Article

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Cyanoacrylate in Colorectal Surgery: Is It Safe?

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Abstract: Anastomotic leakage (AL) of a gastrointestinal (GI) anastomosis continues to be an important complication in GI surgery. From its introduction more than 60 years ago, Cyanoacrylate (CA) has gained popularity in colorectal surgery to provide "prophylaxis" against AL. However although in surgical practice it is increasingly used, evidences on humans are still lacking. The aim of this study is to analyze in humans the safety of CA to seal colorectal anastomosis. All consecutive patients from Jannuary 2022 through December 2022 who underwent minimally invasive colorectal surgery were retrospectively analysed from a prospectively maintained database. Inclusion criteria were histological diagnosis of cancer, totally minimally invasive procedure and absence of intraoperative complications. 103 patients were included in the study, N-butyl cyanoacrylate with metacryloxisulfolane (Glubran 2 ®) was used to seal colorectal anastomosis, no adverse reactions to CA or postoperative complications related to inflammation and adhesions occurred, only one case of AL (0.9%) was recorded. We can consider this study an important proof of concept on safety of CA to seal colorectal anastomosis. It opens the possibility to start performing prospective and comparative studies in humans to evaluate effectiveness of CA in preventing colorectal AL.

Keywords: cyanoacrylate; colorectal surgery; minimally invasive surgery; anastomosis; leakage; inflammation; adhesions

Background

Anastomotic leakage (AL) of a gastrointestinal (GI) anastomosis continues to be an important complication in GI surgery. The development of AL depends on several risk factors which can be divided into patient-related risk factors and operative factors. AL rates in colorectal surgery (less than 3–23%) has decreased due to several surgical innovations which include stapling techniques, intraoperative air testing, direct sigmoidoscopic visualization and use of tissue adhesives to seal colorectal anastomosis [1–15]. Cyanoacrylate (CA) is a type of tissue adhesive CE certified for internal and external use. It has haemostatic, adhesive and antiseptic properties and, once injected, it polymerises in contact with vital tissues to create an elastic layer with a high tensile strength. The use of CA, from its introduction more than 60 years ago, has increased in various fields of surgical practice, especially in GI surgery [16,17] for different purposes such as to seal gastrointestinal and rectal anastomoses, anastomoses in biliary tract and appendix stumps, to control hemostasis, to close mesenteric defects and to treat gastrocutaneous, anal and perianal fistulas. In this study we focused on its role as sealant of colonic anastomosis. Between other applications of CA, its use in emergency surgical procedures and in treatment of upper and lower gastrointestinal fistulas are very interesting. In 1998 Dermabond (2-octylcyanoacrylate) was approved for topical skin wound closure by Food and Drug Administration (FDA) [18]. Since the medical use of CA tissue adhesives has been established, many experimental animal studies have been performed to evaluate their use in colonic anastomosis [19,20]. However although in surgical practice CA is increasingly used, evidences on humans are still lacking. This study involved cancer patients who underwent minimally invasive colorectal surgery. In all operations N-butyl cyanoacrylate with metacryloxisulfolane (Glubran 2 ®), CE certified for internal and external use, was used as anastomotic sealant and it was applied on colonic anastomosis after its creation with a Spray Device for Surgical Glue Glubran 2. N-butyl cyanoacrylate with

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metacryloxisulfolane (Glubran 2 ®) was also indicated as CA in the rest of the text. The aim of this study was to analyze in humans the safety of CA to seal colorectal anastomosis.

Materials and Methods

All consecutive patients from Jannuary 2022 through December 2022 who underwent minimally invasive colorectal surgery were retrospectively analysed from a prospectively maintained database. Inclusion criteria were histological diagnosis of cancer, totally minimally invasive procedure and absence of intraoperative complications to avoid bias in the safety assessment of CA to seal colorectal anastomosis. Written informed consent was obtained from all subjects enrolled in the study.

Before surgery each patient received a complete history and physical examination with blood tests and tumoral markers research, a colonscopy with both biopsy of the lesion to obtain histological diagnosis of cancer and the endoscopic tattooing of the lesion to facilitate surgeon's work, a total body Computed Tomography (CT) for tumor staging and a Magnetic Resonance Imaging (MRI) in case of medium-low rectal lesions. After a careful evaluation of the clinical case, the operative technique was chosen. Moreover after the patient admission bowel preparation with osmotic laxative when it was possible and preoperative antibiotic and heparin prophylaxis were administered to each patient.

All patients underwent a minimally invasive procedures under general anesthesia. All operations were performed by experienced colorectal surgeons. In right colectomy, the ileocolic pedicle was identified and the peritoneum of the mesentery was opened creating a mesenteric window. After identification and preservation of the right ureter, duodenum, and pancreatic head, Toldt's fascia was separated from Gerota's plane. The ileocolic pedicles, the right colic vessels and the right branch of the middle colic vessels were tied at their origin and the right colon was mobilized from the right parietocolic gutter. Then the right hemicolectomy with a linear stapler and the subsequent intracorporeal ileo-colic anastomosis fashioning in a side-to-side isoperistaltic way were performed. In the left colectomy, the surgeon started with the colo-epiploic detachment and the mobilization of the splenic flexure. Toldt's fascia was separated from the Gerota's plane preserving the left ureter and gonadic vessels, then the Inferior Mesenteric Vein (IMV) and the Inferior Mesenteric Artery (IMA) could be isolated, clipped, and divided. Left hemicolectomy with a linear stapler and the subsequent colorectal end-to-end anastomosis according to Knight–Griffen technique were performed. In the anterior rectal resection, after the aforementioned steps a Partial or Total Mesorectal Excision (PME or TME) was added to the procedure. In case of segmental splenic flexure resection, after the descending and transverse colon were mobilized, the left branches of the middle colic vessels and the left colic artery were isolated, clipped, and ligated. For transverse colon resection, after the complete mobilization of both the colic flexures, a resection of the mesentery including the middle colic artery was performed. Segmental resections included the intracorporeal colo-colic anastomosis fashioning in a side-to-side isoperistaltic way. Moreover to control that colorectal vascularization was adequate, Near-Infrared Fluorescence-Indocyanine Green (NIR/ICG) system according to a standardized technique was carried out for each patient at two different moments: before and after the anastomosis creation to control the proper stumps vascularization and to control anastomosis perfusion respectively. In detail, a bolus of 0.2 mg/kg of ICG was administered by the abesthesiologist before the intestinal resection and after the anastomosis creation and if an adequate vascularization was present, after 25 seconds it was visible.

After the creation of colonic anastomosis and control of its proper vascularization with ICG-test, one millilitre of N-butyl cyanoacrylate with metacryloxisulfolane (Glubran 2 ®) (CA) was applied on colonic anastomosis by using a Spray Device for Surgical Glue Glubran 2. This device allowes you to apply CA in nebulized form and to evenly release it on the area of interest in 60-90 seconds. After its application, the surgeon placed a gauze over or in contact with CA paying attention in removing the product in excess. If the intervention was performed with the robotic approach, CA was applied by assistant surgeon.

The study was conducted according to the guidelines of the 1975 Declaration of Helsinki. The study findings have been reported in compliance with the STROBE checklist. [21]

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Demographic informations and surgery-related data were extracted. Demographic informations included sex, age, BMI, obesity, smoking, comorbidities, ASA score, previous abdominal surgery. Surgery related-data involved operative time, time to first flatus and stool, time to tolerance to solid diet, lenght of hospital stay, postoperative complications (adverse reactions to CA, AL, other complications).

Primary outcome was occurrence of adverse reactions to CA.

Secondary outcome were occurrence of AL, other complications and postoperative recovery assessment.

SPSS 28 system (SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis. Continuous data were expressed as mean ± standard deviation, categorical variables were expressed as percentages.

Results

156 patients were eligible for study inclusion and they were enrolled in the analysis but 53 were excluded because of the following reasons: 22 patients underwent surgery for diverticular disease, 20 patients received an open approach, 8 patients required conversion to open because of adhesive syndrome and 3 patients had intraoperative complications of which 2 intraoperative bleedings and 1 splenic lesions.

Thus 103 patients were included in the study. 57 patients previously underwent open or minimally invasive abdominal surgery while 46 of them didn't receive previous abdominal interventions, 14 patients underwent neoadjuvant therapy.

Demographic characteristics, tumor localization and type of surgical procedure are showed in Table 1.

Table 1. Demographic characteristics, tumor localization and type of surgical procedure of the included patients.

CHARACTERISTICS	
M/F (%)	57/46 (55%/45%)
Age (years)	67.2±10.1
BMI (kg/m^2)	26.2±5
ASA 1 (%)	0
ASA 2 (%)	50 (48%)
ASA 3 (%)	48 (47%)
ASA 4 (%)	5 (5%)
Hypertension (%)	72 (70%)
Diabetes (%)	18 (17%)
Obesity (%)	18 (17%)
Smoke (%)	26 (25%)
TUMOR LOCALIZATION	
Caecum (%)	5 (5%)
Right colon (%)	18 (17%)
Liver flexure (%)	7 (7%)
Transverse colon (%)	5 (5%)
Splenic flexure (%)	4 (4%)
Descending colon (%)	6 (6%)
Sigma (%)	26 (25%)
Rectum (%)	24 (23%)
Colorectal junction (%)	6 (6%)
Right colon and colorectal junction (%)	1 (1%)
Caecum and sigma (%)	1 (1%)
TYPE OF SURGERY PROCEDURE	

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Right colectomy (%)	33 (32%)
Transverse colon resection (%)	2 (2%)
Splenic flexure resection (%)	6 (6%)
Left colectomy (%)	31 (30%)
Anterior resection of the rectum (%)	27 (26%)
Total colectomy (%)	2 (2%)
Subtotal colectomy (%)	1 (1%)
Proctocolectomy (%)	1 (1%)

Categorical variables are expressed as numbers and (percentages), while continuous variables are expressed as mean ± SD. M: male; F= female; BMI: Body Mass Index; ASA score: American Society of Anesthesiology score.

Of the 103 enrolled patients, 57 (55%) were men and 46 (45%) were women. Mean age was 67.2 ± 10.1 and mean BMI was 26.2 ± 5. 50 patients (48%) presented an ASA grade 2, 48 (47%) of them an ASA grade 3 and the other 5 (5%) an ASA grade 4. Arterial hypertension affected 72 patients (70%), diabetes affected 18 patients (17%), obese patients were 18 (17%) and smokers were 26 (25%).

About tumor localization, in 5 cases it was located to the caecum (5%), in 18 cases to the right colon (17%), in 7 cases to the liver flexure (7%), in 5 cases to the transverse colon (5%), in 4 cases to the splenic flexure (4%), in 6 cases to the descending colon (6%), in 26 cases to the sigma (25%), in 24 cases to the rectum (23%), in 6 cases to the colorectal junction (6%), in one case there were two lesions located to the right colon and to the colorectal junction (1%) and in another case there were two lesions located to the caecum and to the sigma (1%).

About surgical procedure were performed 33 right colectomy (32%), 2 transverse colon resection (2%), 6 splenic flexure resection (6%), 31 left colectomy (30%), 27 anterior resection of the rectum (26%), 2 total colectomy (2%), 1 subtotal colectomy (1%) and 1 proctocolectomy (1%).

All patients underwent minimally invasive procedure with the laparoscopic approach in 61 cases and the robotic approach in 42 cases using CA to seal anastomosis.

Surgery-related data are showed in Table 2.

Table 2. Surgery-related data of the included patients.

SURGERY-RELATED DATA	
First flatus (days)	1.91±0.87
First stool (days)	3.01±1.72
Lenght of hospital stay (days)	6.08±2.63
Time to tolerance to solid diet (days)	3.27±1.44

Categorical variables are expressed as numbers and (percentages), while continuous variables are expressed as mean ± SD.

No adverse reactions to CA or complications related to inflammation and adhesions occurred, only one case of AL (0.9%) was recorded in a patient with a BMI greater than 30 kg/m ^{2}. Other complications were classified according to Clavien-Dindo Score. Particularly a Clavien-Dindo grade 2 occurred in 8 patients (8%), 6 of them had nausea (6%) and they were treated with antiemetic drugs while the other two patients had fever (2%) and they were treated with antipyretic drugs. Clavien-Dindo grade 3 occurred in 11 patients who had anemia (11%) and who received blood transfusions.

Other postoperative complications are showed in Table 3.

Table 3. Postoperative complications.

CLAVIEN-DINDO (CD) SCORE	N (%)
CD 1	8 (8%)
Nausea	6 (6%)
Fever	2 (2%)
CD 2	11 (11%)

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Anemia	11 (11%)
CD 3	0
CD 4	0
CD 5	0

Categorical variables are expressed as numbers and (percentages).

Mean operative time was 210.2 ± 55.21. Mean lenght of hospital stay was 6.08 ± 2.63, mean time to first flatus was 1.91 ± 0.87, mean time to first stool was 3.01 ± 1.72 and mean time to tolerance to solid diet was 3.27 ± 1.44.

Discussion

The anastomotic leakage (AL) is a serious complication in colorectal surgery. In the past, it's occurence ranged from 17% to 77% [22–26]. It is a multifactorial problem. The development of AL depends on several risk factors which vary between different populations and which can be divided into patient-related risk factors and operative factors. In details patient-related risk factors involve comorbidity, body mass index and drug use while operative factors include surgeon's experience, after-hours surgery, anastomotic location and operating time [13–15]. Of interest one of the causes of AL is ischemia, thus between the comorbidities it is important to consider vascular diseases such as atherosclerosis, whose risk factors are hypertension, dyslipidemia, smoking and diabetes mellitus [15]. About BMI it has been showed that a BMI ≥ 30 is predictive for AL [27]. About drug use it has been reported that patients on corticosteroids who are in poor clinical conditions or who suffer major blood loss or when the intervention is longer than usual could have a higher risk of AL [28]. Surgeon's experience in very important in influencing outcomes following colorectal cancer surgery, especially rectal cancer surgery, in fact this type of surgery should be performed by high-volume surgeons [29]. Moreover the creation of the anastomosis is one of the most technically difficult steps, particularly when it interests the rectum with an AL risk which is seven times higher than it is located to the right colon and four times higher when it is located to the left colon [30]. However even in high-volume centres there are several features which influence AL development such as delays in diagnosis or neoadjuvant therapy. After-hours surgery is defined as the period in which patients undergo an intervention performed by on call operating team and it has been reported that these patients have more than a twofold increased risk of AL [15]. Finally prolonged operative time could lead to AL probably because it could reflect intraoperative complications [30].

Recently, the adoption of surgical innovations which include stapling techniques, intraoperative air testing, direct sigmoidoscopic visualization and use of tissue adhesives to seal colorectal anastomosis have reduced the AL rate (3% to 23%) [1–12] and the risk of a serious clinical leakage [31]. Tissue adhesive can be defined as any substance which allows for polymerization both to hold tissues together and to avoide leakage [32]. They are less invasive than sutures and staples and don't affect the wound-healing process due to their flexibility. Moreover their application is easy and standardizable, resulting in less variation between different surgeons. There are different categories of tissue adhesives based on their chemical composition: fibrin sealants, albumin-based compounds, cyanoacrylates, hydrogels, and collagen compounds.

N-butyl cyanoacrylate with metacryloxisulfolane (CA) is a class III medical device for internal and external use. It is a synthetic cyanoacrylate liquid modified by addition of a monomer. It has haemostatic and adhesive properties, moreover once solidified it provides an effective antiseptic barrier against infectious agents or pathogens of surgical settings. It is a waterproof pale yellow, transparent liquid which polymerises in contact with vital tissues to create an elastic layer with a high tensile strength ensuring firm adhesion to tissue. A temperature of approximately 45°C is generated during the polymerisation reaction. The layer fits to the anatomy of the underlying tissue. The polymerisation time depends on the type of material with which CA comes into contact. After its application, the glue starts to set after 1-2 seconds and ends its setting reaction in 60-90 seconds. Once set, tissue or surgical gauzes may be placed over or in contact with CA.

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There are several accessory devices for CA administration such as insulin syringe, drop control device, dispensing tip, laparoscopic catheter, spray device that we used for our cases, Glubran 2 sealing device and glutack.

CA, from its introduction more than 60 years ago, has gained popularity in colorectal surgery [16,17,33] showing to have lower toxicity to the tissues. However it is used in various field of surgical practice such as cardiac surgery, pediatric cardiac and general surgery, vascular surgery, neurosurgery, ophthalmology, maxillofacial surgery and odontostomotology, plastic surgery, thoracic surgery, gyneacological and breast surgery, urological surgery, digestive endoscopy, interventional radiology and vascular neuroradiology, interventional cardiology and angioplasty. Particularly in GI surgery it applies for different purposes such as to seal gastrointestinal and rectal anastomoses, anastomoses in biliary tract and appendix stumps, to control hemostasis, to close mesenteric defects and to treat gastrocutaneous, anal and perianal fistulas. In this study we focused on its role as sealant of colonic anastomosis and the evidences we found in literature are controversial [34–48]. On a clinical point of view some surgeons believe in the useful advantages of CA in preventing AL. Other surgeons think about the potential risks of CA in creating inflammation and adhesions which could lead to possible postoperative complications. So far, the only certain adverse effects could be rare inflammatory reactions at the application site due to an excessive amount of CA, allergic reaction and anaphylaxis.

This is the first study which evaluated the safety of a CA to seal colorectal anastomosis in humans. In fact available data on the use of CA both for sutureless colonic anastomosis and for colorectal anastomotic sealant were only showed in experimental animal studies [34–48]. Bae et al. [36] performed a study on male Sprague-Dawley rats and divided them in three group where the group 1 received an anastomosis sutured in a single layer, the group 2 received an anastomosis fixed using CA and the group 3 received an anastomosis both sutured and sealed with CA. They didn't observe AL in any group showing that CA could be a useful technique for sutureless colonic anastomosis. Similar results were reported by Kanellos et al. [37]. Of interest were several studies on pigs [42,48–52] which had physiological reactions similar to that than humans. These studies demonstrated some advantages of CA. In details Tebala et al. performed a study on Wistar rats and Landrace pigs [48] to analyze the tissue reaction to CA and its adhesive features and another study on Landrace pigs [49] to evaluate the efficacy and patient tolerance of CA when employed as a sealant for high-risk intestinal anastomoses. It was found that CA had a good adhesive effect in the first study [48], that it was efficacy as a sealant for high-risk anastomoses and that it supported the wound healing process in the second study [49]. Similar results were also reported by Wu et al. [50] who demonstrated that CA is the most important factor to determine the strength of a both normal and insufficient sealed colorectal anastomosis and that the mechanical strength of a colorectal anastomosis increased with CA application probably contributing to the decrease of AL occurrence. Moreover Boersema et al. [51] investigating the effect of CA in prevention of leakage in a porcine model of ischemic colorectal AL, found that its use prevented from leakage in cases with partially ischemic colo-colonic anastomosis. Paral et al. [52] compared the resistance of glued versus stapled colonic anastomosis to intraluminal pressures at different times during healing. They found that not only gluted anastomoses resisted to pressure significantly higher than that physiological pressures but also that CA didn't affect anastomoses healing. On the other hand in a clean contaminated or bacterial peritonitis environment [53] CA determined inflammatory reaction, necrosis, and adhesion formation.

Of interest was a case report [54] of a patient who underwent an emergency surgery of a total gastrectomy with CA application on the side-to side esophago-jejunal (E-J) anastomosis after caustic ingestion. This study showed that even in emergency surgical procedures CA could be used to seal the anastomosis due to its utility and efficacy. This was an important food for thought because it increased the fields in which CA could be use such as non-elective interventions and operations complicated by intraoperative problems. Their application is easy and standardizable so their use in emergency situations would not lead to a significant impediment for the surgeon who could find CA a valid tool, fast and convenient to use. In this study intraoperative complications were exclusion

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criteria and patiets affected by them weren't included in the analysis to avoid bias in the safety assessment of CA to seal colorectal anastomosis. However the aforementioned case report led us to think that intraoperative complications didn't influence the judgment on CA safety but high-quality studies on humans have to be performed on this topic to obtain certain results.

Between other applications of CA, the treatment of upper and lower gastrointestinal fistulas was one of the most interesting. Few case reports were presented in literature [55–58]. In details Anoldo et al. [55] reported a case of cervical esophageal perforation which was successfully treated with CA injection after the failure of the other conservative options. Thus it was possible to consider CA a promising minimally invasive alternative for the treatment of cervical esophageal perforation. Alharbi et al. [56] described a case of a low-output enterocutaneus fistula treated with CA applied on sutures. They showed that the glue can be a safe minimally invasive treatment for this type of fistula. Moreover it seems possible to use safely also in pediatric surgery as showed by Hosseini et al. [57] who reported the treatment of cases of tracheoesophageal atresia with fistula, hypospadias, cases of vesicutanouse fistula after bladder extrophy and cases of cloacal extrophy.

All patients enrolled in the analysis underwent minimally invasive procedure with the laparoscopic approach in 61 cases and the robotic approach in 42 cases. Laparoscopic surgery is the gold standard for the treatment of colorectal cancer given its proven advantages such as smaller abdominal incisions, lower manual traction and abdominal tissue manipulation, shorter postoperative recovery with better operative outcomes and oncologic safety [58,59]. However laparoscopic approach presents some technical difficulties when it is performed in small field such as the pelvis requiring an high surgeon expertise. The robotic approach could help to solve these problems with 3D-magnified view with better ergonomics and lower physiologic tremor due to EndoWrist instruments. In fact it was reported that the robotic technique for rectal resection is the best way to perform a complete TME [60].

In our series before CA application on colorectal anastomosis, its proper vascularization was checked with (NIR/ICG) system. Indocyanine green (ICG) is a tricarbocyanine compound which, once injected intravenously, through blood perfusion reached the liver and its fluorescence was captured and activated by a system with the power of a light emitted by a led. ICG fluorescence decreased when the vascularization of a tissue was reduced [61].

After checking the anastomotic vascularization, it could proceed with CA application. The amount we used was one millilitre of product in 60-90 seconds. The device we preferred was a Spray Device for Surgical Glue Glubran 2 to deliver CA in an atomised form evenly on the interested area. It was important not to apply more that of the fixed dose because it could lead to inflammatory reactions, allergic reactions and anaphylaxis thus causing possible bias in the safety assessment of CA to seal colorectal anastomosis. If an excess of product occurred, the surgeon removed it with a gauze. Thus CA dosage played a central role in its application. Unfortunately current literature did not show certain results on this. However an high dose of CA could cause CA overdose with tissue distruction and adhesions formation so it was important to remove excess of CA from the colonic anastomosis.

According to our results we can propose safety of CA as an anastomotic sealant. All consecutive 103 enrolled patients had no adverse reactions to CA or postoperative complications related to inflammation and adhesions. This can support safety of CA in colorectal cancer patients and it can help reassure surgeons who worry about the potential risks of tissue adhesives and to encourage them to use it as sealant. Regarding leakage prevention, only one case of leakage occurred (0.9%) in our series with an AL rate lower than that showed in literature (3 to 23%). It could make us think that it is possible that the adhesive properties of CA decrease the risk of leakage development. Anyway CA in our study certainly didn't lead to an increase of leakage occurrence. However this result should not be generalized to all colorectal cancer series because other comparative studies on widest sample sizes are needed to give certain results.

We can consider this study only an important proof of concept on safety of CA to seal colorectal anastomosis. It opens the possibility to start performing prospective and comparative studies in

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humans to evaluate effectiveness of CA in preventing colorectal AL and to explore its real advantages in clinical practice.

Conclusions

CA is safe as anastomotic sealant. It is less invasive than sutures and staples like the other tissue adhesives. In addition it has lower toxicity to the tissues. The application of a fixed amount of product on the colorectal anastomosis seems avoid inflammatory reactions, allergic reactions, anaphylaxis and complications related to inflammation or adhesions. About leakage prevention there are promising results but high quality studies on widest sample sizes remain to be required to evaluate in humans its effectiveness and its real advantages.

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Informed Consent Statement: Informed consent was obtained from all subjects enrolled in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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