Archives of Medical Research 45 (2014) 331–336

ORIGINAL ARTICLE

Further Experimental Studies on a Biodegradable Adhesive for Protection of Colorectal Anastomosis

Jorge Cueto, Tomás Barrientos, Ernesto Rodriguez, Lorena Espinosa, Julio Palma, Jimmy Cojab, Tania Orozco, Apolonio Haro, and Pamela Del Moral

Health Sciences Faculty, Universidad Anahuac and Hospital Juárez de México S.S., Mexico City, Mexico

Received for publication October 17, 2013; accepted March 21, 2014 (ARCMED-D-00575).

Background and Aims. Anastomotic leaks (AL) continue to be a devastating complication after colorectal surgery. The purpose of this experimental study was to confirm if Pebisut® applied to intestinal suture lines increases tensile strength in the critical days of healing and to evaluate its anti-inflammatory properties.

Methods. Bursting pressures and histological evaluation of suture lines in dogs were performed, comparing the burst strength with collagen or fatty tissue patches with/without Pebisut® (patent granted in the USPTO 8,252.333, 26.01.2006, in the European Union 2,062,602, 01.12.2010, in Canada 2,661,686, 21.08.2007 and in Mexico P.C.T./MX/a/2009/001737).

Results. Pebisut® significantly increases burst strength in suture lines in long-term procedures with both collagen and fat pad patches. The adhesive penetrates rapidly into the suture lines, sealing them and progressing towards the intestinal lumen, disappearing in 14–20 days. It was well tolerated without any evidence of ''foreign body'' reaction.

Conclusions. Application of the biodegradable adhesive Pebisut® is easy, well tolerated by mammalian tissues and consistently increases the burst strength of suture lines. Therefore, it may provide more tensile strength in anastomosis and help protect AL, one of the most serious complications in gastrointestinal surgery. If this experimental finding could be translated to clinical surgery, the protection of colorectal anastomosis could be beneficial to patients. Additionally, this could also have a positive impact on the economic expenditures of healthcare systems and patients.

Key Words: Anastomosis, Leaks, Bursting pressure, Collagen patch, Surgical adhesives.

Introduction

Anastomotic leaks (AL) remain as one of the most lethal complications after colorectal surgery as well as in other high-risk surgical procedures. Improvements in anesthetic and surgical techniques continually allow the performance of high-risk procedures; therefore, further chances of complications such as AL exist (1).

These also produce a significant decrease in the quality of life postoperatively and impose a major economic impact on hospitals and health system providers (1–4).

Another frequently ignored problem of AL is that patients with malignant tumors and dehiscence have reduced survival rates (5). A high percentage of ostomies performed are never converted for various reasons such as patient ages and comorbidities (5,6).

To protect high-risk gastrointestinal anastomosis during the critical days of healing, collagen patches have been applied with and without fibrin adhesives in order to compare the outcomes of the anastomosis measuring tensile force and complications between treated and control groups, without any significant differences (7). Other studies that measured hydroxyproline concentration demonstrated that fibrin adhesives do not contribute to the protection of the anastomosis and, on the contrary, may have a negative effect on the healing process (8,9). Granulomas have also been found as a result of the application of fibrin materials in anastomoses and it is well

Address reprint requests to: Jorge Cueto, Universidad Anahuac, Bosque de Magnolias No 87, Bosques de las Lomas, CP 11700, México D.F., Mexico; Phone: (+52) (55) 55960804; FAX: +52-55-55200964; E-mail: cuetoj1@gmail.com

0188-4409/$ - see front matter.
http://dx.doi.org/10.1016/j.arcmed.2014.03.007

known that granulocytes contained in the granulomas are a potential source of collagenase that could produce breakdown of collagen fibers, which may be deleterious in wound healing and may contribute to the production of leakage (10). Due to the lack of an effective sealant, the use of defunctioning stomas has been suggested to avoid AL (5).

Several additional methods tested have been equally ineffective. Therefore, there is an urgent need for surgeons to have an effective and safe adhesive protector for those high-risk anastomoses as stated by the review of Spotnitz et al. (9).

The purpose of this experimental study was to confirm the results of previous reports of our group with the biodegradable adhesive Pebisut® and its protective effects on suture lines in order to determine the intestinal tissue tolerance to this product during the critical days of healing and to evaluate its local anti-inflammatory properties which, if confirmed, may be useful for clinical application (11).

Materials and Methods

Pebisut®, a water-sensitive adhesive, is based on a naturally occurring complex carbohydrate polymer (85% of the mixture) which, among other applications, has been used extensively in human nutrition and medicine for decades. It is combined with an adhesive-modifying agent (15%), a metal oxide that includes a zinc ion. Zinc plays an important role in the healing processes. It has been approved by the U.S. Food and Drug Administration (FDA) as a pharmaceutically acceptable additive and is widely used in orthodontics and in dermatology. It provides adequate viscosity and adhesive strength and reduces tack time. The adhesive is biologically impermeable and has a high resistance to humidity. It is biodegradable and nontoxic and does not require special storage conditions. It does not allow microbial colonization and has a 2-year shelf life. Its use is intended to provide temporary protection in high-risk anastomosis and suture lines. Once prepared (20–25 sec) and in gel form, it is applied (3–4 g) over the suture lines using a blunt metal tip or cotton swab.

Recently, potent anti-inflammatory activity *in vivo* in pooled human mononuclear cells and *in vitro* in mice have been found in our laboratory that may explain some of the properties of Pebisut® (12).

The research protocol was reviewed and approved by the research committee of the Faculty of Health Sciences of the Anahuac University in Mexico City. The protocol complies with the Regulations of the General Law of Animal Health Research in Mexico (NOM-062-ZOO-1999).

Animals were placed in individual cages under the care of an experienced veterinarian and assistants, as well as medical students assigned to the project. Bursting pressures were measured in the sutured intestinal lines and data of chronic inflammation and/or infection were carefully recorded and evaluated.

Experiment #1

Twenty six male and female nonrandomized mongrel dogs (weighing 12–22 kg) were subjected to an 8-day observation period by a veterinarian prior to the experiment. Animals were fasted the night before the procedure. A 500-mg dose of a first-generation cephalosporin was administrated intramuscularly 1 h preoperatively. Anesthesia was induced with intravenous pentobarbital (0.0025 mg/kg). Antisepsis in the abdominal wall was done with surgical soap. Using a sterile technique, a 15-cm upper vertical mid-abdominal incision was made. A proximal jejunal loop 15–20 cm from the ligament of Treitz was exteriorized with Babcock forceps and fixed to the edge of the aponeurosis of the anterior rectus muscles.

In the jejunal loop, two 4-cm-long transverse incisions were made 15 cm from each other. Both were closed in one layer with a continuous inverting suture of 3–0 polyglycolic acid using a 4-mm distance in each bite, the distal one being the first to be sutured. Hemostasis was achieved carefully and a 4 x 2 cm rectangular patch of collagen (Lyostipt, B. Braun Medical, Mexico City) was placed on top of the suture lines covering the entire length of the incision. In group 1 (the proximal suture), 2 g of Pebisut® was applied with a swab completely covering the suture line. This seemed to be the adequate dose required for said incision and the collagen patch was then placed on top. The adhesive tack time was estimated at 12 min in the exteriorized loop.

The midline incision was sutured continuously in one plane with 2–0 polyglycolic acid. A subdermal continuous polyglecaprone 3–0 suture was made to complete the procedure. An antiseptic and a sterile dressing were placed over the incision.

On the 7th postoperative day, under the same type of general anesthesia and using the previous incision, the status of the abdominal cavity was inspected and the area of the surgical procedure was identified and was inspected to assess qualitatively the number and consistency of adhesions. The intestinal loop was carefully freed of adhesions to the abdominal wall avoiding tears of neighboring tissues and was exteriorized and then fixed at the border of the midline incision as previously described in the first procedure. Bursting pressure was determined, placing three large occlusive straight forceps: the first at the middle distance between the two lesions, the second and third, at 4 cm to the proximal and distal ends of both incisions. A #14 gauge catheter was inserted 1 cm proximal to the distal end of the occlusive clamp. The pressure required to produce saline leakage (“bursting pressure”) was measured with a manometer connected in a “Y” manner to a simple mechanic hydraulic pump-infusion line.

After completion of the procedure the dog was euthanized with a large dose of intravenous barbiturates and the intestinal loop was removed, placing it in 10% formaldehyde. Paraffin blocks were submitted for histological analysis.