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Review Article

Critical analysis of cyanoacrylate in intestinal and colorectal anastomosis

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Abstract: Background: Although cyanoacrylate glue (CA) has been widely used in various kinds of medical applications, its application in gastrointestinal anastomosis remains limited, and outcomes of experimental studies have not been satisfactory. This systematic review summarizes research regarding CA application in intestinal and colorectal anastomosis, and correlates methodological aspects to experimental outcomes.
Methods: A systematic literature search was performed using Medline, Embase, Cochrane, and Web-of-Science libraries. Articles were selected if CA was applied to intestinal or colorectal anastomoses. Included articles were categorized according to CA molecular structure; the method details in each study were extracted and analyzed.
Results: Twenty-two articles were included. More than half of the inclusions reported positive outcomes (seven articles) or neutral outcomes (eight articles). Analysis of the methods revealed that methodological details such as CA dosage, time of polymerization were not consistently reported. Porcine studies, inverted anastomosis, and *n*-butyl-cyanoacrylate studies showed more positive outcomes; everted anastomosis, and oversized sutures might negatively influence the outcomes.
Conclusions: Owing to the positive outcome from the porcine studies, application of CA in gastrointestinal (GI) anastomosis still seems promising. To achieve a better consistency, more methodological details need to be provided in future studies. Optimizing the dosage of CA, choice of animal model, inverted anastomosis construction, and other method details may improve intestinal and colorectal anastomoses with CA application in future studies. © 2013 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater, 102B: 635–642, 2014.

Key Words: cyanoacrylate, colorectal anastomosis, sealant, sutureless, anastomotic leakage

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INTRODUCTION

Cyanoacrylate (CA) was invented more than 60 years ago for industrial applications.[1,2] Famous for its strong adhesiveness, various commercial names such as "crazy glue" or "instant glue" are well known in daily life. Moreover, the strong adhesiveness of CA also made it an ideal candidate for replacement of conventional sutures in medical use, for example, wound closure. In addition to a strong bond, a fully and evenly sealed anastomosis can be created with CA, avoiding excessive tissue approximation that can induce disturbances in the microcirculation.[3,4] In 1998, the Food and Drug Administration (FDA) approved Dermabond (2-octyl-cyanoacrylate) for topical skin wound closure,[5] which was the first FDA approved CA for medical use. Ever since then, more and more medical-use CA has appeared on the market for different indications.[6,7]

Except for skin wounds, the gastrointestinal anastomosis is another important type of wound closure. However, the use of CA in this field is still limited, and no clearly documented clinical attempts have been made so far. Although substantial experimental efforts have been made, the results of animal studies have not yet been encouraging. Some experimental studies reported anastomoses could be well constructed with CA[8,9]; whereas others reported a mortality rate as high as 30–40%.[10,11] Besides large variations in results, inconsistencies with regard to the methodology

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were also noticed in those experiments. As it has been demonstrated that the anastomotic technique used in clinical gastrointestinal surgery influences the outcomes, we hypothesized that the inconsistent results of experimental studies are partly due to differences in their methods. Thus, the purpose of this systematic review is to summarize the experimental studies regarding CA application in intestinal and colorectal anastomosis, correlating the methodological details to the experimental outcomes.

METHODS

Search methods

This systematic review was performed according to the PRISMA (Preferred Items for Reporting of Systematic Reviews and Meta-Analyses) guidelines.[12] The systematic literature search was performed on the 5th of November 2012. The systematic search of literature was performed using the databases of Medline, Embase, Cochrane, and Web-of-Science libraries. The same search strategy was used in all the databases. The search strategy encompasses the following:

(cyanoacrylate/de OR 'cyanoacrylate derivative'/de OR 'cyanoacrylic acid octyl ester'/de OR enbucrilate/de OR bucrilate/de OR 'poly (ethyl 2 cyanoacrylate)'/de OR (cyanoacryl* OR 'cyano acrylate' OR 'cyanoacrylic acid' OR 'octylcyano acrylate' OR enbucrilate* OR bucrilate* OR enbucrylate* OR bucrylate* OR butylcyanoacryl* OR fimomed OR histacryl OR histoacryl OR sicomet OR isobutylcyanoacrylat* OR ocrilate OR ocrylate OR octylcyanoacrylat* OR dermabond OR omnex OR glubran OR surgiseal OR floraseal OR 'derma flex qs' OR gluseal OR octyseal OR wormglu OR periacryl OR indermil OR liquiand OR xion):ab,ti) AND ('gastrointestinal surgery'/exp OR (('gastrointestinal tract'/exp OR 'digestive system'/exp) AND (surgery/exp OR (surg* OR operat* OR preoperat* OR postoperat* OR perioperat* OR intraoperat*):ab,ti)) OR (((gastr* OR digestiv* OR intestin* OR anal OR anus OR anorect* OR rect* OR bariatr* OR pancrea* OR stomach* OR antireflux* OR colon* OR colorect* OR bowel* OR duoden* OR esophag* OR oesophag*) NEAR/3 (surg* OR operat* OR postoperat* OR preoperat* OR perioperat* OR intraoperat* OR anastom* OR suture* OR adhesi* OR glue* OR sealant* OR hemosta* OR coat* OR lesion* OR wound* OR dehisc* OR disattach* OR attach*)) OR vagotom* OR colectom* OR gastrostom* OR stoma* OR appendectom*):ab,ti)

Study selection

Two independent researchers (Z.W. and G.B.) screened all the articles (the title and the abstract) in a standardized manner. Articles were included only if the CA glue was applied in an intestinal or colorectal anastomosis. The search was restricted to publications in English. Presentations, reviews and letters to editor were not included. All references from the selected articles were screened for further possible inclusions.

Data extraction

For all selected studies, a standard data extraction form was filled in, and the following data were extracted: year of publication, first author, subject (animal species), number of animals, glue (chemical name), glue (commercial name), usage (CA sutureless anastomosis/sealant), dosage, curing time, anastomotic material (additional material to create the anastomosis other than CA), suture material (chemical component), suture size, suturing technique, gastrointestinal level, and outcome (positive/negative, judged according to conclusions of the articles).

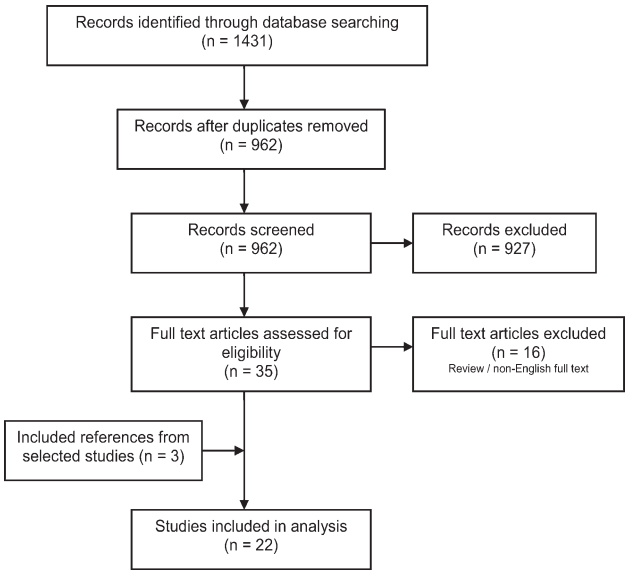

FIGURE 1. Study selection for relevant articles.

RESULTS

A total number of 962 articles were found from which 22 studies were included for final data analysis (Figure 1). Among these, seven articles had positive outcomes; eight had neutral outcomes; the others had negative outcomes. As is listed in Table I, CA with different molecular structures produced by different manufacturers were used and tested. The included articles were divided according to the chemical structure of the CA used, and their chemical names (commercial names if applicable) were listed. Further subdivisions were made according to the use of CA with regard to anastomosis (sutureless anastomosis or sealant).

Methyl-cyanoacrylate (MCA)

Four studies were included that report the use of MCA.[2,10,11,13] A sutureless anastomosis was created in all of them, and none of these studies had positive outcomes (Table II).

In 1962, O'Neill et al. used MCA (Eastman 910) to create a sutureless anastomosis in canines small intestine or colon. In this model, a clamp was used to construct an everted anastomosis.[11] They found that most of the intestinal anastomoses (11/12) were satisfactory and no death occurred, but 28.6% (4/14) of canines died when CA anastomoses were created in the colon.[11] A similar clamp was also used by Weilbaecher et al., who performed the intestinal anastomosis with a greater number of canines. Mortality rate as high as 34% (34/101), and no advantage of MCA were

TABLE I. Cyanoacrylate Adhesives used in the Included Studies

Chemical Structure	Abbreviation	Trade Name	Manufacturer
Methyl-cyanoacrylate	MCA	910 Easterman	Ethicon (Somerville, New Jersey)
Ethyl-cyanoacrylate	ECA	Pattex	Henkel (Dusseldorf, Germany)
N-butyl-cyanoacrylate	NBCA	Histoacryl (blue)	B. Braun (Melsungen, Germany)
	NBCA	Glubran 2	GEM Italia (Via reggio, Italy)
2-Octyl-cyanoacrylate	OCA	Dermabond	Ethicon (Norderstedt, Germany)
	OCA	Gluseal	GluStitch, Inc (Delta, BC, Canada)

found when compared with conventional suture methods.[10] A high mortality rate of 22% (8/35) was also found when Gennaro et al. used an intraluminal gelatin stent to create a colonic MCA anastomosis in a rat model.[2] Different from those experiments, Linn et al. reported a canine study,[13] in which no anastomosis-related mortality occurred. Anastomoses with MCA had less inflammation than the conventional group, but stricture occurred in 40% of the anastomoses when a new invagination technique was used.[13]

Ethyl-cyanoacrylate (ECA)

Only one study used ECA to create the CA sutureless anastomosis,[3] and no study used MCA as an anastomotic sealant (Table II).

In 2009, Elemen et al. used ECA (Pattex) to construct end-to-end, side-to-side, or side-to-end intestinal anastomoses in a rat model. No deaths occurred during follow up, and no differences in bursting pressure were found between the CA anastomosis and sutured anastomosis, whereas higher hydroxyproline levels (a parameter of anastomotic wound healing) and shorter operating time were found in the CA groups.[3]

N-Butyl-cyanoacrylate (NBCA)

Nine studies regarding NBCA were included[8,9,14–20] (Table II). Among these, three studies focused on the sutureless anastomosis,[8,16,17] three studies looked into NBCA sealant,[9,18,20] and the other three tested both applications.[14,15,19] In the NBCA studies, all four large animal studies had positive results,[8,9,14,15] whereas of the other five rat studies only one had positive outcomes.[20]

Matsumoto et al. reported a comparison between CA in different molecular structures (*n*-butyl-, Amyl-, Heptyl-cyanoacrylate) in a canine model of intestinal anastomosis. Only NBCA showed good wound healing without stenosis after 4 or 12 weeks.[14] Another comparison between NBCA (Glubran 2) and OCA (Dermabond) was performed in a porcine model.[8] The CA sutureless anastomoses were constructed in the colorectum with a modified stapling device in which all the staples were taken out in advance. All the NBCA anastomoses were satisfactory, whereas two leakages occurred in the OCA group; NBCA was also superior to OCA regarding to the adhesion and stenosis severity.[8] Tebala et al. also tested NBCA with different suturing techniques in a porcine model.[15] They performed 11 different types of anastomosis. Good wound healing was observed in macroscopic, histological, and angiographic examinations; foreign body reaction was even less in the sutureless anastomosis group than the sealant group.[15] Tebala *et al*. also created an insufficient anastomosis in a pig model by removing 1/5 of the sutures or staples from a normal anastomosis.[9] NBCA was then used to seal the defect. Anastomotic healing was sufficient, and no ileus occurred during the follow up.[9]

Positive results of CA use were reported in a rat study by Ensari et al.[20] In this study, the authors constructed an ischemic-reperfused intestinal anastomosis and used NBCA (Glubran 2) to reinforce it. Higher bursting pressures were found after the CA reinforcement with or without the initial ischemic intervention, while more adhesions were found in the CA groups.[20] Weiss et al. tested another NBCA (Histoacryl) and created gastrojejunal anastomoses in a rat model, comparing it with resorbable sutures. In this study, anastomotic healing regarding leakage rate, stricture, peritonitis, and mortality were similar between both groups. The only significant difference was a shorter operating time in the NBCA group.[16] Bae et al. tested the same glue in a rat model in which they created NBCA (Histoacryl) reinforced anastomoses and the NBCA sutureless anastomoses in the rat colon. No leakage occurred in any of these groups, but more strictures, lower bursting pressure and more severe inflammation was found in the CA reinforced group and the CA sutureless group.[19] Similarly, a lower bursting pressure was also reported by Ozmen et al. in a CA sutureless colonic anastomosis with two holding sutures.[17] NBCA has also been tested in high-risk animal models. Kayaoglu et al. used 0.2 mL NBCA (Glubran 2) as sealant to reinforce the anastomosis in a fecally contaminated environment. Similar macroscopic wound healing and bursting pressure were found on day 3 and day 7 in both the CA group and the suture group; however, more inflammation and necrosis were found in the CA group.[18]

Iso-butyl-cyanoacrylate (isoBCA)

Four studies regarding isoBCA were included[22–25] of which no study had positive results. Dating back to 1980, Kirkegaard et al. used isoBCA to create the sutureless anastomosis with a gelatin stent.[25] They found more stenosis and inflammation in the CA group; however, these complications were significantly reduced when the CA anastomosis was covered with an omental tag.[25]

High mortality was reported by all the other isoBCA studies. Stirling et al. used isoBCA to create the sutureless everted anastomosis, which resulted in a mortality rate of 27.0% (10/37) of canines.[22] In 1968, Hale et al. first used a

TABLE II. Synopsis of Results: Cyanoacrylate Application in Intestinal and Colorectal Anastomosis

Year	Author	Subject	*n*	Glue (Chemical Name)	Glue (Trade Name)	Usage	Dosage	Curing Time	Anastomotic Material	Suture Material	Suture Size	Anastomotic Pattern	GI Level	Outcome
1962	O'Neill et al.[11]	Canine	26	MCA	910 Easterman	Anastomosis	NS	60s	Clamp	–	–	Evert	Intestine Colon	+/–
1964	Weilbaecher et al.[10]	Canine	101	MCA	910 Easterman	Anastomosis	NS	3 min	Clamp	–	–	Evert	Intestine	–
1966	Linn et al.[13]	Canine	30	MCA	910 Easterman	Anastomosis	NS	NS	Invaginate	–	–	Invaginate	Intestine	+/–
1976	Gennaro et al.[2]	Rat	35	MCA	910 Easterman	Anastomosis	NS	10–20s	Gelatine stent	–	–	Evert[a]	Colon	–
2009	Elemen et al.[3]	Rat	96	ECA	Pattex	Anastomosis	NS	NS	Holding suture	Polyglactin 910	5/0	NS	Intestine	+
2011	Paral et al.[8]	Porcine	12	NBCA vs. OCA	Glubran 2 Dermabond	Anastomosis	1.0ml		Modified stapler	–	–	Invert	Colon	+ BCA +/– OCA
2001	Weiss and Haj[16]	Rat	64	NBCA	Histoacryl	Anastomosis	NS	3–4min	Holding suture	Vicryl sutures	6/0	Invert	Stomach-jejunal	+/–
2004	Ozmen et al.[17]	Rat	40	NBCA	Histoacryl	Anastomosis	NS	NS	Holding suture	Polypropylene	5/0	NS	Colon	–
1995	Tebala et al.[9]	Porcine	10	NBCA	NS	Sealant	NS	NS	Suture Stapler	Silk suture	3/0	Invert	Intestine Colon	+
2009	Kayaoglu[18]	Rat	80	NBCA	Glubran 2	Sealant	0.2 ml	NS	Suture	Glycolic acid	5/0	Invert	Colon	–
2010	Ensari[20]	Rat	40	NBCA	Glubran 2	Sealant	0.2 ml		Suture	Polypropylene	7/0	NS	Intestine	+
1967	Matsumoto[14]	Canine	70	NBCA vs. other CA	NS	Anastomosis Sealant	NS	NS	Invaginate	NS	NS	Invaginate	Intestine	+ BCA – others
2010	Bae[19]	Rat	60	NBCA	Histoacryl	Anastomosis Sealant	NS	NS	Suture	Polypropylene	5/0	Evert[a]	Colon	–
1994	Tebala et al.[15]	Porcine/ Rat	55/30	NBCA	NS	Anastomosis Sealant	NS	NS	11 kinds of anastomosis	Silk suture	3/0	Invert	Intestine Colon	+
1965	Stirling and Cohn[22]	Canine	37	isoBCA	NS	Anastomosis	NS	2–3min	Clamp	–	–	Evert	Intestine	+/–
1980	Kirkegaard et al.[25]	Rat	60	isoBCA	NS	Anastomosis	NS	NS	Stent	–	–	NS	Colon	+/–
1968	Hale and Ellis[23]	Rat	66	isoBCA	NS	Anastomosis Sealant	NS	60s	Holding suture	Silk suture	5/0	NS	Intestine Colon	+/–
1971	Uroskie et al.[24]	Canine	15	isoBCA	NS	Sealant	NS	3–4 min	Suture	Silk suture	5/0	Invert	Intestine	–
2002	Kanellos et al.[26]	Rat	40	OCA	Dermabond	Anastomosis	NS	NS	Holding suture	Polypropylene	6/0	NS	Colon	+/–
2004	Nursal et al.[27]	Rat	90	OCA	Dermabond	Anastomosis	0.5 ml	NS	Holding suture	Polypropylene	7/0	NS	Colon	–
2009	Irkorucu et al.[28]	Rat	40	OCA	Gluseal	Anastomosis Sealant	NS	NS	Holding suture/Suture	Polypropylene	6/0	NS	Colon	–
2007	Galvao et al.[29]	Rat	18	NS	NS	Anastomosis	NS	2–4 min	Cuff	–	–	Invaginate	Intestine	+

[a] Shown on the picture of the inclusion.

Abbreviation of different cyanoacrylate is specified on Table I. NS = not specified.

rat model to compare the influence of isoBCA as sutureless anastomosis or as suture reinforcement. Twelve of 16 canines (75%) died in the sutureless anastomosis group, while conventional anastomoses or CA reinforced anastomoses were mostly satisfactory.[23] In 1971, Uroskie et al. used a canine model and performed two intestinal anastomoses in each animal in which the distal anastomosis was sealed with isoBCA. Sixty percent (9/15) of the animals died during the follow-up because of anastomosis-related complications, mostly due to leakage in the CA reinforced anastomoses.[24]

2-Octyl-cyanoacrylate (OCA)

Three studies on OCA were included.[26–28] None reported additional advantages in anastomotic healing when OCA was applied.

Kanellos et al. resected a segment of 1.0 cm in the rat transverse colon, and randomly chose OCA (Dermabond) or sutures to create the sutureless anastomosis. Similar leakage rates, bursting pressures and histological results were found between the CA and suture groups.[26] In 2009, Irkorucu et al. also used OCA (Gluseal) to seal or construct rat colonic anastomoses after inducing wound ischemia. Similar bursting pressure and hydroxyproline concentrations were found between groups, whereas more adhesions were found in the CA reinforced and the sutureless groups than the conventionally sutured groups.[28] However, in an ischemic anastomosis model by Nursal et al., the mechanical strength of the OCA (Dermabond) anastomosis was significantly lower on day 7 than the conventionally sutured groups; furthermore, a higher inflammatory response and necrosis were found in the OCA group.[27]

Other

Galvao et al. used CA to assist a cuff apparatus to create an invaginated anastomosis on rat intestine. The chemical structure of the used CA was not described in this study, but satisfactory anastomoses were still found in both macroscopic and histological evaluations, the CA anastomosis also cost much less time. However, after 1 and 3 days, tissue lesions due to CA toxicity were observed.[29]

METHOD DETAILS

As is shown in Table II, methodological details of each included study were listed. These details mainly focused on the material and technique used for the anastomosis construction.

CA dosage and curing time

Of all 22 included studies, only four studies specified the amount of CA used in each anastomosis. One study used 1.0 mL CA to create the sutureless anastomosis in a pig model,[8] obtaining positive outcomes. A total of 0.5 mL and 0.2 mL CA were also used in three rat models for creating sutureless anastomoses or as an anastomotic sealant.[18,20,27] In these rat studies, only one reported positive conclusions.[20]

Only eight studies listed the curing time after CA application, which varied from 10 seconds to 4 minutes.[2,10,11,16,22–24,29]

Animal species

Three different animal species were used in the included studies. Most studies used rat models (14 studies), and four of them had positive outcomes.[3,20,25,29] Six canine studies were included. All of them were performed in the 1960's and 1970's, whereas only one had positive conclusions.[14] Only three porcine studies were included, all showing positive conclusions.[8,9,15]

Anastomotic construction

Fourteen studies described or had figures demonstrating the anastomotic pattern such as inverted (serosa to serosa), everted (mucosa to mucosa), or invaginated (mucosa to serosa) anastomosis. Six studies employed an inverted anastomosis,[8,9,15,16,18,24] among which three had positive outcomes.[8,9,15] Five studies used an everted anastomosis[2,10,11,19,22]; none of these had positive results. Three studies constructed an invaginated anastomosis,[13,14,29] and two of them showed positive outcomes.[14,29]

Sutureless anastomosis constructed with CA was tested in 18 studies of which five reported positive outcomes.[3,8,14,15,29] Different materials such as clamps, stents, modified staplers or holding sutures were used to approximate the two cutting edges, as is shown in Table II. Within those materials, none of the studies that used an anastomotic clamp[10,11,22] showed positive outcomes. In the other studies that used holding sutures or a modified stapler to create CA anastomosis, mostly the canine and porcine studies (3/4) had positive results.[8,14,15] In contrast, only one rat study (1/8) with holding sutures had positive results.[3]

Nine studies tested CA as a sealant after construction of a primary anastomosis; among these, four reported positive results[9,14,15,20]. Most of these studies used different suture materials (silk, polypropylene, or glycolic acid) and varying suture techniques for the construction of the primary anastomosis. Except for materials, different suture sizes were tested as well. Two porcine studies used 3/0 sutures, both of these having positive outcomes.[9,15] Five studies used 5/0 or 6/0 sutures, mostly in rat models,[18,19,23,24,28] and none of them conclude positively. One rat study used 7/0 sutures, and it had positive outcomes.[20]

DISCUSSION

Substantial efforts have been made to test the feasibility, effect and safety of the use of CA in intestinal and colorectal anastomosis. Using CA as suture-replacement, early experiments in the 1960s and the 1970s failed to create a successful sutureless anastomosis,[10,30] some recent results, although promising, still vary from one to another. Previous opinions mainly blame the chemical characteristics of CA.[2,7] Indeed, intra-abdominal (actually intraperitoneal) application of CA is distinct from its topical use, such as skin wound closure, because intra-abdominally applied CA can only be absorbed, metabolized, and degraded by the body instead of falling off by itself. However, this still does not explain everything, as most current available CA contain longer molecular chain, which are less toxic than short

length CA.[7] Creating anastomoses with artificial materials not only requires a good mechanical strength but should also induce a good physiological wound healing, which eventually supports the bowel continuity and biomechanical strength by itself. All these influences indicate the importance to investigate methodological details in CA application, such as selection of CA molecular structure, dosage, animal model, and anastomotic technique. With this aim, this review summarizes the studies regarding application of CA in intestinal and colorectal anastomosis, linking the method details to the outcomes. We found that these studies contained great inconsistencies in the methods. Furthermore, some important factors and details in the methods might influence outcomes, which are discussed respectively in the following sections.

CA molecular structure

CA was tested as a potential suture replacement because of its strong adhesiveness, which makes it possible to seal a technically flawed anastomosis, and even to create a sutureless anastomosis. Our previous *ex-vivo* study showed that adhesiveness is similar among different types of CA, but is much stronger than adhesive strength in other categories of tissue adhesives (unpublished data). When choosing CA for specific surgical applications, it is therefore more important to take other factors into account, such as tissue toxicity.[31,32]

In general, shorter chain CA monomers (i.e., methylcyanoacrylate) create significant amounts of heat during polymerization, and are known to degrade into toxic endproducts, resulting in severe tissue reaction and inflammation, whereas longer chain-length CA is associated with more hydrophobic and bacteriostatic properties and less tissue toxicity.[2,7] However, in intestinal and colorectal anastomoses, data from the studies that compared different CA seem to prefer in NBCA to other shorter or longer monomers.[8,14,27] Our results in this review also agree with this, as most CA studies with MCA, isoBCA, or OCA had negative outcomes, and more than half of the NBCA studies reported positive ones.[8,9,14,15,20] Nevertheless, one must note that, with the current limited data, it is still too early to conclude which CA is the best for intestinal and colorectal anastomoses. The biological properties of CA are influenced not only by its molecule structure but also by the additional components added into the adhesives. Developments in biochemistry may bring further improvements in CA molecule structure for specific use as intestinal and colorectal anastomotic.

CA dosage

As well as the molecular structure, an important role in the tissue reaction of CA is also played by CA dosage. Unfortunately most studies did not provide details on this. One can imagine that an overdose of CA, comparable to a very high number of sutures or staples around the anastomosis, may lead to more side effects rather than a further increase in anastomotic strength. As CA is known to react exothermically during polymerization, CA overdose may cause direct tissue damage during polymerization, and increase adhesion formation, lengthening the long-term degradation time.

The currently available information is not enough to allow an analysis of the optimal amount of CA for intestinal and colorectal anastomosis in different animal models. According to the study of Paral et al., 1.0 mL of CA should be enough to construct a sutureless anastomosis in the porcine model.[8] Compared with the dosage for porcine anastomosis, 0.5 mL and 0.2 mL CA might be too much for rat anastomosis, as the rat colon is more than ten times smaller. Some clues on optimal CA dosage can be found from data in vascular surgery, where only 0.4 μl CA was enough to create vessel anastomosis in rats.[34] Although the manufacturers' original applicator can be directly used in porcine or other big animal models, a small syringe with a blunt needle is recommended in rodent models to ensure accurate CA application.

Animal model

Canine models might not be suitable for future CA studies, not only due to the poor outcomes from the previous literatures but also because of ethical concerns. This review shows that all previous studies using porcine models had positive results, implying that this might be the best large animal model for future CA studies regarding to intestinal and colorectal anastomosis. This is also supported by the previous systematic review, which also found the porcine model to be superior to those with other animal species, as the pig's gastrointestinal tract is much more similar to a human's than a rodents'[35]; this enables human-size surgical tools and human-dose CA to be used directly on porcine. However, the high costs of large animal models result in most animal studies on CA being performed on rat models. As stated earlier, most of the previous rat studies in this field were not a success. This is most probably due to the small size of the rat. Almost all techniques, and also the material size and dosage will thus need to be specifically adjusted for rats.

Anastomotic technique

Construction of a successful anastomosis is not simply connecting two ends together and reaching a mechanical strength as high as possible. A good and safe physiological wound healing without complications (i.e., anastomotic leakage, adhesion, and stenosis) is more important from a clinical perspective.[36] For anastomosis of the digestive tract, the inverted-suture technique has been demonstrated to lead to a sufficient biomechanical strength as well as a better wound healing than the everted pattern; invaginated anastomosis is hardly used in clinic because of higher risks to develop stenosis and other complications.[36–39] Outcomes from CA research also confirm this, as all the studies using everted anastomosis had negative results, whereas more than half of those using inverted anastomosis had positive outcomes.[8,9,15] Comparing data from the included studies, we recommend that an inverted-suturing technique should also be used in future CA studies.

Overall, the use of CA in intestinal and colorectal anastomosis has two functions: to construct a sutureless anastomosis, or to reinforce a primary anastomosis as an

anastomotic sealant. For sutureless anastomosis, various materials have been used to approximate the two bowel endings before CA application. Among these materials, the modified circular stapler (in which the staples are removed prior to use) in large animal models might be a good option because the CA can easily be applied on the inverted anastomosis.[8] As a small stapler for rodents is lacking, the use of holding sutures was described in most of the rat studies. However, it does not yet seem to be satisfactory according to our results. One possible reason is that the holding sutures are not able to guarantee the inverted connection, thus creating an everted anastomosis that may complicate wound healing if CA is polymerized between the two wound edges. Also, instructions for topical usage of CA in skin wound closure indicate that the application of CA between the wound edges should be prohibited.[7] To ensure an inverted anastomosis, a special stent might be a good replacement for holding sutures, but more work on this is still required.

For the use of CA as a sealant, the suture material and its size are also important factors for a good anastomosis. Our data shows that 3/0 sutures, often used in human intestinal and colorectal anastomosis, are suitable for large animal models; 5/0 sutures may be inappropriate for the rat intestinal and colorectal anastomosis, as no study reported positive outcomes with these. This may be due to the large size of the 5/0 sutures (diameter of absorbable 5/0 suture: 0.15–0.199 mm[40]) relative to that of the rat colon (thickness of adult male rats: around 0.6 mm[41]). The 3/0 sutures (0.30–0.349 mm[40]) are much smaller and lighter compared with the human colon (thickness: 2.6 mm[42]) or porcine colon. For rat intestinal and colorectal anastomosis, smaller size sutures such as 7/0 (0.07–0.099 mm[40]) or 8/0 (0.05–0.069 mm[40]) seemed to be proper while more evidence is still required.

CONCLUSIONS

In view of the positive outcomes of the large animal experiments, the application of CA in intestinal and colorectal anastomosis seems promising. However, the great inconsistency and lack of detailed information in the previous literature made comparison of methodology difficult. To achieve a better consistency, studies should provide more details in the methods. If the dosage of CA, the choice of animal model, inverted anastomosis construction, and other method details also are improved, future studies will achieve better intestinal and colorectal anastomoses with CA.

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