe the size of the cystostoma (usually < 2 cm), inadequate drainage of the cyst, the type of TS used, and other features, which are characteristics that radically influence the therapeutic success *(Table 1)*.[28]

### Therapeutic success

The definition of therapeutic success was included in four of the six studies; for the purposes of this research, it is defined as the clinical resolution of symptoms during the first four weeks of patient follow-up with a complete resolution or decrease in the size of the collection to 2 cm or less on the computerized tomography scan. We found a therapeutic success ratio in the surgically managed group of 95.1% (91.1 to 97.7%) and 87.8% (82.2 to 92.1%) in the endoscopically managed group with an OR of 2.41 (95% CI 1.08 to 5.38) in favor of surgical management with statistical significance (p = 0.03). Heterogeneity tests found and $I^2$ 0.0% (p = 0.86 heterogeneity) *(Figure 2)*.

### Adverse events

Four of the six studies contain definitions of adverse events. A prevalence of adverse events was observed in the group managed with surgery of 18.3% (13.1 to 24.5%), and in the group managed with endoscopy of

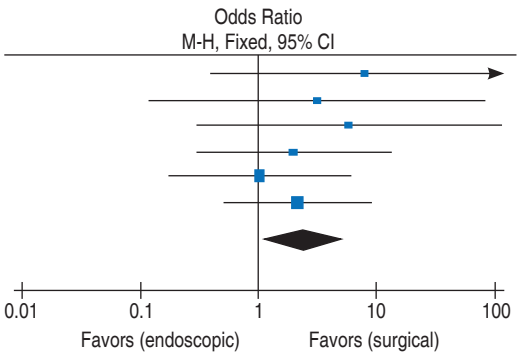
**Table 1: Summary of characteristics in the studies analyzed.**

| Features | Study | | | | | |
|---|---|---|---|---|---|---|
| | **Redwan, 2017 N = 71** | **Saluja, 2016 N = 55** | **Saul, 2015 N = 61** | **Varadarajulu, 2013 N = 40** | **Johnson, 2009 N = 54** | **Melman, 2009 N = 83** |
| Design | Retrospective | Randomized clinical trial | Retrospective | Randomized clinical trial | Retrospective | Retrospective |
| Follow-up [months] | Not reported | Not reported | Not reported | 24 | | Not reported |
| Endoscopy | | | | | 0 a 43 | |
| Surgery | | | | | 1 a 74 | |
| Size of pseudocysts assessed [cm] | | | | | | |
| Endoscopy, mean | 10.3 | 11.0 | 6.7 | 10.5 | 9.5 | 9.1 |
| Surgery, mean | 10.0 | 14.2 | 10.0 | 11.0 | 9.1 | 9.5 |
| Presence of disconnected PD syndrome | | | | | | |
| Endoscopy | Not reported | Not reported | 13 | 15 | Not reported | Not reported |
| Surgery | | | 7 | Not reported | | |
| Transpapillary pancreatic stent | 2 de 35 | Not reported | Not reported | 10 de 50 | Not reported | Not reported |
| Therapeutic success | | | | | | |
| Endoscopy, n (%) | 32 (91.4) | 31 (85.0) | 19 (90.5) | 19 (95.0) | 21 (87.5) | 38 (84.4) |
| Surgery, n (%) | 36 (100.0) | 20 (100.0) | 39 (90.7) | 20 (100.0) | 28 (93.3) | 35 (92.1) |
| p | 0.01 | 0.14 | 0.74 | 0.50 | 0.39 | ≤ 0.01 |
| OR | 0.12 | 0.17 | 0.97 | 0.32 | 0.5 | 0.23 |
| Adverse events | | | | | | |
| Endoscopy, n (%) | 3 (8.6) | 10 (28.5) | 5 (23.8) | 0 (0) | 3 (12.5) | 7 (15.6) |
| Surgery, n (%) | 7 (19.4) | 2 (10.0) | 11 (25.5) | 2 (10.0) | 6 (20.0) | 5 (22.7) |
| p | 0.08 | 0.17 | 0.87 | 0.24 | 1.0 | ≥ 0.05 |
| OR | 0.38 | 0.27 | 0.91 | 0.47 | 0.57 | 0.63 |
| Recurrence | | | | | | |
| Endoscopy, n (%) | 4 (11.4) | Not reported | 2 (9.5) | 0 (0) | Not reported | Not reported |
| Surgery, n (%) | 1 (2.78) | | 2 (4.5) | 1 (15.0) | | |
| OR | 0.3048 | N/A | 2.16 | 1 | N/A | N/A |
| In-hospital stay [days] | | | | | | |
| Endoscopy, mean | 3.9 | 6.4 | 0 | 2 | Not reported | Not reported |
| Surgery, mean | 7.1 | 5.9 | 7 | 6 | | |
| In-hospital cost [USD] | | | | | | |
| Endoscopy, mean ± SD | Not reported | Not reported | 3,092 ± 1,705 | 7,011 ± 4,171 | Not reported | Not reported |
| Surgery, mean ± SD | | | 7,734 ± 623 | 15,052 ± 10,670 | | |
| p | N/A | N/A | < 0.0001 | 0.001 | N/A | N/A |

PD = pancreatic duct. N/A = not applicable.

| Study or subgroup | Endoscopic Events | Endoscopic Total | Surgical Events | Surgical Total | Weight (%) | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Redwan, 2017 | 36 | 36 | 32 | 35 | 5.5 | 7.86 [0.39, 158.01] |
| Varadarajulu, 2013 | 20 | 20 | 19 | 20 | 5.7 | 3.15 [0.12, 82.16] |
| Saluja, 2016 | 20 | 20 | 31 | 35 | 6.8 | 5.86 [0.30, 114.65] |
| Johnson, 2009 | 28 | 30 | 21 | 24 | 19.1 | 2.00 [0.31, 13.06] |
| Saul, 2015 | 39 | 43 | 19 | 21 | 29.2 | 1.03 [0.17, 6.11] |
| Melman, 2009 | 35 | 38 | 38 | 45 | 33.7 | 2.15 [0.52, 8.97] |
| Total (95% CI) | | 187 | | 180 | 100.0 | 2.41 [1.08, 5.38] |
| Total events | 178 | | 160 | | | |

Heterogeneity: $\chi^2 = 1.91$, df = 5 (p = 0.86); $I^2 = 0\%$
Test for overall effect: Z = 2.15 (p = 0.03)




Fixed effects diagram comparing the results of the therapeutic success regarding endoscopic vs. surgical approaches.

***Figure 2:*** *Therapeutic success.*

| Study or subgroup | Endoscopic Events | Endoscopic Total | Surgical Events | Surgical Total | Weight (%) | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Johnson, 2009 | 3 | 24 | 6 | 30 | 16.6 | 0.57 [0.13, 2.57] |
| Melman, 2009 | 7 | 45 | 5 | 38 | 23.1 | 1.22 [0.35, 4.20] |
| Redwan, 2017 | 3 | 35 | 7 | 36 | 17.8 | 0.39 [0.09, 1.64] |
| Saluja, 2016 | 10 | 35 | 2 | 20 | 14.3 | 3.60 [0.70, 18.46] |
| Saul, 2015 | 5 | 21 | 11 | 43 | 23.9 | 0.91 [0.27, 3.07] |
| Varadarajulu, 2013 | 0 | 20 | 2 | 20 | 4.3 | 0.18 [0.01, 4.01] |
| Total (95% CI) | | 180 | | 187 | 100.0 | 0.88 [0.46, 1.69] |
| Total events | 28 | | 33 | | | |

Heterogeneity: $Tau^2$ 0.08; $\chi^2 = 5.67$, df = 5 (p = 0.34); $I^2 = 12\%$
Test for overall effect: Z = 0.39 (p = 0.70)

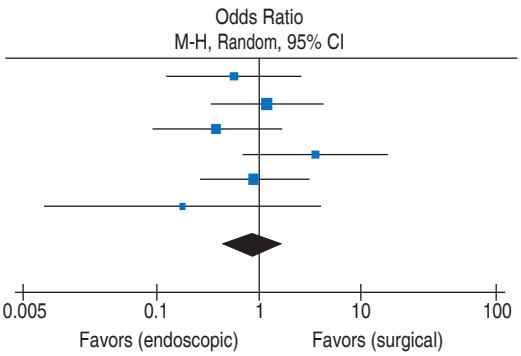



Diagram of random effects showing adverse events found with both interventions.

***Figure 3:*** *Adverse events.*

15.1% (from 10.3 to 21.1%), adverse events occurred with an OR of 0.90 (95% CI 0.51 to 1.58) (heterogeneity test $I^2$ 12% p = 0.34) no statistically significant differences were found in both groups (p = 0.70) *(Figure 3)*.

## Recurrence

Only three of the publications analyzed reported recurrence, with a total of 11 of 175 cases corresponding to 6.28% in both groups; 6.07% of the cases in the surgery group showed recurrence, 8.12% evidenced this characteristic in the group managed with endoscopy; with an OR of 1.54 (95% CI 0.48 to 4.98) with a heterogeneity $I^2$ 29% p = 0.24, without statistical significance (p = 0.47) *(Figure 4)*.

## Endoscopy

In the individual review of the available evidence for the group managed with endoscopy, six publications with the inclusion criteria were found, with a total population of 617 participants, of which 526 had resolution of the picture, which represents 86.25% (75.20-97.30%); 122/617 had complications, which represent 19.94% (5.20-26.30%). Recurrence was not reported in one publication, observed in 52/518 cases, representing 9.18% (5.0-15.50%), and 95/617 required salvage surgical management representing 15.39% (2.0-27.50%). The results are detailed in *Table 2*.

Weckman and collaborators reported one of the most extensive series with 179 patients evaluated retrospectively, in whom

endoscopic management was performed during a period from 1998 to 2003 by means of transpapillary drainage, with pancreatic STs of 7 to 10 Fr. Transmural methods were performed in the PP in immediate contact with the duodenal and/or gastric wall by means of a papillotome and NK with subsequent use of an 8 mm balloon dilator. Therapeutic success was achieved in 86.1% of the patients, 13.9% required rescue surgical management, and no mortality was reported during the procedures; however, four patients were excluded from the study due to mortality, and although it is stated that they died of causes unrelated to the management, the circumstances and time of death were not specified. Patients with infected PP were observed within the evaluation, with no difference in effectiveness concerning patients with non-infected PP 86.1%. In half of the patients, necrotic material was reported inside the cyst. Recurrence was reported in 4.8% of patients in a mean of 17.5 months. A 10% complication rate was reported, and seven patients (4%) required salvage surgery. In patients in whom only papillotomy was performed as part of the treatment, successful treatment was reported in 85.3% of these patients, while 14.7% failed and required additional procedures.[29]

Park et al. performed a randomized clinical trial with 60 patients in 2009, comparing ultrasound-guided versus conventional endoscopic management. Treatment was successful in 94% of ultrasound-guided patients and 72% of patients with conventional endoscopic drainage. Complications were reported in 7% of patients in the ultrasound-guided group and 10% in the conventional group. The resolution was achieved in 97 versus 91%. Long-term results found no difference in long-term clinical prognosis, 89 versus 86%.[30]

Kahalek and his team conducted a randomized clinical trial with 53 patients to evaluate the effectiveness of ultrasound-guided versus conventional management over 13 years, in 46 patients; they found no significant differences in therapeutic success between the two groups, 93 versus 94%; However, at six-month follow-up, they reported 84 versus 91%, respectively, complications that occurred in 19% versus 18% and consisted of bleeding with infection n = 3, infection of collections n = 8, ST migration n = 3, and pneumoperitoneum n = 5; only one complication required surgical management.[17]

Seewald et al. evaluated 80 patients with pancreatic collections, a total of 24 pseudocysts, 20/80 abscesses, and 36/80 infected necroses from October 1997 to March 2008. Retrospectively, initial therapeutic success was obtained in 97.5% with clinical resolution of collections in 83.8%, 13/80 required surgical management due to complications or technical difficulties, 5/80 required surgical management after six months due to recurrent collections, and long-term success was reported in 72.5% of patients.[31]

Will and colleagues in a prospective study conducted between 2002-2008 with 147 patients, n = 32 with pseudocysts, n = 81 with abscesses, n = 34 with necrosis, therapeutic success was achieved in 100% of patients guided by external ultrasound and 97% with

| | Endoscopic | | Surgical | | | Odds Ratio |
|---|---|---|---|---|---|---|
| Study or subgroup | Events | Total | Events | Total | Weight (%) | M-H, Fixed, 95% CI |
| Redwan, 2017 | 4 | 35 | 1 | 36 | 19.4 | 4.52 [0.48, 42.59] |
| Saul, 2015 | 2 | 21 | 2 | 43 | 26.4 | 2.16 [0.28, 16.50] |
| Varadarajulu, 2013 | 0 | 20 | 2 | 20 | 54.2 | 0.18 [0.01, 4.01] |
| Total (95% CI) | | 76 | | 99 | 100.0 | 1.54 [0.48, 4.98] |
| Total events | 6 | | 5 | | | |

Heterogeneity: $\chi^2 = 2.82$, df = 2 (p = 0.24); $I^2 = 29\%$
Test for overall effect: Z = 0.73 (p = 0.47)

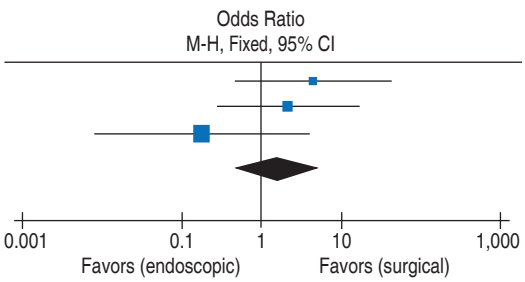



Diagram of random effects showing adverse events found with both interventions.

***Figure 4:*** *Recurrence.*

**Table 2: Evidence on endoscopic treatment.**

| Study | Number | Therapeutic success, n (%) | Complications, n (%) | Recurrence, n (%) | Surgery required, n (%) | Follow-up [months], mean |
|---|---|---|---|---|---|---|
| Baron, et al 2002 | 95 | 82 (86.316) | 17 (17.895) | 9 (9.474) | 7 (7.368) | 25.0 |
| Kahaleh, et al 2006 | 99 | 93 (93.939) | 19 (19.192) | Not reported | 2 (2.020) | 13.9 |
| Weckman, et al 2006 | 170 | 124 (72.941) | 38 (22.353) | 8 (4.706) | 23 (13.529) | 4.1 |
| Park, et al 2009 | 60 | 50 (83.333) | 8 (13.333) | 9 (15.000) | 28 (46.667) | 12.0 |
| Will, et al 2011 | 113 | 110 (97.345) | 19 (16.814) | 17 (15.044) | 13 (11.504) | 21.0 |
| Seewald, et al 2012 | 80 | 67 (83.750) | 21 (26.250) | 9 (11.250) | 22 (27.500) | 31.0 |
| Total | 617 | 526 (86.253) | 122 (19.940) | 52 (9.977) | 95 (13.990) | – |

transmural drainage; the transpapillary drainage reported success in 92. The complications of external drainage were 3.7% transmural and 9.6% transpapillary complications, bleeding n = 3, perforation = a migration of the stent with perforation of the terminal ileum n = 1. After a follow-up of 20.7 months the therapeutic success was 96.2% on average, 96.9% of the PP, abscesses 70.5% and necrosis 94.1% respectively. There was recurrence in 15.4% and a mortality of 0.7% unrelated to the intervention.[32]

In 2002 Baron reported complete resolution in 113/138 patients (82%) with peripancreatic collections managed endoscopically, of which 64 were PP; the success rate in patients with an acute PP was 74%, 23/31 patients. For chronic PP it was 92% 59/64 (p = 0.02). For patients with walled necrosis, only 72% efficacy was reported (p = 0.006). In multivariate analysis, chronic pseudocyst predicted successful drainage (OR 2.1: 95% CI 0-4.5), while necrosis was a predictor of lousy drainage (OR 0.64 95% CI 0-3.1). When the approach was compared, transpapillary (OR 3.1: 95% CI 0.3-67.9) and transduodenal (OR 1.7: 95% CI 0.4-7.0) were suggestive of better therapeutic success, although neither reached adequate statistical significance.[33]

## DISCUSSION

Over the years, different techniques have been described for the drainage of pancreatic pseudocysts. Different research studies have widely evaluated their effectiveness; although percutaneous drainage has been generally discarded as a primary therapeutic measure, the current controversy concerns surgical and endoscopic techniques. Due to the low incidence of the disease, there are not enough studies for its analysis, and unfortunately, those found in the literature are inconsistent in the appropriate application of terminology, and some of them have heterogeneous populations where drainage was evaluated for PP, walled necrosis, infected necrosis as equivalents, resulting in clinical heterogeneity. The presence of necrosis within the PP, distance to the enteric wall where the fistulous tract will be performed, size of its wall, direct communication with the PD, the size of the cystostoma (< 2 cm) and the presence of disconnected PD syndrome as well as PD obstruction could help to establish predictors of endoscopic drainage failure in search of generating markers for risk stratification. This theory was contrasted by Nealon and collaborators, who found no significant

statistical difference between ductal anatomy, the relationship of the PP with the PD, and its relationship with the severity of the disease; 83.5% of the patients managed endoscopically and percutaneously who presented failure required rescue surgery. Although these results are referenced in some publications as support for not stratifying their patients, they should be interpreted cautiously since only patients with unsatisfactory management and who developed complications were included in this study. Two-thirds had pancreatic ductal disruption and did not have a pancreatic ductal TS prior to the procedure. There were other variables (such a cystotoma < 2 cm, presence of necrosis, among others) that are considered to have a greater probability of manifesting in patients with failure of primary therapy, which were not evaluated, in addition to the fact that patients with percutaneous drainage were used, which is not currently accepted as a definitive treatment modality.[34]

During the last few years, some studies suggest a discreet improvement in the therapeutic effectiveness offered by endoscopy, related to the arrival of endoscopic ultrasound and FCSEM and SEM, which generate more stable fistulous tracts with less risk of collapse. In a retrospective cohort, Sharaiha and collaborators found superiority in the resolution of PP with the use of FCSEMS about plastic ST.[35] The advent of luminal apposition STs is theoretically supposed to improve the effectiveness of endoscopic procedures, which should be evaluated against laparoscopy, which offers, according to the data presented, a more traditional approach with better therapeutic success, theoretically with a lower prevalence of complications, less days of in-hospital stay and a lower cost of medical care concerning the open approach. Siddiqi and his team reported a series of 313 patients with walled necrosis in whom the use of drainage by double Pigtail, FCSEMS, and luminal apposition ST (LAMS) was evaluated. Complete resolution was 81% in CPs, 95% in FCSEMS, and 90% in LAMS; however, no significant differences were found in the latter two during follow-up, while fewer complications were observed in patients managed with LAMS.[36] The advantages of LAMS compared to other DES included single-step placement and the possibility of direct endoscopic debridement with minimal migration; although its superiority to PD is clear, further studies are needed to evaluate its superiority to FCSEMS.[37]

In relation to the meta-analysis, there is no uniformity of the characteristics observed in the different studies. Essential differences in the methodology, the definitions used, and the reports of the data presented were evaluated and weighted. It was considered that despite the apparent methodological and clinical heterogeneity, there was sufficient evidence and the differences shown do not substantially influence the research questions posed. A meta-analysis was performed, in which the superiority of surgery in obtaining therapeutic success was evidenced without finding a statistically significant difference between both techniques in terms of complications and recurrence. However, the findings in this meta-analysis are limited by the scope of the methodology, the risk of bias, and methodological heterogeneity. Likewise, we performed a purposive search for studies that evaluated the therapeutic performance of the laparoscopic intervention. Unfortunately, we did not find research studies with a sufficient population to perform an analysis, and we needed to find methodological characteristics that met our inclusion criteria. In the case of endoscopy, six studies with these characteristics were found, which were analyzed, showing that the effectiveness of endoscopic drainage has improved, probably thanks to the ST used and the advent of endoscopic ultrasound. The main arguments supporting endoscopic techniques are similar effectiveness, fewer complications, lower cost, and shorter hospital stay. We consider that the possibility of placing a stent in the PC, performing papillotomy, and better categorization by endoscopic ultrasound are characteristics that, over time, incline the tendency to prefer this approach since it provides additional therapeutic and diagnostic elements, which is not reflected in the present meta-analysis. Resolving the controversy may be less critical than evaluating new techniques that help to resolve this pathology

more effectively. Patil et al. reported in a systematic review that included 298 patients in 11 studies a 96% therapeutic success using luminal apposition TS.[37] There are case reports of therapeutic success in patients with NOTES management (endoscopic surgery through natural orifices).[38] Despite the logical assumption of their effectiveness, the advent of these techniques still needs to be improved by the high specialization of their performers and the need for complex equipment and high cost. Due to these causes, the possibility of performing a hybrid NOTES procedure, as described in some recent case reports, is being considered.[38,39] This approach offers the logical assumption of ERCP's possibilities in transpapillary management plus the arsenal of tools offered by laparoscopy. This technique is described using the placement of a transgastric laparoscopic trocar, which allows the use of laparoscopic instruments for debridement, necrosis control, cleaning, and widening of the anastomoses, complemented or not with the placement of transgastric and transabdominal drainage to the outside. Although these techniques have not yet been evaluated, some characteristics imply better results than those evaluated in the present work. However, there is a clear need for risk stratification measures that, by means of a predictive model, would allow improving the therapeutic indication of one procedure over another based on the characteristics of the patients. This model would imply that endoscopic procedures would be indicated in patients without poor prognostic factors. Patients in the group with these factors could be managed with a therapeutic spectrum ranging from luminal apposition ST to Hybrid NOTES management. From this perspective, future medical training could contemplate the possibility of hybridization that would allow comprehensive management of peripancreatic collections with these emerging techniques to compare the results of this management in relation to current results.

## CONCLUSION

Surgical techniques are slightly superior to endoscopic techniques in terms of therapeutic success and lower recurrence; however, they are associated with more significant complications, higher costs, and extended hospital stays. Endoscopy supported by ultrasound provides therapeutic (papillotomy and transpapillary TS) and diagnostic elements that translate into therapeutic success, which has yet to be evaluated individually. More studies are needed to consider these characteristics and evaluate the impact of anatomical factors on poor prognosis to know their translation into complications and efficacy of the procedures, which could lead to a system for risk stratification that would allow a standard working algorithm. The emerging techniques, NOTES/Hybrid notes, and the use of luminal apposition TS contain the theoretical elements that may allow us to solve the problems encountered with current endoscopic techniques.

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*Correspondence:*
**Francisco Javier Hernández-Hernández**
Mexican School of Medicine La Salle
University of Mexico
**E-mail:** javierausland@gmail.com