The American Journal of Surgery (2017) 213, 151-158

The American Journal of Surgery®

Research

Sutureless closure of colonic defects with tissue adhesives: an in vivo study in the rat

Konstantinos A. Vakalopoulos[a,*], Zhouqiao Wu[a], Leonard F. Kroese[a], Johannes Jeekel[b], Gert-jan Kleinrensink[b], Dimitra Dodou[c], King H. Lam[d], Johan F. Lange[a]

[a]Department of Surgery, Erasmus University Medical Center, Room Ee-173, Postbus 2040, 3000 CA, Rotterdam, The Netherlands; [b]Department of Neuroscience, Erasmus University Medical Center, Rotterdam, The Netherlands; [c]Department of Biomechanical Engineering, Delft University of Technology, Delft, The Netherlands; [d]Department of Pathology, Erasmus University Medical Center, Rotterdam, The Netherlands

KEYWORDS:
Surgery;
Colorectal;
Tissue adhesive;
Glue;
New techniques;
Sealing

Abstract

BACKGROUND: Tissue adhesives (TAs) in gastrointestinal surgery are gradually gaining acceptance. Before implementation as colonic sealants, an evaluation of the sealing capability of a TA when in contact with fecal matter, as in a leaking anastomosis, is needed. In this study, we used clinically available TAs for the sutureless closure of colonic defects evaluating mechanical strength and tissue healing.

METHODS: A total of 160 rats were divided into 8 groups. Two .5-cm incisions were created, one in the proximal and another in the distal colon. Incisions were sealed with a TA: Histoacryl Flex, Bioglue, Dermabond, Tissucol, Duraseal Xact, gelatin-resorcinol-formaldehyde or Glubran 2. A control group was included in which the colonic defects were not sealed. Follow-up time was 3 or 10 days. Clinical complication rate, bursting pressure, and histopathologic analysis was included.

RESULTS: Leakage rates in the TA groups were highest for Duraseal Xact, Bioglue, and gelatin-resorcinol-formaldehyde at 3 and 10 days. The cyanoacrylates Glubran 2, Histoacryl Flex, and Omnex, and the fibrin glue Tissucol showed the lowest overall clinical complication rates while maintaining the highest bursting pressure at day 10. Histoacryl Flex exhibited significantly higher collagen formation at day 10 than the other TAs.

CONCLUSIONS: This experimental model evaluates the protective effect of a TA seal on a leaking colonic defect. We found large differences in leakage rates and inertness of the tested TAs. The cyanoacrylates Histoacryl Flex, Omnex, and Glubran 2 as well as the fibrin glue Tissucol demonstrated the lowest leakage rates and the most inert histopathologic profile while maintaining high mechanical strength.

Anastomotic leakage (AL) rates in gastrointestinal (GI) surgery remain unacceptably high, ranging from 5% to 15%, with subsequent mortality rates of up to 32%.[1–3] The sealing of a GI anastomosis with a tissue adhesive (TA) has been a major focus of surgical research during the past years.[4–7] Present-day TAs can be grossly divided into 4 categories based on their chemical composition:

There were no relevant financial relationships or any sources of support in the form of grants, equipment, or drugs.

The authors declare no conflicts of interest.

* Corresponding author. Tel.: +31 10 70 43 683; fax: +31 10 70 44 746.
E-mail address: k.a.vakalopoulos@gmail.com

Manuscript received February 8, 2016; revised manuscript April 21, 2016

0002-9610/$ - see front matter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.amjsurg.2016.05.009

cyanoacrylates (CAs), fibrin glues (FGs), polyethylene glycol (PEG) adhesives and, at last, biological adhesives, which contain albumin and/or gelatine.[8] In upper GI surgery, the use of TAs has become standard clinical practice, for example, in staple line sealing with FG after gastric bypass in bariatric surgery.[9] Furthermore, research indicates that the sealing of the esophageal and the pancreaticoduodenal anastomosis with PEG adhesives and FGs may decrease AL and leakage-related complications.[10–16] In colorectal surgery, despite a broad range of experimental studies, anastomotic sealing with TAs has not yet been implemented into regular clinical practice.[6,8]

To investigate the potential of TA use in colorectal surgery, we have proposed a stepwise validation of TAs for the sealing of the colorectal anastomosis, minimizing confounding factors and enabling a sound comparison between various TAs by using the same experimental model for all TAs. In this bottom-up approach, we started with an experimental model in which 11 TAs were applied on ex vivo rat colon to evaluate mechanical strength. Rheologic characteristics of the TAs were also studied to provide information on their degree of cohesiveness, and in turn, flexibility. We found that CAs were the most promising TAs, maintaining high mechanical strength and flexibility of the glue bond with a high amount of cohesiveness, enabling the absorption of external forces.[8]

In a follow-up in vivo study, the best performing 7 of the 11 TAs were used to glue the serosal surface of 2 intact (eg, without any defect) colonic segments to each other in a sutureless manner, providing information on the inertness of each TA when used on the colon. Clinical, mechanical and (immuno)histopathologic analysis pointed toward large differences between TAs, with the biological TAs (gelatin-resorcinol-formaldehyde [GRF] and Bioglue) showing high mechanical strength but also toxic effects on the colonic wall, leading to ulceration and necrosis. FGs and PEG adhesives exhibited an inert (immuno)histopathologic profile, combined with low mechanical strength. CAs demonstrated high mechanical strength while remaining inert, not causing any toxic effects on colonic tissue.[17]

In the present study, we continue this stepwise validation with a novel in vivo model in which iatrogenic colonic defects are sealed using the same set of 7 TAs, as included in our previous in vivo study. The present model evaluates the protective effect of a TA barrier in terms of intraperitoneal leakage of bowel contents and healing capability, when used to seal a colonic defect in a sutureless manner.

Methods

This study was approved by the ethical committee on animal experimentation, under supervision of the Erasmus University Rotterdam (permit number 105-12-03). This manuscript was written according to the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines.[18] One hundred and sixty inbred specified-pathogen-free male Wistar rats of 2-month-old weighing 250 to 300 gm were obtained from a licensed breeder (Charles River Laboratories, MA). Rats were housed according to standard laboratory conditions, including individually ventilated cages with unrestricted access to standard rat chow and water. An acclimatization period of 1 week was observed before the start of the experiment. Rats were scored daily using an adapted wellness score to assess the onset of peritonitis.[19]

We evaluated 7 TAs, as listed in Table 1. In total, 20 rats were included per TA: 10 rats for short-term (3 days) and 10 rats for long-term (10 days) follow-up. A power analysis was calculated based on an increase of 25 mm Hg (δ) in bursting pressure (BP) between the different experimental groups at day 3. With a standard deviation of 20 mm Hg and an alpha of .05, for a power of 80%, 10 rats were needed per group. All TAs except GRF and Glubran 2 were approved by the US food and drug administration at the time of the study and were used in an off-label manner for the purposes of the present study. Glubran 2 and GRF TAs were CE approved at the time of the study. A control group was also included, in which no TA was applied to the defect, simulating the natural course of an untreated colonic perforation. Rat allocation to each group was performed in a randomized manner by an independent researcher not involved in the experiment. In this study, we opted for a novel model in which the colonic defect location and technique was highly standardizable and comparable to our previous in vivo study.[17] It was decided not to use a colonic anastomosis model, as to minimize confounding factors associated with variations in surgical technique and TA application. Furthermore, AL especially when due to

Table 1 Included study groups and information on included tissue adhesives

Group	Tissue adhesive	TA category	Composition	Manufacturer
0	None	—	—	—
1	Bioglue	AB	Glutaraldehyde-albumin	Cryolife (Kennesaw, GA)
2	GRF glue	AB	Gelatin-resorcinol-formaldehyde	Microval (St. Just Malmont, France)
3	Histoacryl Flex	CA	n-butyl-2-cyanoacrylate	B. Braun (Tuttingen, Germany)
4	Omnex	CA	2-octyl-cyanoacrylate/butyl lactoyl cyanoacrylate	Ethicon (J&J, Sommerville, NJ)
5	Glubran 2	CA	n-butyl-2-cyanoacrylate and methacryloxy sulfolane	GEM S.r.l. (Viarregio, Italy)
6	Duraseal Xact	PEG	Polyethylene glycol with N-hydroxy succinimide	Covidien (Mansfield, MA)
7	Tissucol	FG	Fibrin glue with aprotinin	Baxter (Deerfield, IL)

AB = albumin-based glue; CA = cyanoacrylates; FG = fibrin glues; GRF = gelatin-resorcinol-formaldehyde; PEG = polyethylene glycol; TA = tissue adhesive.