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EN ISO 13485:2012

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Introduction

During the recent Congress of the *Società Italiana di Chirurgia Oncologica (SICO)* (Italian Society of Surgical Oncology), the symposium held by GEM S.r.l. (Viareggio, www.gemitaly.it) highlighted some interesting applications of Glubran®2.

Based on a growing body of evidence, this modified-cyanoacrylate surgical medical device, which has been on the market for over 20 years, exhibits special properties enhanced by the spray application of the product, which go beyond those of a "haemostatic sealer".

The Speakers, presenting their specific experience with Glubran®2 in the prevention and conservative treatment of serious surgical complications, such as postoperative biliary and digestive fistulas, repeatedly highlighted its preventive use.

Pasquale Talento
Reggio Emilia

Glubran®2 is not only a haemostatic sealer: Clinical evidences of Glubran®2 biliostatic properties

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In the last decades, thanks to the improvements of neoadjuvant chemotherapy and to the availability of biological drugs (molecular targeted), the indications in surgical treatment of primary and secondary hepatic cancers, have greatly expanded.

Significant, in this sense, are the results of the OBELIX study [1], which confirm the efficacy in metastatic, or locally advanced, colorectal cancer, in combination with bevacizumab / oxaliplatin / capecitabine, not only in terms of disease-free survival, but also as "downsizing" that can increase the rate of secondary resection, potentially curative of liver metastases (RO resection, with tumor-free margins).

Therefore, resection surgery is now offered at a growing number of patients: in other words, the limits of resectability/operability (related to the number and volume of lesions, hilar lymph nodes status, etc.) are going to be redefined, and oncologic hepatic surgery has become, so to speak, increasingly bold.

Currently, the hepatic tumour is considered resectable if it is technically possible to completely remove it, by saving, at least, two contiguous liver segments (and its biliary drainage), for a residual volume but not less than 30% or 40%, if coexisting neoplastic disease (cirrhosis, steatohepatitis, or other liver damage from chemotherapy).

The more "aggressive" surgery, even in the treatment of advanced and / or multiple lesions, has in fact resulted, despite technology improvements (staplers, evolved solutions for haemostasis control, etc.), an increase of complications post liver resection [2-10].

In particular, bile leakage, that do not close spontaneously, and which can then hesitate in the creation of a so-called biloma (ie. an encapsulated collection of bile, outside the biliary tree) (Figure 1) or, even worse, in the biliary fistula.

In literature, the incidence of bilomas turns out to be 4-17%, up to 42% in some case studies, with their showing even 10 to 15 days after surgery [11-13].

The borderline resectable patients, undergoing neoadjuvant chemotherapy, are particularly at risk.

Figure 1. Biloma Diagnostic Imaging: A) NMR; B) CT; C) Ultrasound

Glubran®2 is not only a haemostatic sealer: Clinical evidences of Glubran®2 biliostatic properties

GLUBRAN®2 (N-butyl-2-cyanoacrylate and methacryloxy sulfolane co-monomer)

- High adhesive in humid conditions (live tissues), haemostatic, sealant and bacteriostatic (barrier) properties.
- High elasticity and tensile strength for a waterproof and breathable bonding.
- Ready to use, formulated as a clear liquid in single-dose vials of 0.25; 0.50; 1 ml to be kept between 2 and 8°C.
- Single use applicator devices for open and laparoscopic surgery:
  - ✓ Dispensing tip for a topical product distribution
  - ✓ Drop by drop, with needle, blunt tip
  - ✓ 1 ml syringe with Luer Lock
  - ✓ Catheter for laparoscopy, for rigid and flexible 5 mm trocar
  - ✓ Spray devices with a gas autonomous propulsion system (Figure 2A).
- Lower polymerization temperature (45°C), which starts to contact with the tissues (1-2 seconds), and is completed in 60-90 seconds.
- Minimum usage quantity: 1 ml → 20 cm2 of tissue.
- High biocompatibility and slow biodegradability, with no release of toxic products.
- Also applicable in combination with sutures.
- Easy puncture with suture needles.
- Used as embolic agent, it can be mixed with Lipiodol® in endovascular procedures.

For further information, please, refer to the manufacturer's website (www.gemitaly.it)

Available evidence and personal experience [14] show that, compared with patients without biliary fistula, those with post-operative biloma have a higher risk of more severe complications (54.3 vs. 29.2%, P = 0.002), and extended hospitalization (29 days vs 14 days, P <0.001), with a significant increase of mortality (8.6 vs 2.6%, P = 0.045).

Note that the biloma is also a possible complication of thermoablative techniques (radiofrequency) in oncological treatments or arterial chemo embolization [15].

A key factor for the intraoperative control of the bile leakage, that is, for an effective biliostasis that prevents the formation of biloma, is the availability of a sealing substance with an adequate adhesive action to surface, or hepatic resection cut.

We hypothesized, that Glubran®2, due to its peculiar properties (see the above table for any further information on Glubran®2 technical characteristics and properties), could be the best choice (compared with other adhesives/ haemostatic already used). Therefore, we have tested it since 2013, through an observational study in patients undergoing oncologic liver surgery, for a total of 95 major resections, 63 of which for colorectal cancer metastasis, after neoadjuvant chemotherapy (OBELIX Protocol).

Glubran®2 was applied, on the cut section, in two ways:

- drop by drop, on an evident "leaking" biliary duct (which, however, tends to retract) that cannot be securely closed with the common standard approaches such as sutures or clips;
- spray, by means of a dedicated device (Figure 2A), when, through laparoscopy, it was not possible to recognize/suspect the leak point, and/or the cut section was a wide surface (potential biliary outflow).

The spray allows a homogenous and fast distribution of the product (which is likely to polymerize in a very short time: start 1-2 seconds, end 60- 90 sec). Make sure to avoid repeated passages at the same point, in the wrong belief to increase the sealing effect, and that, on the contrary, would lead to the risk of forming a hard-condensed effect, that tends to detach with movements (Figure 2B).

In brief, the absence of complications, relating to the use of surgical adhesive, the incidence of biloma, in patients treated with Glubran®2, was comparable to that reported in the literature (11%) (2-10) and, de facto, halved compared to that recorded (21%) in the two

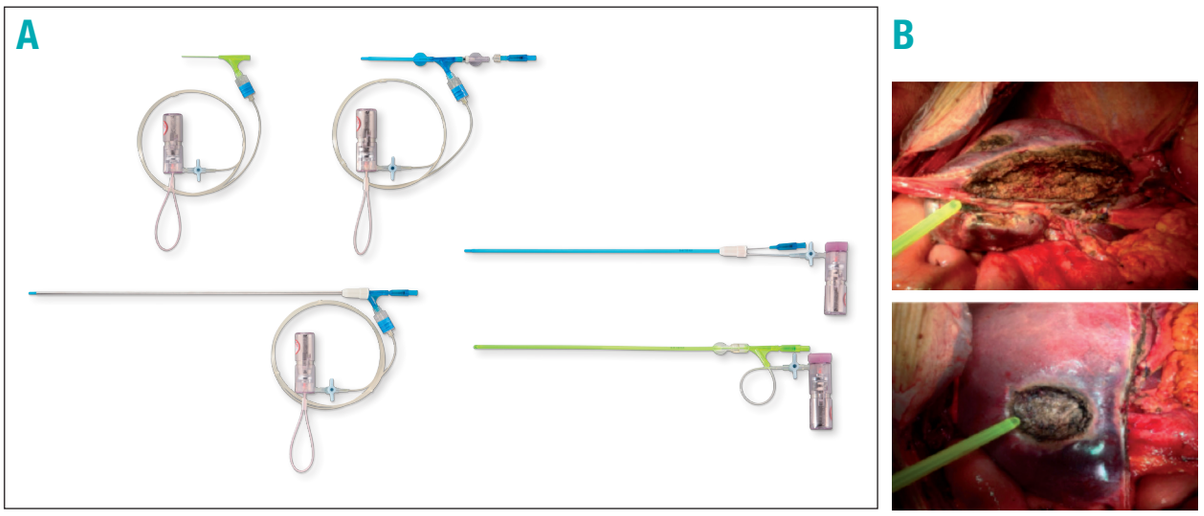

Figure 2. A) Disposable spray devices, with gas autonomous propulsion system, for Glubran®2 application. Laparoscopic and open surgery version, for applications on large [blue] and small [yellow] surfaces. B) Glubran®2 atomising on liver section cut.

years prior to its introduction into routine practice [14].

These results are favourable, of course, to be confirmed on larger clinical case studies but the emerging Glubran®2 significant and peculiar biliostatic action, that is preventive for biloma formation, make it better than other sealants in preventing biliary and/or biliary-enteric fistulas (page 11, report of Dr. Poretti).

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Solid pseudopapillary tumour of the pancreas body in a teenager: case report and literature revision

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Solid pseudopapillary tumours (SPT, Solid Pseudopapillary Tumours) of the pancreas are rare (0.13 to 2.7% of pancreatic tumours), with a slow growth and low-grade malignancy (1); their incidence is increasing after the OMS has included them as a distinct disease entity in the classification of pancreatic tumours. Much more frequent in women [10:1), young people are affected (average age, 24 years old), often in childhood / teenagers. These tumours usually are in the tail of the pancreas and the first symptoms are unclear, correlating to mass effect with compression/dislocation (but, in some cases, also infiltration) of adjacent organs and structures [abdominal pain, feeling of abdominal obstruction, nausea and vomit) (1). The macroscopic histological appearance is that of a well-circumscribed tumour with areas presenting necrosis, haemorrhage and cystic degeneration. Microscopically, it is characterized by pseudopapille coated by layers of epithelioid cells. Clinical, ultrasound and CT contribute to the differential diagnostic orientation. Radical surgery is the only curative treatment, the therapeutic gold standard. The biological behaviour is less aggressive than other pancreatic cancers, and the prognosis is favourable, with overall 5-year survival rate of > 95% and recurrence rate of 5-7% (2).

The resection is however also indicated in the presence of local invasion, recurrence and limited metastasis (10-15% incidence of metastasis to lymph nodes, peritoneum, and liver); the portal vein or superior mesenteric artery infiltration is not indicative for unresectable tumours. The role of adjuvant chemotherapy is debated, however, limited by its high rate of resectability (3).

Pancreatic surgery is burdened by dangerous complications. The most common is the pancreatic fistula (7%), which in our recent experience (June 2011-August 2015: 12 cephalo-pancreaticoduodenectomy - PDC - and 10 distal pancreatectomies with splenectomy). It appeared in two patients (9%); while one patient (4.5%) had the complete dehiscence of the pancreaticojejunostomy with fistula mixed, and needed a totalization re-intervention. In all cases, Glubran®2 was used as a preventive measure: in a thin layer (drop-by-drop) to reinforce the pancreaticojejunostomy in PDCs; by means of the dedicated spray device (see Figure 2A), it was atomised on the mechanical suture line in the distal spleno-pancreatectomies. The mode drop to drop seems to offer a higher precision, while the spray is preferable for uniform application in a thin film of sealant, with a proper technique that avoids the creation of glassy-like aggregates, which would be likely to break away with visceral movements.

We used Glubran®2 even recently, in a girl, 16 year old, affected by SPT of the pancreas body: it started with fever (from left basal "concomitant" pneumonia), and abdominal pain. On physical examination, a mass was palpable in the left flank. The diagnostic work-up, in particular the abdominal CT, showed a pancreatic body-caudal lesion with suggestive aspects of SPT: solid mass, well capsulated and hyper vascularized, infiltrating the splenic vein, with irregular

aspect due to the alternation of solid and cystic areas and peripheral enhancement after administration of contrast medium. The patient was then subjected to distal splenopancreatectomy (en bloc), with mechanical stapling and sealing, of the pancreatic stump, by atomising the Glubran®2. The postoperative recovery was regular with hospital discharge on the 9th day. The histological examination confirmed the diagnosis of SPT with no resection margins infiltration. The 7-month follow-up is positive: the patient is in good condition and has resumed her daily activities. Glubran®2 appears able to reduce the incidence of pancreatic fistulas after pancreatic resection, contributing to the achievement, even in structures with a not high specific operational volume, very satisfactory results, and superimposable to those of the reference Centres.

Essential, for optimal outcomes, are, obviously, experienced and proper surgical technique, but Glubrans®2 appears as an additional product, effective and cost saving, in the difficult and controversial management of the pancreatic stump and in reinforcement of mechanical pancreaticojejunostomy after PDC. Moreover, Glubran®2 has a "history of use" in the closing and sealing of the stump (without pancreatic-digestive anastomosis), with significant Italian experiences (4). The product can, in fact, be used for the occlusion of the main pancreatic duct, after PDC, with selective indication, or in cases of so-called "high-risk" stumps, for reduced tissue consistency. In effect, according to many evidences, in case of a soft and friable stump (or, in any case, not fibrotic, then it is index of an exocrine function preserved), it would be suggested not to pack the pancreatic-digestive anastomosis at risk of dehiscence. This, especially if the Wirsung is normal/not dilated (calibre <3-4 mm), and thus advising to opt for the alternative of a single occlusion/sealing of the duct by means of surgical adhesive ("chemical closure"). It is cautious, on which there is not an unanimous agreement, to be taken into consideration especially in Centres with limited volume of pancreatic surgery; the anastomosis pack requires more experience than the occlusion of the Wirsung with sealant. It should also be underlined that the sealing of the duct contributes, with the extent of the resection, to the absolutely not negligible incidence of postoperative insulin-dependent diabetes. On the other hand, preventing the anastomosis does not make sure advantages in terms of complications, even if the management of a possible fistula is simpler, after exclusive sealing and from the clinical and therapeutic point of view. This is because - contrary to what happens after dehiscence of a pancreatic-digestive anastomosis -, pancreatic enzymes cannot be activated, and any jejunal-contaminated material does not flow into the abdomen. Furthermore, for many, sealing and anastomosis must not be considered as alternatives, but complementary methods, and then applicable simultaneously in the same patient, prior weighted risk/benefit personalized assessment. In conclusion, Glubran®2, already used for digestive anastomosis, is effective and safe in preventing post-pancreatic surgery fistulas, so a routine application is expected, also, and perhaps above all, in a Centre with reduced operating volumes. Glubran®2 can possibly and safely be used for the "chemical closure" of the pancreatic stump in the PDC, ie. without packing of pancreatic-digestive anastomosis.

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Sealing and strengthening the intestinal anastomosis

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The basic principles (subtle dissection, non-touch technique, careful control of haemostasis) of minimally invasive surgery are primarily intended to reduce post-operative complications. In digestive surgery, complications relating to anastomotic dehiscence are still significant - no matter if open or laparoscopic approach - and potentially life-threatening (peritonitis, septic shock, multiple organ failure). Particularly, colorectal surgery, in approximately 30% of postoperative mortality, can be attributed to a "failure" of the visceral anastomosis (leak), which has an incidence of the 8% with the range of between 3 and 23% in the literature [1, 2], and that, anyway, affects adversely clinical outcomes (increased risk of local recurrence in surgical oncology), and hospital costs (longer hospitalisation, intensive care unit (ICU) admission, re-interventions). The estimation, that the therapeutic management, of a patient with anastomotic dehiscence, on average, is 5 times more expensive than that of a patient with post-operative course not complicated [3, 4].

Therefore, preventing anastomotic leak can mean benefit for patient, and health system. An effective prevention is based on the knowledge of the repairing mechanisms that lead to the consolidation of the intestinal anastomosis.

The outcome of the transection of the intestine is an inflammatory cascade, characterized by collagenase, with the local formation of a group of amino acids, especially of proline and lysine, components of collagen. In this inflammatory phase, the peri-anastomotic tissues are particularly fragile and, consequently, regular evolution of the healing process is at risk; it is also shown that in the colon the collagenolysis is more noticeable than in the stomach and small intestine [5, 6].

Clinically, this phase at risk is between the 5th and the 7th post-operative day, and corresponds to the gradual transition to a proliferative phase of collagen for scar repairing. The seventh day is therefore the most feared for the appearance of dehiscence, which, if earlier, on the other hand, recognizes other pathogenic mechanisms related to a not optimal packing of anastomosis [7].

The described pathophysiological processes are, in fact, the rationale that justifies the use of intraoperative procedures to prevent the dehiscence of anastomosis, such as the application of additional manual stitches to the mechanical stiches and / or collagen (known as strengthening or reinforcing) or sealants patch (fibrin glue or cyanoacrylate, such as Glubran®2). Available evidences on the preventive effectiveness of sealants come mainly from experiences in bariatric surgery (page 15, report of Dr. P. Capuano): it is about not conclusive data, which need to be confirmed and validated.

In other words, considering that today we have technologically advanced staplers, and that the correct implementation (well-vascularized margins, not in tension, etc.)

remains essential to prevent anastomotic dehiscence, there is the need to design and implement ad hoc observational clinical studies, which assess the real impact on anastomotic performance of the sealants in a standardized surgery procedure. The true anastomotic sealing effect is an endpoint that places a preliminary methodological problem of measurement. If, in fact, the rationale of the sealant use, based on the pathophysiology knowledge above set out, is to "strengthen" the anastomosis in the critical first days after its packing, by sealing it with a waterproofing resistant membrane. The parameters to be measured, to check the actual and additional effectiveness of the sealant, remain to be defined. It is obvious that we cannot just compare the incidence of postoperative dehiscence (it is too late!), but it is necessary to identify other clinically applicable methods, even intraoperatively. In mainly experimental studies, the tightness of the sealed anastomosis was assessed in a different way: bacterial tracers, colorants, microscopic analysis, resistance to intraluminal pressure or bursting pressure, etc. [8, 9]. In animal models, the Glubran®2 revealed its effectiveness even when used without stapler, with the anastomosis bursting pressure packed with the adhesive only, not markedly lower than that of the non-sealed mechanical suture [9, 10]. Therefore, the experimental outcomes show that Glubran®2 is, at least, a suitable potential "buttress", and seems to have all the features necessary to be defined a sealing adhesive, superlative for patient, surgeon and health system (Figure 3).

Glubran®2 fully meets the principles of minimally invasive surgery, and appears able to centre the primary objective of reducing anastomotic complications in an effective, safe and cost-saving way. Its application potential is greatest, practically on all anastomosis (manual or intracorporeal linear). Glubran®2 polymerises quickly, forming a solid, waterproof, and breathable sealing film. In my personal colorectal surgery experience, the easy and uniform atomisation, at the right distance, of a thin film of Glubran®2, gave preliminary satisfactory results, at least on a ,as much as possible, standardized procedure or mechanical anastomosis, end-to-side, ileo- transverse (linear stapler 28 mm) after right hemicolectomy (Figure 4). It appears debatable and not rational, the hypothesis of an application of sealant before the "shot" on the tissue area, which the stapler

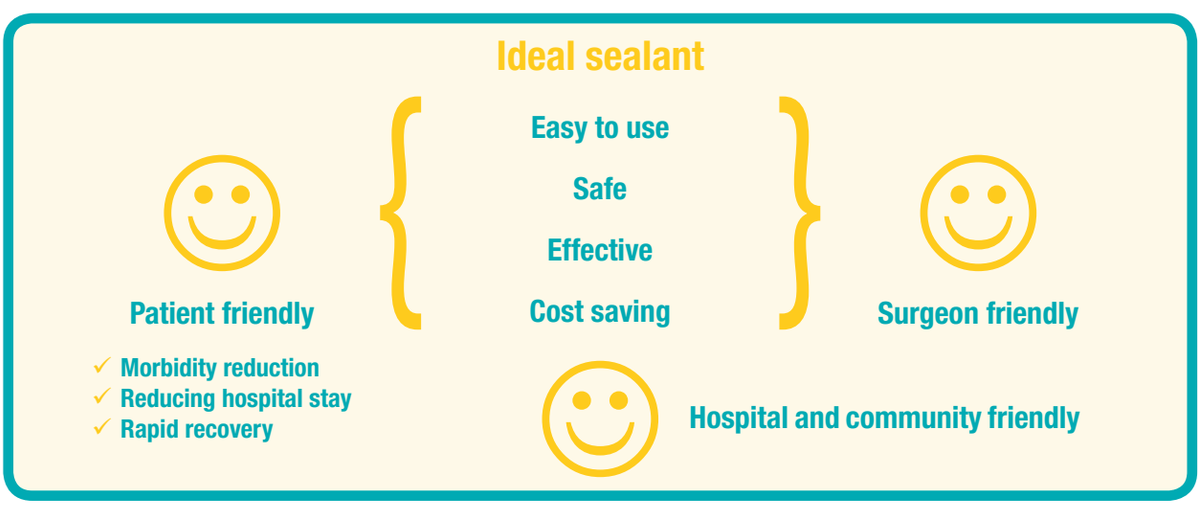

Figure 3. Main characteristics of an ideal sealant. Glubran®2 emerges as the ideal sealant, for the patient, surgeon and health care system: efficient, safe, cost-saving, potential to reduce morbidity, postoperative hospital stay, time to recover normal life (for the patient) and health care costs.

Figure 4. Atomisation of Glubran®2 on end-to-side anastomosis ileo-transverse, by spray catheter for open surgery.

will juxtaposed to the other, because it is intuitive that the blade and points, piercing the cyanoacrylate film, will irreparably impair the waterproof effectiveness.

On the contrary, it is likely that the sealant, applied after the packing of the mechanical anastomosis, acts especially by closing, in a waterproof way, the spaces of the suture line, from one point to the other.

The good outcomes on the right colon make arise interesting improvements for a possible extension in the use of Glubran®2:

- Due to the "reinforcement" of anastomosis, colics are less complex and the risk of fistulisation is lower
- Anastomosis non-colic
- In particularly aggressive surgeries, and at risk of fistulas (cytoreductive surgery using peritonectomy and HIPEC, Hyperthermic Intraperitoneal Chemotherapy).

Therefore, the organization of a consensus conference, dedicated to the design of a clinical multicentre study is suggested. This kind of study should be methodologically correct and objectively support the current evidences, still largely anecdotal, but that - as already mentioned - are significantly converging in indicating Glubran®2 as the ideal sealant also in terms of cost savings.

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Post-surgical enteric fistulas treatment with image-guided injection of modified cyanoacrylate based glue

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Glubran®2 is used in interventional radiology for the treatment of biliary fistulas, but also of enteric ones. Postsurgical biliary fistulas (biliary leaks) have an incidence ranging from 0.1-1.4% after cholecystectomy, to 0.4-3% after cephalo-pancreaticoduodenectomy (PDC), and up to 8% in the liver surgical resection or transplantation (Righi et al., Liver Transpl. 2008; Yeo et al., Ann Surg. 2007; Jukka et al., Surg Endosc. 2007; William et al., Ann Surg. 2002). The post-operative mortality, related to leaking, may reach 19% in transplant patients (Kim et al., Liver Transpl. 2008).

Besides conservative approach, there are other possible therapeutic strategies, such as image-guided percutaneous drainage, endoscopic and / or percutaneous procedures of various types, surgical repair.

The objectives of percutaneous treatments in interventional radiology are (Krokidis M et al., Insights Imaging. 2013):

- dilation of any stenosis coexisting downstream (which increase the endobiliary pressure and help the bile leakage and bilomas formation);
- diversion of bile from the leakage point;
- complete drainage of any collection;
- sealing / embolization, when possible, of the fistula tract with adhesives or other substances.

The sealing / embolization can be limited to the leakage point (block a hole) or extended to the whole of the affected bile duct segment (segmental ablation), to block the production of bile and induce atrophy in the corresponding liver segment. However, a selective catheterization is necessary to reach the bile duct, where is the fistula and / or the collection that this feeds, by a percutaneous approach to the biliary system. This can be done directly or through the already positioned abdominal drainage (Saad WE et al., Tech Vasc Interv Radiol . 2008). The substances used for the sealing / embolization are absolute alcohol (98-99%), spirals and cyanoacrylate or fibrin glues. Other embolizing agents are Gelfoam® (absorbable fibrin sponge) and Onyx® (copolymer ethylene-vinyl-alcohol), commonly used in vascular applications. In qualified Centres, laser is also used.

Note that alcohol finds its elective indication, for the ablation of a liver segment, where the atrophic involution is needed, but after making sure that, it is functionally excluded. If not, the alcohol must be used with caution, as it is difficult to control the accidental spread to the parenchyma areas, that are not involved in the pathological process, and , thus, must be preserved. However, at the end of the procedure, a "sentinel" drain should be left to check the treatment effectiveness.

The physical and mechanical properties of a sealant, for a proper sealing of live biological tissues, are:

- Elasticity
- Tensile strength (and breaking strength)
- Adhesiveness in humid conditions.

Previous works have studied the characteristics of fibrin and synthetic glues. In vitro tests (Kull S et al., J Surg Res. 2009; ASGE

Technology Committee, Gastrointest Endosc. 2013) show, in fact, that the fibrin glues, to be reconstituted prior to use, are completely reabsorbed by macrophages in 14 days, but they do not guarantee, despite their elasticity, any proper tensile or bonding strength. Furthermore, for a safe bonding, they must be applied on a dry substrate (not in a moist environment, such as that of live tissues).

The cyanoacrylate-based adhesives are used as the preferential option for optimum sealing even of post-surgical enteric fistulas. Glubran®2 is a particular cyanoacrylate, second generation, modified by addition of methacryloxy sulfolane, to form a co-monomer with peculiar properties, which distinguish it from the other cyanoacrylate-based adhesives.

Glubran®2 is ready to use, and above all, has a strong adhesiveness to biological tissues (Losi P et al., J Surg Res, 2010) (and so in moist environment), and a high tensile and breaking strength, even if it polymerizes creating a thin film (Kull S et al., J Surg Res. 2009) (Figure 5). It is also absolutely biocompatible, and with a slower biodegradability, that does not release potentially toxic products (Montanaro L et al., Biomaterials. 2001). It is important to underline that, in interventional radiology procedures for the biliary fistulas treatment, there is the need of expert operators in the "navigation" and, especially, a very careful management during the application phase of the glue, that must not be atomized but injected exactly at the site to be treated.

It is just for this reason that Glubran®2 is previously mixed with Lipiodol® , to make it radiopaque (allowing the monitoring of its progression inside the catheter, and the "local" spread, through fluoroscope technique), and get the product polymerization timing suitable to that specific application. Concerning the treatment of enteric fistulas, the use of Glubran®2 finds a solid rational in the peculiarity of its physical and mechanical features, and action mechanism (Romano A et al., Eur Surg Res. 2008).

Glubran®2 not only obliterates the fistula tract by solidifying and creating a filling volume (similarly to fibrin glues), but, by adhering

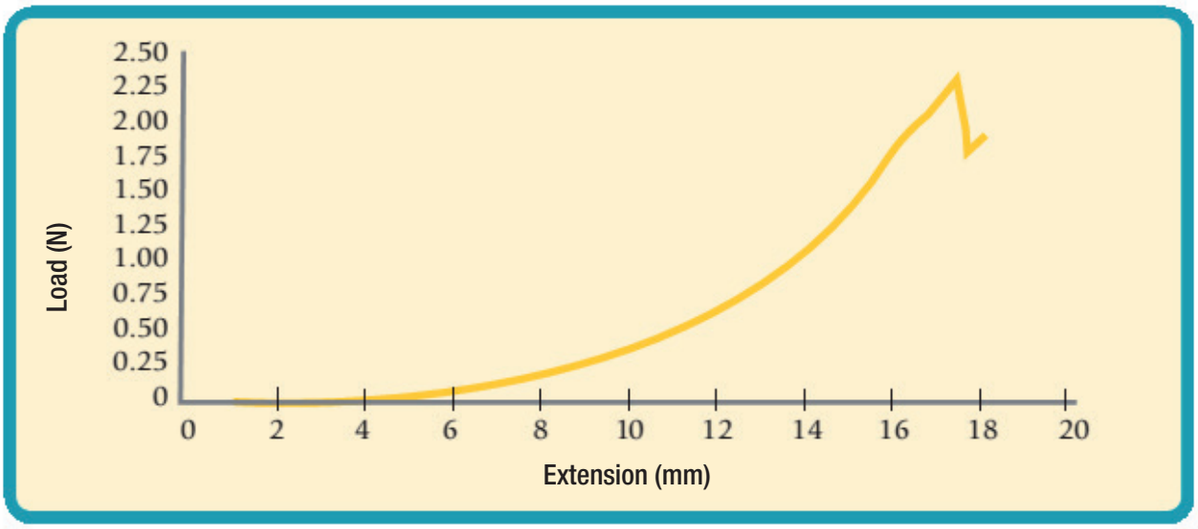

Figure 5. Tensile Test on skin wound sealed with Glubran®2 [experimental model]. The glue shows high tensile strength: the bounding film remains intact until its breaking, as shown in the regular trend cargo curve [modified by Kull S et al., J Surg Res. 2009]
N: Newton: mm: millimetres.

firmly to the tissues, induces an inflammatory response, which stimulates the fibrosis and formation of a foreign body granuloma, with consequent acceleration of the healing process to the final re-epithelialization (ASGE Technology Committee et al., Gastrointest Endosc. 2013). In absence of controlled trials, a recent review of 20 prospective or retrospective observational studies, confirmed that embolization / sealing with cyanoacrylate glues is an endoscopic and/or percutaneous procedure of interventional radiology, feasible and safe for all digestive fistulas, in the high digestive tract (gastroduodenal - foregut), and small intestine, and colon-rectum (mid - and hindgut). The success rate is more than 80%, with an incidence of complications, however not serious, 1% (López J et al., Surg Innov. 2015).

In the review, the first personal experience with Gubran®2 was also considered. It was used on 3 cancer patients with intra-abdominal abscess related to postoperative non-healing fistula: the first patient - dehiscence of the duodenal stump after subtotal gastrectomy; the second patient - jejunal fistula after subtotal colectomy; the third patient - ileocutaneous fistula after abdominoperineal resection (Miles resection treatment) (Lopez J et al., Surg Innov. 2015).

In all cases, the injection of Glubran®2 in the tract area proximity, through percutaneous drainage, and with image guided radiological procedure, was effective and free of complications, avoiding the re-intervention (Mauri G et al., Clin Radiol. 2013) (Figure 6 A, B). The current personal series consists of 3 more patients with enterobiliary fistula after gastrectomy, also treated with Glubran®2 and similar interventional radiology procedure, found to be effective in two cases (median follow-up 15.2 months). Note that more than one session can be necessary to seal permanently the involved intestinal wall section, to reach with the (biliary or angiographic) carrier catheter, eventually through the drain (surgery) or, if feasible and appropriate, combined endoscopic approach. In some cases, biliary drainage with nasojejunal tube facilitated the procedure; the diversion of bile from the digestive tract, however obtained, obviously contributes to healing. The image-guided "navigation" to the fistula, and the collection of the abscesses can therefore be difficult, but the very delicate moment is when the carrier catheter is slowly withdrawn to inject the glue in the fistula. A minimum, accidental spilling into the abdominal cavity of Glubran®2 does not cause any problem, but it is important to measure its quantity, avoiding excessive injection, which delays the obstruction of biliary duct. In this sense, more than the absolute quantity - the necessary quantity must be estimated considering the size of the collection and fistula tract -, it is fundamental the fluoroscopic control of the precise distribution of the sealant, and, especially, the correct timing of the rapid withdrawal to the outside of the carrier catheter ("detachment "), when the amount of injected adhesive is estimated to be satisfactory. A greater dilution with Lipiodol® (usually the ratio is 1:2) can make the procedure less binding, in regard to the withdrawal time of the catheter, but it must be assessed case by case, without impairing the effectiveness of the product.

Therefore, Glubran®2 confirms its effectiveness in the treatment of resistant enteric fistulas, and in particular settings, i.e. when the related abscess collection is more or less directly linked to the biliary system (Mauri G et al., Insights Imaging. 2013), to constitute an enterobiliary fistula. This is a situation where, for some physicians, a re-intervention would be inevitable (Krokidis M et al., Insights Imaging. 2013). Moreover, Glubran®2, as here shown, is also feasible to be used in the treatment of pancreatic fistulas. In our experience, we have two cases, one with total resolution at the first application, where, through a drain, the main pancreatic duct was catheterized directly and embolized backwards with Glubran®2.

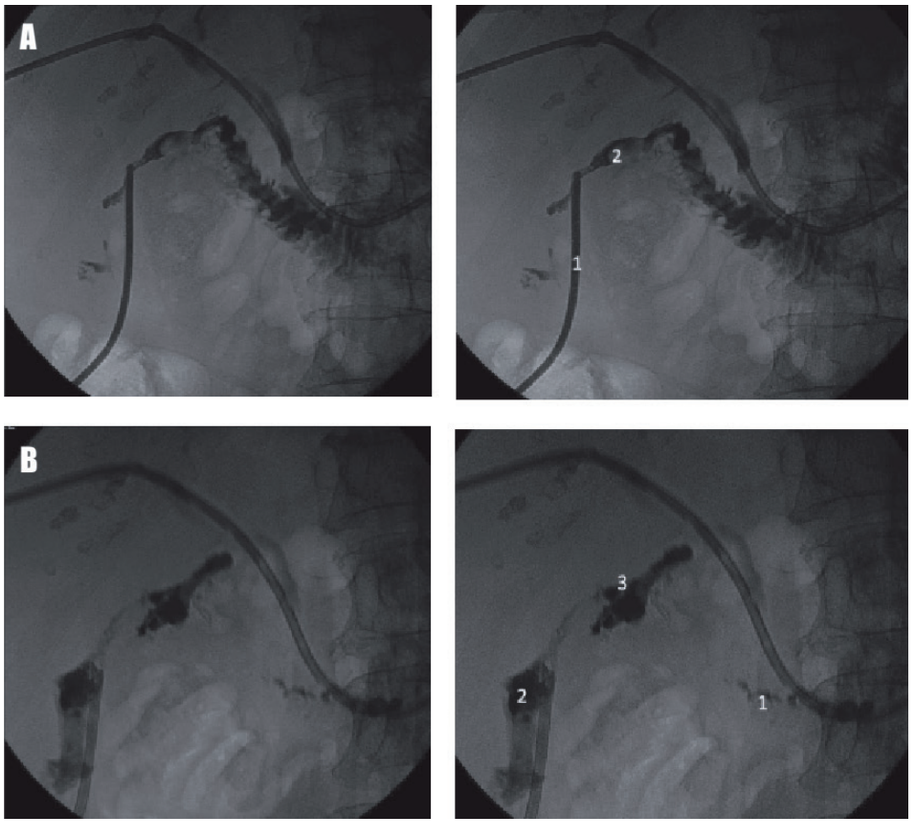

Figure 6.
Fistula of the duodenal stump in gastrectomy outcomes.

A) Opaque tract of the fistula (2), with angiographic catheter (1) replacing the surgical drainage

B) Lumen of the fistula (3) achieved with coaxial angiographic catheter, and embolized with Glubran®2 mixed with Lipiodol®.
A small quantity of glue advanced inside the duodenum (1) and another portion drained along the percutaneous drainage (2).
This had no effect.

The other case concerned a post-traumatic patient, with numerous enteric and pancreatic lesions, and with collections drained for a long time. We tried to close a fistula tract with pancreatic origin, and passing through the retroperitoneum up to the paracolic space. This case was repeatedly treated as it showed a resumption of the collection of pancreatic fluid even after months. Therefore, our preferential choice, for the treatment of enteric fistulas, is Glubran®2, especially as an alternative to Onyx®. This latter is another embolic agent, used in direct percutaneous "navigation" in the biliary system (Uller W et al., Rofo. 2013). It has much higher costs and its properties of adhesiveness and sealing are not the same of Gubran®2.
The results, the available evidences, indicate Glubran®2 as the ideal sealant for the treatment of digestive fistulas, also of the bile and bilioenteric. In experienced hands, this medical device is effective and safe, able to seal the tract and facilitate a faster healing with a very peculiar mechanism of action. In addition, the possibility to avoid the re-intervention and the related potential morbidity contributes, in a relevant way, to make Glubran®2 a cost-saving option, of which a greater widespread use is desirable.

Glubran®2 in bariatric surgery: a single-centre experience

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The experience of the use of nebulized Glubran®2 in strengthening the suturing line in the laparoscopic sleeve gastrectomy (LSG) held at the General Surgery Unit and Liver Transplant (Dir. Prof. V. Memeo) of the University Teaching Hospital of Bari, was presented at the recent Congress of the Italian Society for the Surgery of Obesity (SICOB). It perfectly fits the context of the applications discussed and presented at the SICO Symposium, supporting and completing the rational use of this medical device, already commonly used as a haemostatic agent, in the treatment of anastomotic leaks, and in digestive endoscopy, and as a reinforcement of the mechanical anastomosis in open and laparoscopic surgery. The LSG is currently held, unanimously, a bariatric procedure simple, rapid and less invasive and / or complex of other procedures, such as the gastric bypass (L-RYGB), and the biliary pancreatic diversion (BPD), decreeing its worldwide success. The more or less standardized procedure presents some controversial details on the technique (D'Ugo S et al., Surg Obes Relat Dis. 2014). The rare major complications (1-3%) consist in leaks and bleeding, and are related to the long suture line. This causes an adverse impact on clinical outcomes and on health service costs, therefore most of the surgeons use a buttress for that suture line (Knapps et al., JSLS. July 2013). In fact, the validity of the use of the buttress is still being discussed because the evidences in the literature are not converging. The results of a review of 2009 show that the buttress "not necessarily" reduces the occurrence of fistulas, despite having a favourable impact on the incidence of bleeding (Chen B et al., Obes Surg. 2003). The most important reference, the meta-analysis of the group of Gagner on a cohort of almost 10,000 patients (Parikh M et al., Ann Surg. 2013), concluded that the reinforcement with absorbable material does not show a significant impact on incidence of fistulas. This latter, on the contrary, is related to the size of the bougie and, so, to the long and narrow tubule. More recently, a further systematic review of 88 works (approximately 9,000 patients), showed that the absorbable polymer membrane (APM) seems to have a preventive efficacy for fistulas (with a reduction up to 1.1%). Its efficacy is higher than other options for comparison, such as strips of not absorbable bovine pericardium, over sewing or overlocking, and no buttress (Gagner M et al., Surg Obes Relat Dis. 2014). A randomized prospective study of 2015, which compared various strengthening techniques through simple stomach section without buttress (not including the cyanoacrylate glues), concluded that the buttress only extends the intervention time (Carandina et al., J Gastrointest Surg. 2015).

In personal experience, in the first 20 cases of LSG (average BMI 47), no type of buttress was applied, merely sewing far introflexed stitches on bleeding sites, along the suture line and always sewing an additional stitch on the gastroesophageal junction (average operative time 110 min. + / - 17). Afterwards, (20 patients with average BMI 46) the haemostatic fibrin glue was

atomised (Gigante G et al., G Chir. 2014), in super-obese patients, and in case of re-do surgery, and to unabsorbable buttress material (PERISTRIP DRY® VERITAS®). Recently, in 10 cases (average BMI 47), the Glubran®2, with its spray device (Figure 7), was used as reinforcement. Glubran®2 was easy to apply, and did not make the operating time longer (110 min +/- 20). A small quantity is enough (1 vial of about ml.1) of Glubran®2 atomised, to make a film protective, and bacteriostatic, and sealant, with excellent cost / benefit ratio, compared to buttress materials.

An interesting aspect is that Glubran®2, being a sealant, also allows to reach some sort of "chemical" omentoplasty, that is the bonding of the section margins of the greater omentum without suturing; the adhesive polymerises quickly, with consolidation that is completed in 60-90 seconds.

Preliminary results confirm its efficacy and safety: the postoperative recovery was very good, in all patients, with reduced average of hospital stay (4-6 days) and early drain removal. Results, Glubran®2, with its triple sealing, haemostatic and bacteriostatic (barrier) action, applied in spray formula along the suture line in LSG, may represent an effective, safe and cost-saving option for the management of "at risk" surgical sutures. Randomized trials are still needed to confirm its validity in preventing fistulas.

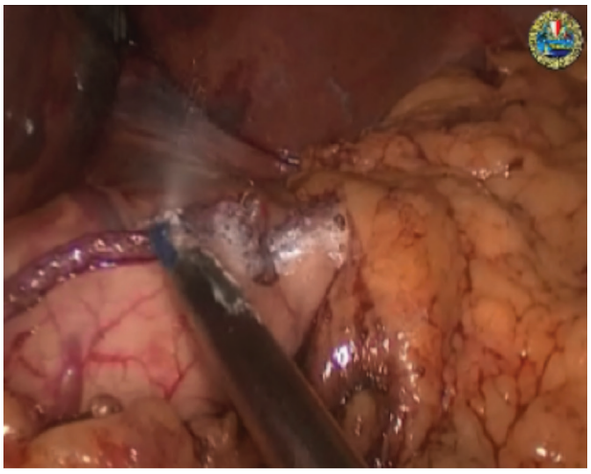


Figure 7. Application of the Glubran®2 protective film on the suture line, by means of a dedicated laparoscopic spray catheter.

GLUBRAN®2

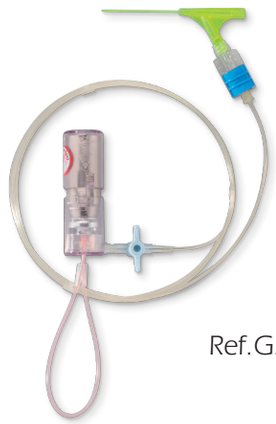
CE 0373

APPLICATION DEVICES

Ref. G-DT

Ref. G-LLS

Ref. G2-DCD-210-8T



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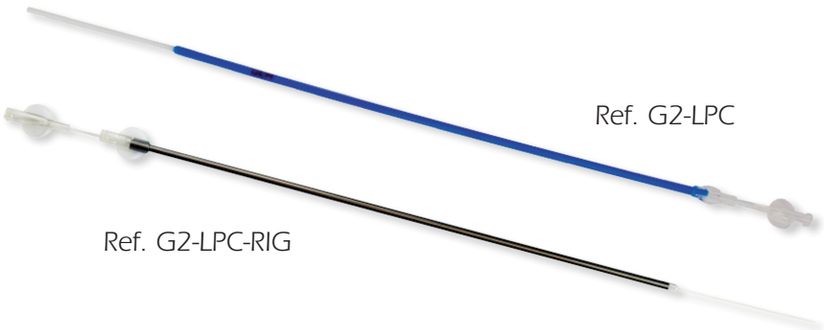

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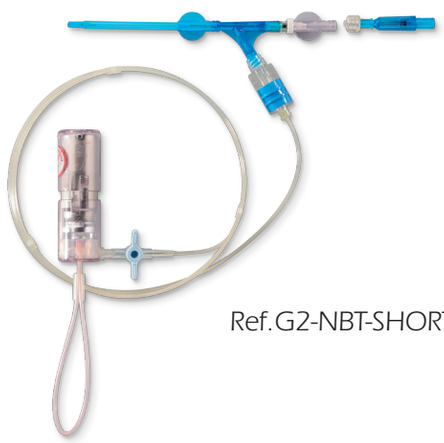

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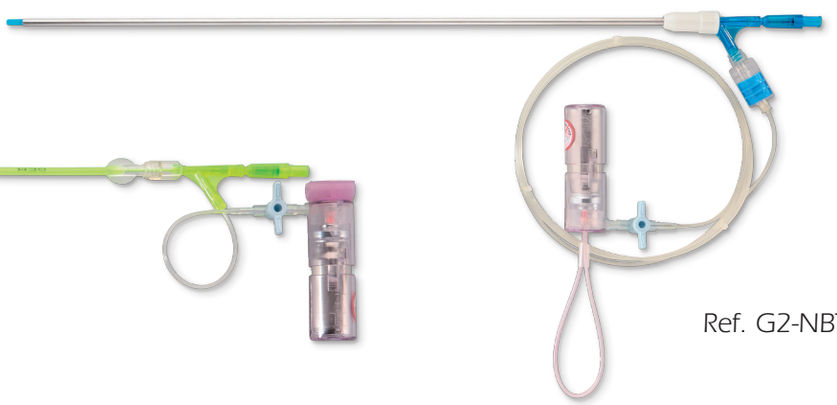

Ref. G2-NBT-RIG

Ref. G2-NBT-SMALL

GEM

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