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Use of Coagulant Spray Glue (Glubran 2®) for Aerostatic Purposes in Pulmonary Parenchyma Resections in Pigs: A Preliminary Study

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Key Words
Pulmonary parenchyma resections · Pigs · Coagulant spray glue

Abstract
Background: The aim of our study was to test the aerostatic validity of a cyan-acrylic glue (Glubran 2®), applied by means of a spray catheter, on an experimental pig model. ***Materials and Methods:*** 15 young pigs were divided into three study groups of 5 based on surgical techniques: (1) atypical pulmonary resection with mechanical suturing and reinforcement with continuous suturing; (2) resection of the pulmonary parenchyma with a cold scalpel, followed by local application of Glubran 2; (3) atypical pulmonary resection with mechanical suturing followed by application of Glubran 2. ***Results:*** The mean aerostasis time was calculated at 3.5 ± 1.26 s. The histopathological analysis did not show any particular differences when comparing the effects of the treatments carried out with Glubran 2 spray glue and the standard treatments. No statistically significant differences were recorded in the short- and medium-term survival of pigs treated with Glubran 2 compared with the respective control groups. ***Conclusions:*** The application of Glubran 2 spray on wounds caused by pulmonary resections in pigs proved to have a rapid and effective influence for the purposes of aerostasis without significant differences in air losses and survivals.

Introduction

Optimum aerostasis is a determining objective for the success of any form of pulmonary surgery. The aim of our preliminary study was to test the aerostatic validity of a cyan-acrylic glue (Glubran 2®), modified by the addition of a second monomer and applied by means of a spray catheter, on an experimental pig model; in addition, the objective was also to assess the acute and chronic effects in pig lung resections by means of histopathological analysis of the portions of operated lungs. The product has been used in all types of surgery without limitations [1–19]; however, no studies confirming or denying the potential indications of this aerostatic product in the field of thoracic surgery have so far been published in the literature.

Materials and Methods

Study

The experimental model, with control group, consisted of the resection of pulmonary parenchyma in 15 young pigs of both sexes, weighing between 35 and 40 kg.

The pigs were divided into three groups.

– Study group 1 (control): 5 pigs treated with conventional techniques. The type of surgery consisted of an atypical pulmonary resection with mechanical suturing and reinforcement with continuous suturing using reabsorbable single-strand thread.

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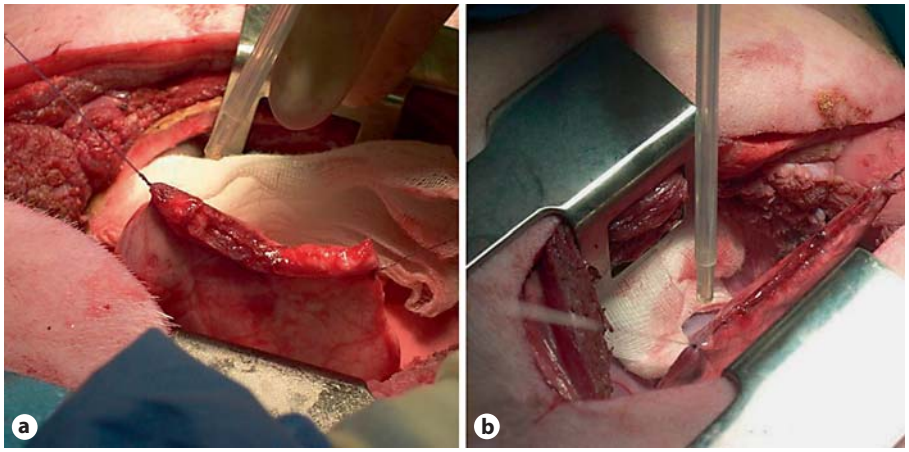

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Fig. 1. a Resection of the pulmonary parenchyma with a cold scalpel, followed by local application of Glubran 2 glue in spray form. **b** Atypical pulmonary resection with mechanical suturing followed by application of Glubran 2 glue in spray form.

- Study group 2 (experimental): 5 pigs treated using the spray form of Glubran 2 glue. The surgical procedure consisted of resection of the pulmonary parenchyma with a cold scalpel, followed by local application of Glubran 2 glue in spray form (fig. 1a).
- Study group 3 (mixed): 5 pigs treated with mixed techniques. The surgical procedure consisted of an atypical pulmonary resection with mechanical suturing followed by application of Glubran 2 glue in spray form (fig. 1b).

Components

Glubran 2 is a cyan-acrylic glue, modified for internal use, which produces a coagulating and occluding effect by means of a low-temperature (40°C) exothermal polymerization reaction. When applied properly, the glue starts to set after 1–2 s, completing its setting reaction after about 60–90 s.

Once set, the glue no longer possesses adhesive properties so that tissues or surgical gauzes may be placed in contact with it without any risk of unwanted adhesion, this last feature being particularly important for its use in thoracic surgery.

In normal surgical procedures, the film of glue is eliminated by means of a hydrolytic breakdown process. The time necessary for completion of this process varies according to tissue type and quantity of glue applied.

The potential indications for its use in thoracic surgery concern the sealing and reinforcement of the manual and/or mechanical suturing performed during major lung resection operations, hemostasis upon bleeding after separation of adhesions, dissections and decortications.

We believe that the new spray formulation, applied by means of a spray catheter, can be validly applied not only in aerostatic control but in all cases in which the resection of vast areas of pulmonary parenchyma lead to abundant microvessel bleeding.

Operative Techniques and Measurements

All the pigs were administered mixed balanced anesthesia with initial intramuscular premedication of azaperone (3 mg/kg), acetylpromazine maleate (0.25 mg/kg) and ketamine (20 mg/kg); intravenous induction (ear margin) with propofol (7.5–15 mg/kg); orotracheal intubation, by means of direct visualization, with an appropriately sized Carlens selective catheter; depth and maintenance with isoflurane in oxygen in intermittent positive pressure ventilation.

Left thoracotomy was performed in the 5th intercostal space, exteriorizing the caudal pulmonary lobe on which an atypical wedge resection was then performed. The surgical specimens were then sent to the relative Institute of Pathological Anatomy for analysis.

In the experimental and mixed groups, the Glubran 2 spray glue was applied with the lung expanded with positive end-expiratory pressure ≥ 5 cm H_2O.

The aerostatic effect in acute conditions was evaluated for at least 20 min with the surgical wound still open, by immerging the portion of treated lung in physiological solution, increasing positive end-expiratory pressure to the value of 10 cm H_2O.

Before closing thoracotomy, an intrapleural drainage tube was then positioned, connected to a Heimlich valve.

Stabling

After waking, the animals underwent clinical evaluation, measuring their breathing rate, heart rate and body temperature, and were administered anti-inflammatory and analgesic therapy (ketoprofen: 3 mg/kg/day/i.m.) for 3 days and oral antibiotics (medicated feed). Expected survival rates were: 48 h for 2 animals from each group and 14 days for 3 animals from each group. Survival, complications, blood and air losses were recorded and specific hematochemical parameters like white blood cell count after surgery were assessed.

Evaluation of aerostasis in chronic conditions consisted of observing the animals for 5–7 days, recording any air leaks from the pleural drainage tube.

In the surviving animals, the drainage tube was removed on the 7th postoperative day under deep sedation (azaperone: 3 mg/kg i.m.; acetylpromazine maleate: 0.25 mg/kg i.m.).

The pigs underwent chest X-ray with lateral and dorsoventral projections at the end of the operation, on the first and second day, after removal of the drainage tube on day 5 and at the end of the stabling period. The pigs were sacrificed at the end of the stabling period by intravenous administration of embutramide, mebenzo-

Table 1. Aerostasis data: immediate aerostasis time calculated after using Glubran 2 and evaluation of aerostasis in chronic stabling measuring air leakage from the chest tube for each group

Subject No.	Sex	Body weight, kg	Group; use of Glubran 2	Aerostasis time, s	Air leakage days
1	♂	36	1; no	2.4	0
2	♂	40	1; no	4.1	1
3	♂	37	1; no	5.2	0
4	♀	38	1; no	1.6	0
5	♀	35	1; no	3.3	0
6	♂	40	2; yes	3.4	0
7	♀	39	2; yes	4.5	2
8	♂	38	2; yes	4.2	1
9	♂	37	2; yes	2.3	0
10	♀	36	2; yes	2.6	0
11	♂	35	3; yes	6.1	0
12	♂	40	3; yes	5.0	1
13	♀	40	3; yes	3.1	0
14	♀	39	3; yes	3.0	0
15	♀	38	3; yes	2.4	1

Table 2. Laboratory and morphologic data

Sex; body weight kg	White blood cell count[a] n × 10^3/μl				Neutrophil count ×10 HPF		
	day 1	day 2	day 7	day 13	RS	IP	OM
Group 1							
♂; 36	7.6	11.4	S	S	9	6	7
♂; 40	9.2	13.5	S	S	8	4	6
♂; 37	8.5	10.1	15.2	9.4	3	5	4
♀; 38	10.1	11.2	12.4	10.2	8	9	5
♀; 35	11.2	13.3	10.3	11.5	4	2	6
Group 2							
♂; 40	9.5	13.3	S	S	5	6	7
♀; 39	10.1	14.2	S	S	3	0	0
♂; 38	11.4	12.4	12.3	10.4	4	2	8
♂; 37	12.2	14.3	9.5	7.6	9	6	4
♀; 36	9.5	8.5	7.6	9.7	8	5	6
Group 3							
♂; 35	10.4	12.5	S	S	5	6	0
♂; 40	12.2	8.4	S	S	7	5	4
♀; 40	9.4	10.0	8.5	9.2	8	5	9
♀; 39	12.2	12.5	9.0	12.2	5	4	0
♀; 38	15.1	14.2	12.3	10.1	6	0	0

HPF = High-power fields; RS = resection and suturing area, site of Glubran 2 application; IP = intermediate pulmonary parenchyma; OM = opposite margin from resection.

[a] On postoperative days 1, 2, 7 and 13.

nium iodide and tetracaine, after deep sedation, followed by autopsy and removal of specimens of the treated organ.

Pathological Anatomy

For each animal, 3 specimens were taken from the wedge resection of the treated lung and 2 specimens from the relative resection of the healthy (untreated) lung. In particular, for the wedge resection of the treated lung the specimens were taken from the resection and suturing area, from the intermediate pulmonary parenchyma and from the opposite margin.

The specimens were fixed in 10% buffered formalin for 48 h, processed according to normal histological routine procedures, by means of an automatic processor (Tissue-Tek VIP, Sakura Finetek, Torrance, Calif., USA), and embedded in paraffin.

For each specimen, 3-μm-thick histological sections were prepared, colored with hematoxylin and eosin. The first histological assessment was performed by two blinded pathologists with experience in pulmonary diseases. The bronchovascular triad, the lobular alveolar structure and the type of inflammation present were evaluated for each specimen of lung tissue; morphological markers of acute phlogosis were assessed by neutrophil count × 10 high-power fields.

Results

The mean aerostasis time was calculated at 3.5 ± 1.26 s (table 1). A comparative analysis of aerostasis time in pigs with and without the use of Glubran 2 performed by a Student t test did not show a statistical difference ($t = 0.4764$; $p = 0.6417$). Aerostasis was confirmed as total at the end of the 20 min established as the control period.

In the space of a few hours after awakening, all the animals recovered all the main physiological functions. They all survived for the times foreseen by the protocol.

The laboratory data recorded during the observation period showed no variations worthy of note; in particular white blood cell count was assayed on the 1st, 2nd, 7th and 13th day after surgery, without showing any remarkable difference between the three groups (table 2).

In the surviving animals the drainage tube was removed without creating any evident respiratory or hemodynamic impairment, either immediately or subsequently. In 5 cases (treated with Glubran), we registered air leakage from the chest drainage tube on 1 day; only in 1 case did air leaks prolong till the 2nd postoperative day (table 1).

The anatomopathological examination of the surgical specimens all showed the presence of a slight to medium exudative-adhesive inflammatory reaction. Macro- and microscopic examination of the pulmonary parenchyma

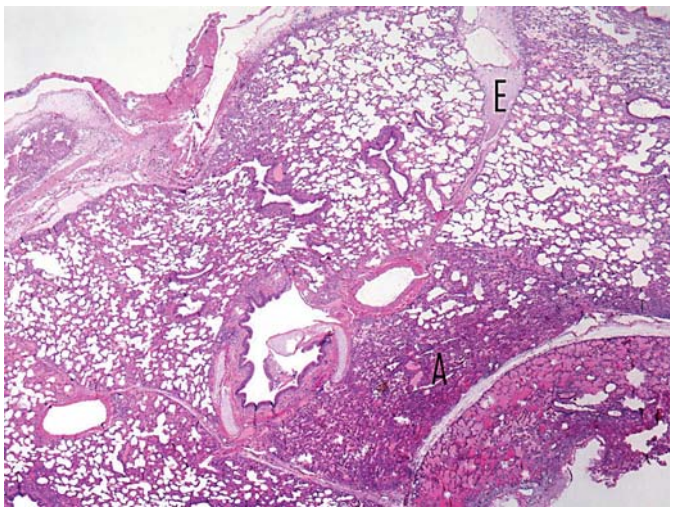

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Fig. 2. Group 2 (EE 4 × 10 high-power fields): E = Interstitial edema; A = areas of pulmonary atelectasis alternating with emphysematous-like areas, with chronic peribronchial inflammation.

showed that all the animals were affected by a moderate unspecific chronic respiratory disease. In particular, histopathological analysis of the pigs from group 1 showed an area of pulmonary atelectasis alternating with emphysematous-like areas, with chronic peribronchial inflammation, focal edema and endoalveolar hemorrhage and slight ectasia of the lymphatic vessels.

Histopathological analysis of the pigs from group 2 similarly showed areas of endovascular edema, interstitial fibrosis, areas of pulmonary atelectasis alternating with emphysematous-like areas, with chronic peribronchial inflammation and focal endoalveolar edema (fig. 2).

Finally, histopathological analysis of the pigs from group 3 showed areas of pulmonary atelectasis alternating with emphysematous-like areas, with chronic peribronchial inflammation and focal endoalveolar edema.

There were no signs of acute inflammation, as revealed by neutrophil count, resulting in <10 high-power fields in each specimen examined (table 2). A comparative analysis of neutrophil count in specimens taken from the resection and suturing area (where we used Glubran 2) performed by a Student t test did not show a statistical difference between the use or not of the glue ($t = 0.3312$; $p = 7.458$).

Discussion

The application of Glubran 2 spray surgical glue on wounds caused by pulmonary resections in pigs proved to have a rapid and effective influence for the purposes of a safe and prolonged aerostasis.

The investigated animals showed signs of a slight to medium specific inflammatory disease attributable to dust inhalation (e.g. feed, hay) already acquired on the farm they came from. These were, in fact, pigs reared on industrial farms where respiratory diseases are subclinically endemic, untreated in view of the food chain destination of the animals. Any pharmacological treatment would in fact be uneconomical, due both to the intrinsic cost of the treatment and to the extended stay on the farm because of the application of the suspension periods foreseen by the law. On the other hand, the presence of exudative-adherent type inflammatory reactions is a notoriously common finding in humans, too.

The histopathological analysis did not show any particular differences when comparing the effects of the treatments carried out with Glubran 2 spray glue and the standard treatments with mechanical suturing and reinforcement with continuous PDS whipstitch sutures. The reparative processes that take place after resection therefore appear, from a morphological point of view, to be more or less identical.

In addition, no statistically significant differences were recorded in the short- and medium-term survival of pigs treated with Glubran 2 spray surgical glue compared with the respective control groups. Similarly, the monitoring of the air and/or blood losses and the radiological controls carried out in the postoperative period did not demonstrate any substantial differences between the pigs treated with traditional thoracic surgery procedures and those in which the protocol included the use of Glubran 2 spray surgical glue alone or combined with traditional surgical techniques. Additionally, the operators did not experience any toxic and/or adverse effects during or after the application of the glue.

In conclusion, the advantages offered by the use of Glubran 2 spray surgical glue can be attributed to the rapidity of its application and to its immediate and permanent effects for the purposes of optimum pulmonary aerostasis. Despite the small number of animals in the experiment, the data are comforting and we intend to continue tests on the use of Glubran 2 spray surgical glue by means of new experimental protocols in the future.

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