

Enterocutaneous fistula treatment: case report and review of the literature

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SUMMARY: Enterocutaneous fistula treatment: case report and review of the literature.

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Objective. *The aim of this work is to evaluate the treatment strategies for a common major surgery complication like the enterocutaneous fistula (ECFs). Since there is not any standard treatment for this common disease and since new therapies, like NPWT and fibrin sealants, have come up a review of all their indications seemed useful. We also present two clinical cases treated in this way.*

Patients and methods. *A research was made in the principle databases such as: "Cochrane", "Pubmed", "Google Scholar" and "Google" using the following Key words "enterocutaneous fistula", "fibrin glue", "VAC", "VAC treatment", "fistula", "conservative treatment", "surgery" and using the MESH Function to search similar key words and expand the research. When two or more article with the same design were encountered (e.g. systematic reviews or case reports etc.) the newest one was chosen as data source.*

Results. *As far as somatostatin and its analogues are concerned, they showed a significant reduction of both time (13.95 vs 20.5 days) and percentage (72% vs 44%) of fistula closure against placebo in 2*

meta-analysis.

NPWT showed a high success rate between 90% and 100% but longer closure time between 4 weeks and 6 months.

Fibrin glues showed heterogeneous results due to the great differences in fistulas anatomy and treatment technique in the various studies, with 64-100% success rate in closure and a median 11,25 vs 23,25 days against total parenteral nutrition (TPN) alone.

Conclusions. *Because of ECFs often come up in patient in bad conditions who are not fitted for surgery and because of their high Mortality and Morbidity, a multimodal approach is necessary.*

Although TPN is a cornerstone of their treatment, NPWT showed is superiority in reducing fistula output and in some cases leading to fistula closure, nevertheless it often needs long treating time. Fibrin glues often needs complex devices and are not as good as NPWT in treating the around tissues, but they can be useful when fistulas are only accessible from a little external orifice or they show a complex branched tract; thus they are good when surgery is not possible and the fistula has a mid- or low- output.

The lack of prospective randomized studies or meta analysis and systematic review to compare the different methodics makes it impossible to show any evidence of superiority, but the combined application seems reasonable for a tailored treatment.

KEY WORDS: Enterocutaneous fistula - Fibrin glue - NPWT - VAC - Conservative treatment - Surgery - Fistula - ECF - Fibrin sealants - Timing - Prognostic Factors - Non-operative treatment

Introduction

Enterocutaneous fistulas (ECFs) are abnormal communications between the gastrointestinal tract and the skin. Most of the scientific works about ECFs classify them according to Berry's classification which is reported in Table 1.

In their work Berry et al. (1) found out the presence of anatomic and etiologic conditions which are predictive of a favourable outcome, which is the clo-

sure of the fistula. Although other authors have shown some different conditions, many of those are still actual.

The treatments of ECFs are various and have changed over time. Recently the management of ECFs with fibrin glues and/or Vacuum Assisted Closure (VAC) therapy have been investigated and added to the previous procedures.

Patients who present prognostic factors of unfavourable outcome with one of the possible procedures may benefit from the use of other treatments (Table 2).

Observing the difficulties our team faced in treating fistulas of the patients in the case reports and trying to avoid surgery, we started searching for oth-

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TABLE 1 - BERRY'S CLASSIFICATION.

Scheme	Classification	Favourable outcome	Unfavourable outcome
Anatomic	Internal External Organ involved	Esophageal, duodenal stump, pancreatobiliary, jejunal, small leak, tract <2 cm, defect <1 cm ²	Gastric, lateral duodenal, ligament of Treitz, ileal, complete disruption, epithelialization, distal obstruction
Physiologic	Output: Low <200 ml/day Moderate 200<x<500 ml/day High >500 ml/day	<i>Output does not prognosticate closure</i> Well nourished, no sepsis, transferrin >200 mg/dL	<i>Output does not prognosticate closure</i> Malnourished, sepsis, transferrin <200 mg/dL
Etiologic	Disease process	Appendicitis, diverticulitis, postoperative	Cancer, inflammatory bowel disease, foreign body, radiation

er possible treatments. This led us to conduct a systematic review of the literature on this field.

Cases presentation

Two cases of patients affected by ECF and treated with different procedures are reported below.

Case 1

A 55-year-old male patient was admitted to hospital on September 2014 after being involved in a car crash. He presented with fracture of several bones, sigmoid perforation and hemothorax. He underwent a Hartmann procedure, an arteriography for a hipogastric artery bleeding, a placement of a pleural drainage and an osteosynthesis of the left fibula; after the recovery he was discharged on October 2014. On the 10th of April 2015 the patient was admitted again for a colostomy closure. This was complicated after a few days by an intestinal obstruction due to adhesions. Thus, the patient was taken for an exploratory laparotomy which revealed the presence of diffuse peritonitis adhesions. Therefore, he was treated with a lysis of adhesions and an ileostomy was then performed on the 24th of April.

After being subjected to parenteral nutrition, the patient was discharged nineteen days later, on the 13th of May 2015.

He was readmitted on the 6th of November for ileostomy reversal. However, three days later, the patient showed a sub-occlusive syndrome and a ECF. After a fistulography, the ECF was treated with the placement of a PICC and total parenteral nutrition (TPN). Later, a VAC therapy was performed. A piece of black foam was put into the fistulous tract but outside the bowel loop. A negative pressure between -50 and -75 mmHg was generated in order to diminish the fistula output. After the VAC treatment, three applications of fibrin glue (Quixil®) from the external hole definitively closed the tract. On the 1st of February 2016 the patient was definitively discharged with the fistula closed and under TPN; he was allowed to eat semi-liquid food after a week and after three months he completely recovered and was able to go back to his normal life.

Case 2

A 78-year-old woman, was admitted to Emergency Department with severe crampy abdominal pain mainly localized in the lower quadrants and radiate

to all abdomen since one day, associated with vomit and diarrhoea. The patient was in bad physical conditions and there were no signs of dehydration.

The temperature was normal, pulse 68bpm and BP 160/90 mmHg. The abdomen was distended and tender in the lower quadrants. Blumberg sign was negative and peristalsis was lower. Routine investigations showed no abnormality (white blood cells 7.580/mm³). The patient was sent to medical department for observation. A plain X-ray of the abdomen was performed 10 hours after admission: it showed multiple air fluid levels. Abdominal symptoms gradually became worse and a new plain abdominal radiograph after 13 hours was performed. It was similar to the previous one. Twenty-three hours after admission a CT examination was required: it showed distended small bowel loops and multiple air fluid levels.

A diagnosis of volvulus was made and a laparotomy was performed 24 hours after admission. At surgery bloody peritoneal fluid and a volvulus were found. The strangulated bowel was greatly congested and not viable. The gangrene extended up to 50 centimetres from the ileocaecal junction and involved the bottom of caecum. At the base of the volvulus, the appendix was wrapped around the last loop of ileum. A resection of caecum and about 70 centimetres of ileum was performed. Reconstruction of bowel was made by end-to-end anastomosis. Histology examination allowed to make diagnosis of appendicular mucocele, showing the presence of an appendix chronically inflamed. The post-operative course was complicated by infection of wound and pneumonia. The patient was discharged 31 days after admission in good general condition.

After 8 months a new intestinal obstruction caused by a volvulus occurred, thus another ileal resection was performed with end-to-end anastomosis; two days later was noted an anastomotic leakage and the anastomosis was pulled out in an ileostomy way. The patient was then discharged and re-admitted after two months to close the ileostomy.

Seven days after the last operation, she developed a high output enterocutaneous fistula with short enterocutaneous tract. Because of the high risk of developing a short bowel syndrome after another surgical resection, we chose for a conservative treatment. TPN was started and after three days the fistula output stopped and we started to apply the Tisseel glue from the external hole for a total of four applications.

The patient was discharged after 20 days in good conditions and at follow-up she did not show any gastrointestinal problems.

Methods

Various authors have reported different results with different types of treatments ranging from classical conservative management to fibrin glue closure, VAC system and surgery. We have been looking for progresses in each of these fields, investigating in databases such as Cochrane, PubMed and Google Scholar with keywords as: "enterocutaneous fistula", "fibrin glue", "VAC", "VAC treatment", "fistula", "conservative treatment" and "surgery" using also the Mesh term function. Whenever we found two or more articles regarding the same topic and with the same study design we chose the latest one as source of data.

Discussion

Non-surgical treatments have changed since 1996. The VAC and the fibrin sealants have been added to the classical conservative treatments which are: TPN, administration of somatostatin analogues (octreotide), bowel rest, prevention of sepsis and local wound care (2, 3).

We made a review of the various techniques used in the treatment of enterocutaneous fistulas and their results.

Classical conservative treatment

While the debate on which physical treatment is better in allowing for fistula closure is still open, conservative treatment being often the first treatment. Total Parenteral Nutrition is a Corner Stone of fistula treatment; its efficacy has been widely proven even if it may lead to complication such as sepsis, because of its need for a central venous access (3).

Recently, enteral nutrition has been demonstrated to increase GI immunity, reduce the risk of infection, decrease the fistula output and increase the probability of fistula closure (60% vs 37%) when compared to TPN, especially when combined with an immunonutrition protocol; however, it does not affect mortality (4). On the other hand, enteral nutrition alone is more difficult to achieve as it needs at least 75 cm of healthy small bowel; moreover, under 120 cm there is a risk of developing a short bowel syndrome. Further-

TABLE 1 - THIS TABLE COMPARES THE RESULTS OBTAINED IN CLOSING THE FISTULAS BY AUTHORS WHO USED A VACUUM DEVICE (VAC) VS AUTHORS WHO USED THE FIBRIN GLUE. IN THE CENTRAL COLUMN IS INDICATED THE KIND OF FISTULA (VVKK MEANING FISTULA ARISING FROM VARIOUS PART OF THE GI TRACT FROM THE STOMACH TO THE ILEO-CECAL VALVE), THE LAST COLUMN ON THE RIGHT REPORTS THE TIMING OF CLOSURE AS INDICATED IN THE ARTICLE WHILE THE 4TH COLUMN FROM THE LEFT INDICATES THE METHOD USED VAC VS GLUE.

Author	Year	Type of fistula	Method	Mean closure time
Cro et al.	2002	High Output	VAC	Case 1 : 5 w + 5 m spontaneous; Case 2 : 5 w + surgery Case 3: 3 w
Gonzalez et al.	2010	VVKK	Glue	7.6 ± 2.6 d duodenojejunal; 16,1 ± 21.6 d ileocutaneous; all 12.5 ± 14.2 d
Rabago et al.	2006	VVKK , two internal and 13 external	Glue	95 +/- 199 d
Hyon et al.	2000	jejuno ileal	VAC	50 d
Medeiros et al.	2004	jejunal lateral without tract; closure rate 58/74, all with low output	VAC + balloon	48 in 5 d 16 in 10 d 4 in 15 d
Banasiewicz et al.	2011	EAF + ECF 2 small bowel + 1 colonic	VAC	28--> 35 d + surgery
Erdamann et al.	2000	ileo colonic anastomosis ecf	VAC	8w
Hwang et al.	1996	ECF	Glue	4 patient in 4 d 2 in 7 d
Murakami et al.	2009	VVKK	Glue	1 to 9 sessions of glue treatment
Lange et al.	1990			
Kurokawa et al.	2002	VVKK	Glue	6/7 fistulas closed in 6 weeks

Legend: W, week; m, month; d, day.

more, length alone is not a rigorous standard to assess the absorption rate of the gut, thus other parameters might be used such as citrulline level (5).

General contraindications of enteral feeding are shown in Table 3. It should be started between 24-48 after admission if not contraindicated, while if contraindicated standard electrolyte balanced solutions should be administered (3-5).

Somatostatin and its long acting analogues were the subject of three meta analyses between 2012 and 2017. They demonstrated the efficacy of these med-

ications in reducing closing time and increasing the number of fistulas closed without surgery or other advanced medications. However, they do not reduce mortality nor fistula output.

Also comparing the RR between Somatostatin vs control and Long Acting Analogue vs control, Somatostatin in continuous infusion leads to better outcome in terms of closing time and spontaneous closure (7, 9). However, those analyses are based on low to moderate quality evidence according to the GRADE system (4, 7-9).

Regarding the efficacy of serum markers on monitoring the feeding status of the patient, they are strongly influenced by the acute phase of inflammation which may alter their level so that they should not be considered to evaluate nutritional status. Nevertheless, after the acute phase has passed, some markers may be good predictors of a favourable outcome (6):

- albumin >3 g/dL; some studies have shown that a lower value correlates with poor prognosis and higher rates of recurrence (10).
- transferrin >140 mg/dl; it is demonstrated that reduces mortality from 56 to 19% and improves spontaneous closure rates from 18 to 67% (11).
- citrulline > 20 µmol/L; a lower value is a good predictor of intestinal failure (5).

Fibrin sealants

Kurokawa et al. reported seven cases of complex fistulae with more than two branches. The sites of the fistulae were different as well as the prior diseases and the original diseases. The fibrin glue was injected selectively into each fistula branch, in combination with fistuloscopy, after removal of necrotic tissue and foreign bodies and after the irrigation of the fistulas' interior with antibiotics to which the culture was sensitive. A Beriplast glue was infused. They also provided irrigation of the fistula with an antibiotic to which the germs had resulted sensitive. In six cases the closure of the fistula was obtained within two weeks with no sign of recurrence. In the other patient a surgical fistulectomy was needed.

Rabago et al. reported fifteen cases of postoperative digestive fistulae resistant to two weeks of conservative treatment. Two were internal fistulas while thirteen were external. 2 ml of Tissucol 2.0 at 37 C was injected in the fistulas' tracts with an average of 2.5 sessions per patient. The closure of the fistulas was obtained in sixteen days on average (5-40 days). Over three years of follow-up, only one fistula reopened.

Murakami et al. noted that in complex fistulas with large tracts the fibrin glue coagulated before it fill the cavity, leading the creation of dead spaces. They noted also that the concentration of thrombin was the mean factor determining coagulation speed and that the coagulated fibrin glue had enough tensile strength even with the diluted thrombin solution. Therefore, they diluted the solution B of a Beriplast kit in various ratios ranging from 1 to 125 showing that the 1:31 dilution ratio was the best compromise between prolonged coagulation times and tensile strength. Eighteen patients were treated with the injection of the fibrin glue with diluted thrombin solution. Sixteen patients achieved the complete closure of the fistula (89%) with an average of 1.96 ± 1.37 treatment sessions.

Lange et al. reported 17 patients with gastrointestinal-cutaneous fistulas in which the intestinal opening of the fistula could not be reached or adequately exposed via conventional gastroscopic or colonoscopic approach. They occluded the fistulas via fistuloscopy with 10 ml of fast-hardening fibrin glue (Tissucol, Immuno) plus, in cases of large cavities, the addition of Prolamine (Ethibloc) allowed a better distribution of the glue. 11 out of 17 enterocutaneous fistulae and 5 out of 8 abscesses were treated successfully. A single fistuloscopy was performed in 21 patients and was successful in 13; 4 out of 13 had a second "blind" injection of fibrin glue through the skin opening, which completely stopped secretion.

In 1996 Hwang et al. performed a randomized controlled trial on thirteen patients with low output (less than 20ml per day) enterocutaneous fistulas. All were treated with TPN. Six of them had the fibrin glues injected into the fistula tract, while seven acted as a control group. The fistulas in the first group healed within four days and the patients were discharged within one week with no recurrences in one year of follow-up. The controls treated with

TABLE 3 - CONTRAINDICATIONS TO ENTERAL NUTRITION.

Absolute contraindications	Relative contraindications
Continued obstruction of the gastro-intestinal tract	Presence of high-output fistulas
Bowel discontinuity	Severe malabsorption
Increased risk for bowel ischemia	Shock
Ongoing peritonitis	Severe sepsis if achieved stability for at least 24-36 hours
< 75 cm of usable small bowel	<120 cm of usable small bowel

TPN alone recovered within 7-21 days, a time considerably longer than the patients in the study group.

In 2010 Gonzalez et al. included 70 patients with postoperative ECFs with an output of < 500 mL/d, a fistulous tract of > 2 cm and no local complication in a prospective case-control study, dividing them into study (n= 23) and control group (n = 47). In the study group Quixil® was applied through the external opening of the fistula and the fistulas were controlled endoscopically to assure total occlusion of the tract. Both received the same conservative treatment. Closure time in all patients for the study group was 12.5 ± 14.2 d and 32.5 ± 17.9 d for the control group. In patients with colonic fistulas, complete closure occurred 23.5 ± 19.5 d after the first application of fibrin glue, and spontaneous closure was observed after 36.2 ± 22.8 d in the control group. Recurrences were observed in 2 patients because of residual disease. One patient from each group died during follow-up because of septic complications related to parenteral nutrition (17).

NPWT (Negative Pressure Wound Therapy)

Banasiewicz et al. described three patients with complex postoperative wounds complicated by multiple fistulas. Multiple VAC dressings were applied over the wounds. Wound healing was noted within 2-4 weeks and both the number of fistulas and the volume of excreted contents decreased. Between 22 and 35 days the outputs of the fistulas were all <500 ml. No complications occurred after a follow-up of six weeks.

Goverman et al. proposed the "fistula VAC" method to treat EAF. They reported 5 cases of patients with EAF treated by covering the wound with a sheet of Xeroform dressing, leaving a hole for the enteric opening. A 2 cm hole was cut in the drape directly over the enteric opening to allow for the placement of an ostomy, which was then attached to a Foley bag to allow for gravity drainage. They then put the ostomy over the matured skin graft and performed a fistula resection with complete abdominal closure after 6 to 10 months (19).

Cro et al. reported three cases of high output enterocutaneous fistulas of the midline wound. They put the VAC sponge into the wound over the fistula and covered all the wound with the film. In the end, two patients with an initial > 1/L/day output went to surgical resection with a low output (<200ml/day) fistula after 5 week of VAC treatment and 1 patient with initial 300ml/day output com-

pletely healed in 3 weeks. In their report VAC was also found useful for skin protection (20).

Sung et al. reported a case of two postoperative, high output enterocutaneous fistulas in a 67-year old patient. After several operations, the patient developed two jejunoileal fistulas located at the upper and the lower aspects of the wound. The output of the fistulas was 900 ml per day on average (range, 400-1600 ml per day). The first treatment was conservative: TPN, bowel rest, octreotide and gauze dressing. After 15 days of no response, VAC therapy was started (negative pressure 350-400 mmHg). After 24 hours, fistula output fell to 250 ml and continued to decrease over the next days. Median output for the 50-day period that composed the treatment was 10 ml/day (range, 0-250 ml/day). At one year follow-up no complications were noted.

Medeiros et al. treated 72 patients over a period of ten years with postoperative enterocutaneous fistulas of different etiology. The fistulas were treated with a Foley catheter connected to the high negative pressure flask. The tip of the catheter was put outside the bowel wall and the balloon was inflated in order to close the tract and keep the catheter in place. Sixty-eight patients recovered within fifteen days: forty-eight after five days, sixteen after ten days and four after fifteen days. The therapy failed in six patients; four out of the six patients whose fistula did not close had a high output fistula.

Erdmann and colleagues obtained the closure of an enterocutaneous fistula in a patient with Crohn's Disease. They applied a VAC dressing over the midline incision fistula with an adjunctive sponge into the hole in 6 weeks and complete healing of the wound in 8 weeks.

Pepe et al. treated eight patients with VAC therapy; four of them had enterocutaneous fistulas while the others had enteroatmospheric fistulas. The standard technique for VAC therapy was modified to adapt to the fistula circumstances. In all four cases of ECF fistula healed spontaneously. In the EAF group, in three cases fistula turned slowly into an ECF, and in one out of four it closed spontaneously. The mean length of VAC therapy was 35.5 days (range 8-50 days). Mean interval to spontaneous closure was 36.4 days (range 10-57 days). All patients returned to oral feeding.

Surgery

Many factors influence the decision between the possibility of operating or trying a conservative

treatment and the main point is choosing the right time to switch from a conservative to operative treatment. This choice does not include the case of Chron's disease where there is low probability of fistulas spontaneous healing and frequent cases of relapse (25-27).

According to Lynch (28) et al. and Rose (29) et al. surgical closure of ECF reported a better outcome between 2 and 12 weeks after its appearance. According to Fazio and al., the fistulas which are more likely to close spontaneously heal between four and five weeks. Delaying surgery from ten days to six weeks after the fistula presentation results in a lower mortality rate because of the presence of a "obliterative peritonitis" (30). All authors agree to improve patient general conditions before surgery: Lauro et al. suggest a period ranging from 3 months up to 1 year (33)..

Once the time for operation is reached, it is useful to find out which factors need to be considered in terms of prognosis. In a longitudinal retrospective study, Martinez et al. evaluated 71 patients over 5 years and they found out that only high output (>500ml per day) and type of surgical treatment (operations not involving resection of ECF) are associated with recurrence. Noncolonic ECF origin, high output and non-resective surgical options were risk factors for recurrence, while malnutrition, sepsis, fluid and electrolyte imbalance and serum albumin <3 g/dl at diagnosis were risk factors for mortality (10).

Martinez et al. in a retrospective study analysed 174 Postoperative Enterocutaneous Fistulas treated in their department over a period of 10 years. The study showed different factors compared to Berry's classical work. Jejunal site, high output and multiple fistulas were identified through univariate analysis as factors favouring the need for surgery. In their work they also mention distal obstruction as a risk factor for non-successful non-operative treatment but they don't include this parameter in the statistical analysis. They also found that proximal origin of the ECFs, the presence of multiple ECFs and sepsis correlated with a higher mortality. The authors suggested the need to switch from conservative to surgical treatment after a period according to the localization of the fistulous tract (31).

Results

By confronting the results obtained by the vari-

ous authors in the fibrin glue arm of this article is possible to see how they achieved to speed up the closure time of their fistulas. In those articles which reported the time to closure in "days", the median time to closure was 11,25 days vs 23,25 days of the controls. By the way the majority of the fistulas were low- or mid-output fistulas and there was not homogeneity in the anatomic origin of the various fistulas treated.

NPWT suffers the same problems in statistical terms. The bias due to the poor study design, the anatomical differences doesn't allow us to report any sure advantage; yet it's still possible to appreciate the efficacy in diminishing fistula's output even in short period's (24h).

On the other hand somatostatine and its analogues showed a significative reduction of both Time (13.95 vs 20.5 days) and Percentage (72% vs 44%) of fistula closure against placebo in 2 meta-analysis. And in particular Somatostatine in continuous infusions leads to a shorter closure time against its analogues (7-9).

Various studies report a spontaneous time to closure ranging from 4 to 5 weeks (7, 9, 30) when the characteristics of the fistula are favourable to spontaneous closure (10-31). In all those patients who don't fit this model the use of one or more of the above solutions may lead to healing, as it was in our case.

GMV had a proximal fistula with an high output and distal obstruction due to recent surgery (30, 31). This combined to the obliterative peritonitis (30) inside his abdomen made surgery unuseful to resolve his condition; this alongside with the literature led us to combine the treatment strategies, N.P.W.T. was applied after three weeks of unsuccessful "*nihil per os*" treatment; after 60 days of vacuum treatment the fistula output had fall to almost 30 ml/day, at this point three bedside application standing 2 days one from each other led us to complete healing.

Conclusion

ECFs often occur in a background of severe bowel and peritoneal stress and surgery is not always the best treatment as it may lead to a high rate of recurrence and to a high mortality (10-32). Our patients had a history of several operations, thus we started to look for the latest studies on conservative treatments in order to avoid surgery.

TPN is the foundation of successful treatment as it allows us to improve patients' conditions and provide them with all nutrients in order to face sepsis and malnutrition which may lead them to death.

VAC therapy has shown its efficacy in reducing fistula output, which is one of the worst prognostic factors because is linked to increased mortality and relapse rates. Moreover, if there is a low-output fistula, VAC therapy may lead to complete healing, thus it should be considered for initial treatment.

Biological glues are able to speed up the fistula closure time and achieves high success rate ranging from 65 to 98%; they are indicated in cases in which surgery should be avoided and fistula is accessible only from the external opening or from a natural orifice.

They are not as efficacious as VAC in caring the tissues around the orifice and cannot close directly high output fistula (16). Furthermore, if the fistula tract is long and complex they need a complex equipment which is not always available.

On the other hand, glues are faster than VAC and TPN alone, even when more than one application is needed.

At the time this article is being drafted, randomized trials to evaluate the effectiveness of the different treatments alone or combined are lacking and data from different studies are not comparable because the origin of the fistulas and the physical conditions of the patient.

Considering the relatively poor number of every kind of ECFs compared with their collective one, regarding their anatomical origin, a multicentre trial with patients divided in three branches of treatment (VAC alone, fibrin glue alone, and VAC + fibrin glue) would be a useful method to reach statistical significance and define a therapy which is often still left to clinician's intuition even though 30 years of research have passed.

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