

Is Endoscopic Treatment of Bronchopleural Fistula Useful?

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OBJECTIVE: New endoscopic techniques have been developed as an alternative to surgical treatment of bronchopleural fistula. The objective of this study was to analyze our experience with endoscopic treatment of such fistulas.

MATERIAL AND METHODS: We conducted a retrospective study of patients with bronchopleural fistula diagnosed by fiberoptic bronchoscopy. Patient characteristics, underlying disease, fistula size, and outcome of endoscopic treatment were analyzed. The endoscopic technique consisted of injection of fibrin sealants (Histoacryl[®] and/or Tissucol[®]) through the catheter of the fiberoptic bronchoscope.

RESULTS: Between 1997 and 2004, 18 patients were diagnosed with bronchopleural fistula by fiberoptic bronchoscopy. All were men with a mean (SD) age of 62 (12) years. Bronchopleural fistula was diagnosed after neoplastic surgery in 16 patients, in the bronchial suture after lung transplantation in 1 patient, and concurrently with pleural effusion due to hydatidosis in the remaining patient. The size of the fistula ranged from 1 mm to 10 mm (mean 3.6 [2.7] mm). Fibrin sealants were applied in 14 patients, 2 underwent direct surgery after diagnosis, and the bronchopleural fistula closed spontaneously in the remaining 2. The fibrin sealant used was Histoacryl[®] in 12 patients and Tissucol[®] in 2. Pleural drainage was employed simultaneously and antibiotic therapy was administered at the discretion of the surgeon. The 4 patients whose bronchopleural fistula was associated with empyema also underwent pleural lavage. In 12 patients the fistulas closed as a result of the endoscopic technique (85.7%), and no complications were observed. For 85.7%, fewer than 3 applications of fibrin sealant were necessary.

CONCLUSIONS: The success rate of closure of bronchopleural fistula with fibrin sealants injected under guidance with fiberoptic bronchoscopy is high and there are no complications. This technique can render surgery unnecessary.

Key words: Bronchial fistula. Endoscopic treatment. Fibrin sealants. Histoacryl[®].

¿Es útil el tratamiento endoscópico de las fístulas bronquiales?

OBJETIVO: Se han desarrollado nuevas técnicas endoscópicas como alternativa al tratamiento quirúrgico de las fístulas bronquiales (FB). El objetivo de nuestro trabajo ha sido analizar nuestra experiencia en el tratamiento endoscópico de las FB.

MATERIAL Y MÉTODOS: Hemos realizado un estudio retrospectivo de los pacientes con FB diagnosticados por fibrobroncoscopia analizando sus características, enfermedad causal de la fístula, tamaño y resultados del tratamiento endoscópico. La técnica endoscópica consistió en la instilación mediante catéter a través del fibrobroncoscopio de sustancias sellantes (SS) (Histoacryl[®] y/o Tissucol[®]).

RESULTADOS: Entre 1997 y 2004 diagnosticamos 18 FB a través de fibrobroncoscopia, todas ellas en varones con una edad media (\pm desviación estándar) de 62 \pm 12 años. En 16 pacientes la FB se produjo tras cirugía de neoplasia, en uno apareció en la sutura bronquial de un trasplante pulmonar y en otro fue simultánea a un derrame pleural por hidatidosis. El tamaño osciló entre 1 y 10 mm (media de 3,6 \pm 2,7 mm). Aplicamos SS en 14 pacientes, en 2 se realizó cirugía directamente tras el diagnóstico y en otros 2 la FB cerró espontáneamente. Las SS utilizadas fueron Histoacryl[®] en 12 pacientes y Tissucol[®] en otros 2. Simultáneamente se empleó drenaje pleural y antibioterapia sistémica según criterio del cirujano. En los 4 casos donde la FB estaba asociada a empiema se aplicaron además lavados pleurales.

La técnica endoscópica cerró la FB en 12 pacientes (85,7%) sin complicaciones asociadas. En el 85,7% fueron necesarias menos de 3 aplicaciones de SS.

CONCLUSIONES: La utilización de SS, mediante técnicas de fibrobroncoscopia, permite el cierre de las FB con un alto porcentaje de éxito, un número reducido de aplicaciones y nula morbilidad, evitando la cirugía de la fístula.

Palabras clave: Fístula bronquial. Tratamiento endoscópico. Sustancias sellantes. Histoacryl[®].

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Introduction

Bronchopleural fistulas remain an important complication after both pneumonectomy and lobectomy. The incidence of such fistulas has decreased in recent years due to advances in surgical techniques

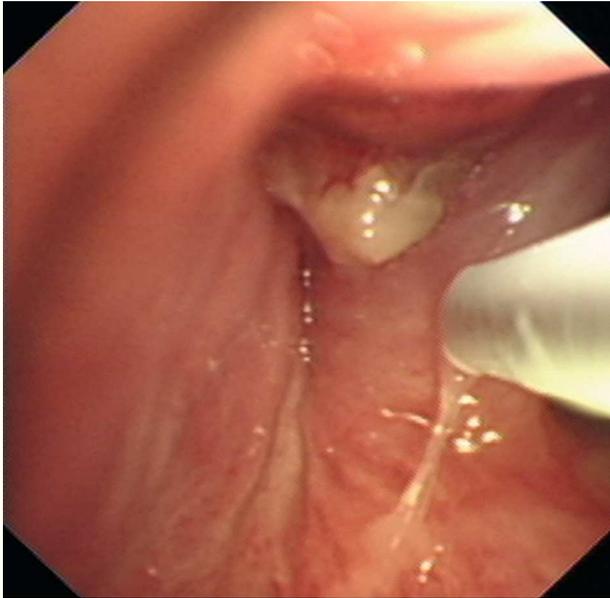


Figure 1. Fistula in a bronchial stump with angioplasty catheter positioned by fiberoptic bronchoscopy before instilling Histoacryl.

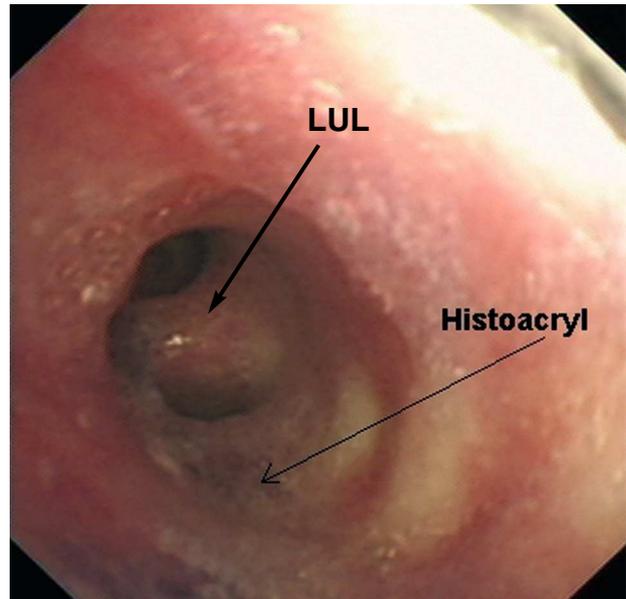


Figure 2. Fistula covered by Histoacryl immediately after application. LUL indicates left upper lobe.

but remains between 0.8% and 15% after pneumonectomy and approaches 1% after lobectomy.^{1,2} Factors associated with the appearance of bronchopleural fistulas include prior chemotherapy and radiotherapy, corticosteroid treatment, limited margin around the tumor resection, a long bronchial stump, right pneumonectomy, and prolonged postoperative mechanical ventilation.^{2,3}

For many years, further surgery was thought to be the only way to resolve this complication, despite a high rate of associated mortality and additional complications (79%).^{2,4} Therefore, nonsurgical alternatives were developed to close bronchopleural fistulas with potentially fewer complications. Endoscopic alternatives to surgery include application of fibrin sealants,⁵⁻⁹ occlusion of the fistula with vascular catheters or coils,¹⁰⁻¹² silicone or metal prosthesis,^{13,14} and submucosal injection of substances to force the edges of the fistula together.^{12,15,16} The aim of this study was to analyze our experience of bronchopleural fistula closure with fibrin sealants applied by fiberoptic bronchoscopy.

Material and Methods

This was a descriptive, retrospective, observational study. Data were collected on a standard form after reviewing the medical histories of all patients with bronchopleural fistulas diagnosed by fiberoptic bronchoscopy in our hospital between October 1997 and October 2004. Demographic data and information on the fistula etiology, site, size, days between surgery and presentation, type of endoscopic treatment, number of applications of fibrin sealants, adjuvant treatments, success of the procedure, and need for subsequent surgery were analyzed.

Bronchopleural fistulas were diagnosed by endoscopic imaging. For very small fistulas, saline solution was instilled,

and the presence of a passage between the pleural cavity and the lung was confirmed if the solution bubbled and disappeared. The size of the fistula was calculated from the endoscopic image. Early fistulas were defined as those that appeared within 15 days of the resection operation, otherwise the fistulas were considered as late.

The endoscopic technique consisted of instillation of sealing substances through an angioplasty catheter (Bard, Karlsruhe, Germany) attached to a flexible fiberoptic bronchoscope (Figures 1 and 2). Methyl-2-cyanoacrylate (Histoacryl[®], Braun Medical S.A., Tuttlingen, Germany) and/or fibrinogen plus thrombin (Tissucol[®], Baxter S.L., Vienna, Austria) were used as sealants. Initial applications of Histoacryl were unable to fully seal the 4-mm fistula, and so submucosal injection of physiological saline solution was required to force the fistula edges of closer to one another immediately before the third application of Histoacryl. For each application, 1 mL of Histoacryl and 3 mL of Tissucol were used. Once the sealant had been applied, the fiberoptic bronchoscope was withdrawn with the catheter still inside the working channel to prevent the fibrin sealant from adhering to the channel and the optics of the bronchoscope. The distal end of the catheter (where traces of Histoacryl remained) was then cut and the catheter removed. The endoscopic technique was performed with an Olympus BF P-40 fiberoptic bronchoscope (Tokyo, Japan) under local anesthesia. Sedative was also administered at doses tolerated by the patient (2-4 mg of intravenous midazolam).

After the fibrin sealant had been applied, we assessed whether closure of the fistula had been achieved by observing whether the air leak through the pleural drainage tube had stopped and whether symptoms improved. If no improvement was observed, the endoscopic procedure was repeated after 3 to 5 days.

In addition to endoscopic treatment, the surgeon could decide to perform pleural drainage and lavage and administer antibiotic therapy when empyema or pleural effusion occurred.

We proceeded directly to surgery when patients presented with fistulas with complete dehiscence of the suture or with

TABLE
 Characteristics of the Fistulas and Treatments Applied*

Cases	Etiology	Site	Size, mm	Time to Appearance, Days	Fibrin Sealant	No. of Applications	Fistula Closure	Surgery
1	Right pneumonectomy	RMB	1	6	Histoacryl	1	Yes	No
2	Right pneumonectomy	RMB	2	15	Histoacryl	1	Yes	No
3	Right pneumonectomy	RMB	4	30			Yes	
4	Left pneumonectomy	LMB	4	16	Histoacryl + tissue expansion	3	Yes	No
5	Left pneumonectomy	LMB	10	2			Yes	
6	Left pneumonectomy	LMB	3	32	Histoacryl	2	No	Yes
7	Left pneumonectomy	LMB	2	58	Histoacryl	1	Yes	No
8	Left pneumonectomy	LMB	3	7	Histoacryl	2	Yes	No
9	Left lower lobectomy	LLL	1	18			Yes	No
10	Left upper lobectomy	LUL	2	4	Histoacryl	1	Yes	No
11	Bilobectomy ML RLL	IB	5	13	Histoacryl	5	Yes	No
12	Right lower lobectomy	RLL	5	12	Histoacryl + Tissucol	9	No	No
13	Left upper lobectomy	LUL	1	7	Histoacryl	1	Yes	No
14	Bilobectomy ML RLL	IB	1	21	Histoacryl	1	Yes	No
15	Right lower lobectomy	RLL	5	16	Histoacryl	1	Yes	No
16	Left upper lobectomy	LUL	5	13	Histoacryl	2	Yes	No
17	Lung transplant	RMB	9	30	Tissucol	2	Yes	No
18	Pleural effusion due to hydatidosis	RLL	1	No				

*IB indicates intermediate bronchus; LMB, left main bronchus; RMB, right main bronchus; RLL, right lower lobe; LLL, left lower lobe; ML, middle lobe; LUL, left upper lobe.

extensive endobronchial infection and fibrin around the edges. Surgery was also indicated when endoscopic treatment failed.

We analyzed the data collected with descriptive statistics using the SPSS statistics program version 10.0 (Chicago, Ill, USA).

Results

Between October 1997 and October 2004, bronchopleural fistula was diagnosed in 18 patients by fiberoptic bronchoscopy. All patients were men, with a mean (SD) age of 62 (12) years. The fistula occurred after surgery for lung cancer in 16 (89%) of the patients (3 right pneumonectomies, 5 left pneumonectomies, and 8 lobectomies). In 1 patient, the fistula was attributed to pleural effusion due to hydatidosis, and in the remaining patient, it was due to a cul-de-sac in the bronchial suture of a transplant. The cul-de-sac of this patient (case 17 of the Table) measured 9 mm in diameter and 5 mm deep. There was no passage between the pleural cavity and the lung, but because the patient was a severely immunosuppressed transplant recipient with confirmed bacterial and fungal infection of the cul-de-sac, it was necessary to close the wound.

Fifty-three percent of the fistulas were early and 47% were late, with a mean time to appearance of 18 (14) days. The sizes of the fistulas ranged from 1 mm to 10 mm (mean 3.6 [2.7]) mm. The characteristics of the fistulas of all the patients are presented in the Table.

Fibrin sealants were applied in 14 patients (details of the treatment applied in each case are presented in the Table). All fistulas were 5 mm or smaller in diameter, with 1 exception. In most cases, Histoacryl was applied (12 cases). In 1 patient, this sealant was combined with Tissucol and Tissucol alone was applied in case 17 in order to fill a cul-de-sac 5 mm deep in the suture of a transplanted lung. Submucosal injection of

physiological serum solution at the edges of the fistula was used only once when Histoacryl was unable to completely cover the fistula. In 12 cases (85.7%), 3 or more applications of fibrin sealant were necessary. Application was repeated 5 times in 1 patient and 9 times in another; in both cases the patients had a large 5-mm fistula. Surgery was performed in 2 cases without first attempting endoscopic treatment. One of these patients had complete dehiscence of the bronchial suture and the other had a 4-mm fistula associated with empyema, with abundant fibrin and purulent secretions. A further 2 fistulas of 1 mm in diameter closed spontaneously.

At the surgeon's discretion, patients simultaneously underwent pleural drainage (16 cases) and/or were given systemic antibiotics (14 cases). The 4 patients who presented with empyema underwent lavage of the pleural cavity. One was referred directly for surgery whereas endoscopic treatment was chosen for the other 3 patients. Fistula closure was achieved with endoscopic treatment in 2 of the 3 patients (1 early 1-mm fistula and 1 late 4-mm fistula). Complete closure of the other fistula was not achieved in the other patient despite 9 applications, but the size of the fistula was halved (case 12). This patient did not undergo surgery because of the high surgical risk after further surgery for bleeding within 48 hours of lung resection and the appearance of brain metastases 1 month after surgery.

The bronchopleural fistula was closed with the endoscopic technique in 12 patients (85.7%) with no associated complications. Failure was reported in 2 patients (cases 6 and 12). In case 6, tumor relapse at the edges of the fistula was documented, and the patient died after surgery. Case 12 died due to brain metastases after 4 months without closure of the fistula. A further 3 patients died, 1 on the same day that the fistula was diagnosed after further surgery and 2 because of

tumoral dissemination 18 months and 3 months after closure of the fistula with endoscopic techniques.

Discussion

Management of bronchopleural fistulas should be individually tailored. The approach will depend on a number of factors such as the size and site, time between surgery and presentation, whether or not empyema is present, the general state of health, and the underlying diseases of the patient.³ Further surgery is highly risky, and so less aggressive techniques for quickly closing the fistula are preferred. A variety of therapeutic options have been described as an alternative to surgery, such as application of fibrin sealants,⁵⁻⁹ the introduction of different materials, vascular catheters and coils that occlude the fistula,¹⁰⁻¹² silicone or metal prostheses,^{13,14} and submucosal injection of substances such as povidocanol or aqueous gel suspensions of pyrolytic-carbon-coated beads to bring the edges of the fistula together.^{12,15,16}

One of the most widely used sealants is Histoacryl. The main advantages of this sealant are that it can be easily applied, does not need prior preparation, solidifies immediately, and can be readily removed if bronchial obstruction occurs. In the case of Tissucol, formed from a mixture of fibrinogen and thrombin, the 2 separately-applied components come into contact at the angioplasty catheter outlet. On mixing, the 2 components form a gel which takes hours to solidify, but which can cover a larger extension. Some authors prefer submucosal injection of povidocanol to the fistula edges to enhance the formulation of granulation tissue.¹⁶ Another similar technique comprises the use of nonresorbable carbon beads in a gel that is injected submucosally in order to bring the edges of the fistula together and so favor healing.¹²

Randomized studies comparing the different therapeutic options have not been conducted and almost all publications discuss isolated cases. It is therefore difficult to draw firm conclusions. The most extensive series are those reported by Scappaticci et al¹⁷ in Turin, Italy, who studied 12 patients treated with Histoacryl and Varoli et al¹⁶ in Milan, Italy, who achieved a success rate of 63% in a series of 35 patients treated with submucosal injection of povidocanol.

One of the most important factors when deciding whether to opt for an endoscopic procedure is the size of the fistula.^{15,17} The sealants currently available are more effective when applied to fistulas less than 5 mm in diameter. The technique can however be attempted in almost all patients given that no complications are associated with the procedure. Moreover, treatment can be applied with the same fiberoptic bronchoscope used to confirm diagnosis of the bronchopleural fistula and the technique does not interfere with or delay reparative surgery should this be considered necessary. When the edges of the fistula are too far apart or closure is not achieved after sealant application, submucosal injection of tissue expander may help fistula closure, as has already been reported.^{12,15,16}

Our group started to practice endoscopic treatment of fistulas with Histoacryl (methyl-2-cyanoacrylate) and Tissucol (fibrinogen plus thrombin) because the surgical team was experienced with the intraoperative application of these materials. Most fistulas in our hospital are treated with Histoacryl. In our experience, Tissucol, with its gelatinous characteristics, can fill larger areas, so we reserve its use for larger fistulas, although other authors prefer Tissucol for smaller fistulas as well.¹⁸ Both substances are applied with a fiberoptic bronchoscope and achieve fistula closure in most cases (85.7%), thus avoiding surgery. As yet, we have no experience with submucosal injection of nonresorbable substances, but they could be useful in fistulas larger than 5 mm in combination with sealants to achieve closure in a single bronchoscopic procedure.

The only drawback of the technique is the possible damage to the fiberoptic bronchoscope. In our series, only once did Histoacryl become stuck to the working channel of the fiberoptic bronchoscope and repair was necessary. Greater experience with the application allows the catheter tip to be kept at a sufficient distance to avoid such damage. The cost of endoscopic treatment (€80 for application of Histoacryl and €300 for submucosal injection of pyrolytic carbon) is less than for any surgical procedure.

Empyema is a complication frequently associated with fistulas, particularly the larger ones and those that present late.¹⁹⁻²¹ This complication is associated with increased morbidity in patients and some authors are of the opinion that it reduces the chances of success with endoscopic techniques and so surgery is often recommended.¹⁰ In our series, the fistula was closed in 2 patients with empyema by combining pleural drainage, antibiotic therapy, lavage of the pleural cavity, and application of Histoacryl by fiberoptic bronchoscopy.

To date, our endoscopic treatment of bronchial fistulas has been guided by the experience of the endoscopist and the underlying diseases of the patient. However, after analyzing our results, we have introduced a decision-making protocol for treatment. According to this protocol, on confirmation of bronchial fistula, all patients receive endoscopic treatment. If the fistula is 5 mm or less in diameter, Histoacryl is applied. When the diameter is greater than 5 mm, Tissucol is applied alone or in combination with Histoacryl to occlude the opening. For very large fistulas in which Histoacryl does not adequately cover the area between the edges, we inject tissue expander comprising pyrolytic carbon beads¹² and apply Histoacryl immediately afterwards. Within 24 to 48 hours, the patient undergoes a further clinical evaluation and the persistence of air leaks is assessed. If closure is not achieved, bronchoscopy is repeated to check how the fistula is progressing. If it is getting smaller, endoscopic treatment is repeated until closure is achieved. If the second bronchoscopy reveals no improvement in the fistula and the risk of further surgery is not high, then the patient undergoes surgery.

Among the limitations of this study, we should highlight that this is a descriptive, retrospective series,

and so comparisons between different endoscopic techniques cannot be made. Second, treatment decisions for these 18 patients were not taken according to a protocol. Nevertheless, our series and that of Scappaticci et al¹⁷ are the largest reported series published on endoscopic treatment with sealants. Both used Histoacryl. Closure was achieved in more than 80% of our patients with no associated complications; 8 of our patients and 2 in the study by the Italian group had empyema. These findings support the use of this technique in the treatment of bronchopleural fistulas.

In conclusion, use of sealants with fiberoptic bronchoscopy is a good therapeutic option for closing bronchopleural fistulas in most patients, regardless of the size and appearance of the fistula. For fistulas larger than 5 mm and those that present with bronchial secretions, abundant fibrin at the edges, or with associated empyema, the failure rate is higher. Even so, endoscopic interventions are safe and free from associated complications. We therefore think that closure should first be attempted by a combination of endoscopic techniques (sealants, submucosal injection of tissue expander, etc), especially when further surgery would be extremely risky.

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