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CYANOACRYLIC GLUE: A MINIMALLY INVASIVE NONSURGICAL FIRST LINE APPROACH FOR THE TREATMENT OF SOME URINARY FISTULAS

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ABSTRACT

Purpose: We evaluated the adaptability and the efficacy of a cyanoacrylic glue for the conservative treatment of urinary fistulas of different etiologies using an endoscopic, percutaneous or endovaginal approach.

Materials and Methods: From May 1998 to July 2004, 13 patients with long lasting iatrogenic and/or inflammatory urinary fistulas were treated conservatively with endoscopic, percutaneous or endovaginal application of 1 to 3 cc of cyanoacrylic glue.

Results: The complication rate in this cohort of 13 patients was low. Occlusion therapy failed in 2 genitourinary fistulas which were wider (diameter greater than 1 cm) and short. In the remaining 11 cases urinary fistulas were successfully sealed and at a median followup of 35 months no relapses were observed.

Conclusions: Cyanoacrylic glue is suitable for endoscopic, percutaneous and endovaginal use. This occlusion therapy represents a safe and minimally invasive approach that might be offered as a first line option for the treatment of urinary fistulas, especially narrow and long tract fistulas.

KEY WORDS: adhesives, cyanoacrylates, urinary fistula

Since 1996 our Department has been using a synthetic cyanoacrylic sealant in major pelvic surgical procedures or nephron sparing surgery to prevent intraoperative and postoperative bleeding and/or lymphorrhea. This glue (Glubran 2®) is composed by n-butyl 2-cyanoacrylate (monomer) and metacryloxysulpholane (monomer). It has high adhesive and hemostatic properties. Once its polymerization is completed, it becomes a thin elastic impermeable film which is resistant to stretching. The hemostatic and adhesive properties of cyanoacrylate depend mainly on a significant decrease of activated partial thromboplastin time. In addition, cyanoacrylate properties include good biocompatibility, gradual reabsorption without foreign body response and a short polymerization time (less than 90 seconds) even in a wet environment.[1] Inflammatory fistulas and iatrogenic persistent urinary fistulas complicating pelvic surgery are usually first treated with urinary drainage. Once previous conservative maneuvers have failed fistulas usually require difficult surgical repair.[2–4]

Various biological agents (thrombin, fibrin, collagen glues) have been tailored for endoscopic and/or percutaneous use. Technical simplicity and good results of conservative treatments using biological sealants (particularly fibrin glue), have been reported,[5–14] and our previous positive experience with this glue led us to try its adaptability to treat these cases. Thus, since 1998 we have used this synthetic glue as a minimally invasive alternative to traditional surgery for the treatment of prolonged urinary fistulas of iatrogenic and inflammatory etiology. In 2001 we published our preliminary favorable experience.[15]

MATERIALS AND METHODS

From May 1998 to July 2004 a cohort of 13 consecutive patients with a mean age of 55.8 years (range 34 to 76) with persistent iatrogenic and/or inflammatory urinary fistulas were admitted to our department. Once previous attempts of urinary drainage had failed, the patients were treated conservatively with endoscopic, percutaneous or endovaginal cyanoacrylic glue application.

The cases in our series had different etiologies, including 1 prostato-perineal fistula following incorrect urethral catheterization in the perioperative period of a Miles abdominoperineal amputation for rectal adenocarcinoma. This patient had undergone transurethral prostate resection for benign prostate hyperplasia. We also treated 2 neovesicoileal fistulas (fig. 1), 2 anastomotic neovesicourethral fistulas, 1 neovesicocutaneous fistula (fig. 2) complicating radical cystectomy with a Camey II orthotopic bladder substitution for invasive transitional bladder cancer, 2 vesicosigmoid inflammatory fistulas complicating a sigmoid diverticulitis, 3 vesicovaginal fistulas (2 complicating laparoscopic hysterectomy and 1 a subcervical urethral diverticulectomy), 1 vesicouterine fistula complicating a cesarean, and 1 caliceal fistula

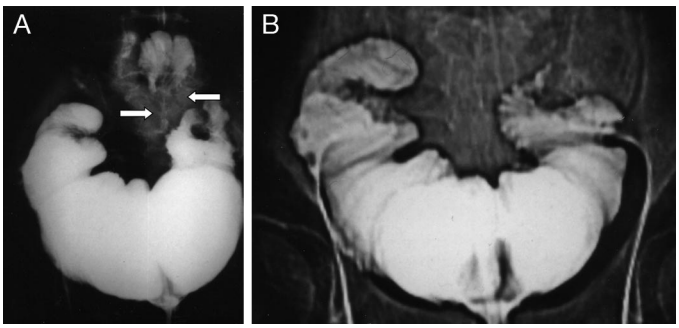

FIG. 1. *A*, neovesicoileal fistulas as early complication (postoperative day 21) of radical cystectomy with Camey II orthotopic neobladder (arrows indicate fistulous tract on left horn of pouch). *B*, neocystography performed 1 month after endoscopic plugging of fistulous tract with Glubran2® sealant. Complete healing of fistulas is shown.

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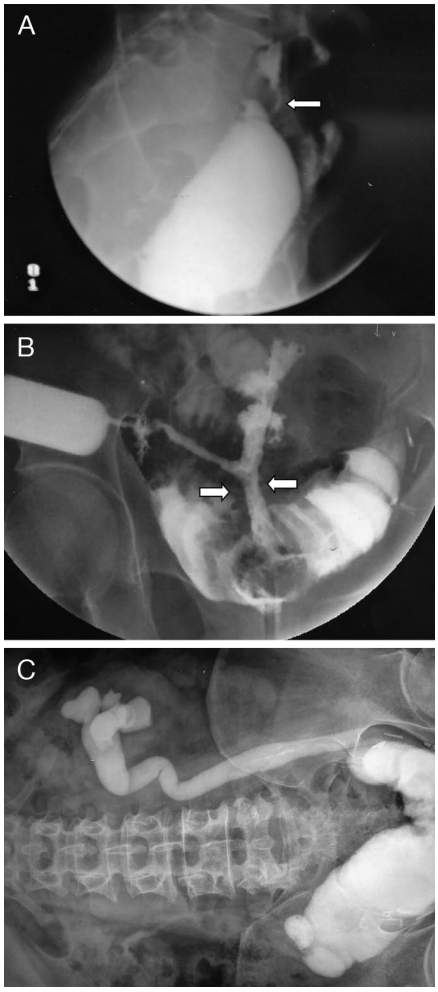

FIG. 2. *A* and *B*, neovesicocutaneous fistulas as late complication (20 months) of radical cystectomy with Camey II orthotopic bladder substitution (arrows indicate fistulous tract on neocystography and fistulography). *C*, neocystography performed 2 months after percutaneous plugging of fistulous tract with cyanoacrylic glue through cutaneous opening. Left neovesicoureteral reflux is evident.

complicating a complex pyelonephrolithotomy for staghorn renal calculi (see table).

In terms of surgical technique, urinary fistulas are plugged endoscopically, percutaneously or endovaginally with cyanoacrylic glue. With the endoscopic approach the synthetic glue is injected in the fistulous hole and an open-end 6Fr ureteral catheter is inserted through the cystoscope operative channel to attain complete obliteration. As the prostato-perineal fistula was under the bladder it was not necessary to fill the bladder with saline in this case. In the remaining 6 patients treated endoscopically, the procedure was performed on patients with a full bladder since the fistulous orifices were at bladder level (1 vesicouterine, 2 vesicosigmoid) or neobladder level (1 neobladder-urethral, 2 neobladder-ileal). In none of the cases was it necessary to preventively cannulate the ureters. To facilitate the correct placement of the glue, taking advantage of its rapid polymerization time (beginning after 5 to 6 seconds and completed within 60 to 90 seconds), it is useful to use moderately warm saline. The polymerization of cyanoacrylic glue is more favorable at 45C and it can be performed in a wet environment.

An open-end 6 Ch ureteral catheter was also used for the 3 percutaneously treated cases. It was inserted percutaneously under fluoroscopic guidance using the cutaneous drainage path. In the case of the lower pole caliceal fistula complicating a complex pyelonephrolithotomy, the accuracy of the maneuver was monitored with a retrograde pyelogram, which also showed the absence of ureteral obstruction. In the cases of neovesicourethral leakage from the posterior side of the anastomosis and of the neovesicocutaneous fistula, respectively with early and late (20 months) complication of radical cystectomy with orthotopic bladder substitution, the maneuvers were also performed under fluoroscopic guidance and monitored through a neocystogram.

For the 3 cases of vesicovaginal fistulas the approach was endovaginal. The glue was applied with an oxidized regenerated cellulose strip into the fistulous hole, preceded and followed by cystoscopic control. Preparation of the fistula tract, such as scarification, to enhance the formation of granulation tissue, was never performed. One to 3 ml of cyanoacrylic glue sufficed for all cases. When using a ureteral catheter about 1 ml of glue is lost inside the catheter itself.

At the end of the procedure urine was drained by a urethral catheter left for 48 hours for up to 1 week. With the lower pole caliceal fistula the upper urinary tract was drained only by nephrostomy for a week (the Double-J® ureteral stent previously inserted was removed before the procedure). The nephrostomy was removed after the antegrade pyelogram had excluded the persistence of fistula.

Patients were followed up clinically and with imaging with excretory urography, computerized tomography (CT) or retrograde cystography at 1 to 3 months after the procedure in

Pt No.	Diagnosis (fistula type)	Etiology	Diameter (cm)	Approach	Outcome	Mos Followup	Catheter Duration (before glue)
1	Vesicovaginal	Laparoscopic hysterectomy	0.7	Endovaginal	Cured	37	6 Mos
2	Vesicovaginal	Subcervical urethral diverticulectomy	1.5	Endovaginal	Failed	35	6 Mos
3	Vesicovaginal	Laparoscopic hysterectomy	1	Endovaginal	Cured	9	5 Mos
4	Vesicouterine	Post-cesarean	2	Endoscopic	Failed	32	3 Mos
5	Neobladder-ileal	Radical cystectomy + orthotopic bladder substitution (early day 21)	0.8	Endoscopic	Cured	74	3 Wks
6	Neobladder-ileal	Radical cystectomy + orthotopic bladder substitution (20 mos)	0.5	Endoscopic	Cured	27	4 Mos
7	Vesicosigmoid	Sigmoid diverticulitis	0.5	Endoscopic	Cured	36	3 Mos
8	Prostato-perineal	Urethral catheterization—previous transurethral prostate resection + Miles abdominorectal amputation	0.6	Endoscopic	Cured	76	2 Mos
9	Neobladder-urethral	Radical cystectomy + orthotopic bladder substitution complicated by pelvic hematoma	1	Endoscopic	Cured	53	6 Wks
10	Neobladder-urethral	Radical cystectomy + orthotopic bladder substitution	1	Percutaneous	Cured	6	2 Mos
11	Neovesicocutaneous	Radical cystectomy + orthotopic bladder substitution	0.5	Percutaneous	Cured	30	4 Mos
12	Vesicosigmoid	Sigmoid diverticulitis	0.7	Endoscopic	Cured	10	3 Mos
13	Nephrocutaneous	Pyelonephrolitotomy for staghorn renal calculi	Less than 1	Percutaneous	Cured	35	2 Mos with Double-J® stent + nephrostomy

the absence of clinical signs of persisting fistulas. In the absence of relapse, successive followup was only related to the pathology necessitating the initial treatment (Appendix 1).

RESULTS

Median followup was 35 months (range 6 to 76). The last control was in February 2005. There was no intraoperative or postoperative mortality. No significant early and late complications were observed. In the first case of vesicosigmoid fistula, 4 months after the sealant application a 2 cm bladder stone had developed on the glue surface protruding in bladder. This complication required endoscopic laser lithotripsy, and the endoscopic sight indicated the area of the previous fistula which was completely covered with urothelium. The bladder stone was not attached to the previous fistulous hole. In 1 patient with a vesicovaginal fistula and in the case of vesicouterine fistula, endoscopic removal of intravesical redundant polymerized glue with cystoscopic forceps was required within 48 hours of glue application. All 3 patients were symptomatic after the procedure (dysuria and hematuria in the first after 3 months, strangury and urgency in the other 2 after catheter removal).

Occlusion therapy failed in 2 of 13 cases (1 vesicouterine and 1 vesicovaginal fistula) in which the fistulas were wider (orifice diameter greater than 1 cm) and short. Both patients had persistence of urinary incontinence. After 2 months the first patient underwent a subtotal hysterectomy and vesical fistula repair. After 3 months the second patient underwent a fistulectomy with epiploon interposition. In the remaining 10 cases fistulas were successfully sealed and no relapses were observed at followup. Operative time varied depending upon the site of the fistulas, the approach and the difficulties thereafter in locating the fistulous orifice. In our series operative time ranged from 10 to 20 minutes.

DISCUSSION

Urinary tract fistulas often develop as an early complication of gynecological or urological surgery, or as a result of trauma, inflammatory disease or radiotherapy. Urinary drainage by itself is sufficient to cure some small urinary tract fistulas, whereas for the complex and larger ones this approach is often ineffective. Thereafter, prolonged urinary leakage might require difficult surgical procedures, potentially burdened by a higher complication rate. Time to surgery can vary depending on the etiology of the urinary fistulas. For instance, in genitourinary fistulas (vesicovaginal and vesicouterine), a waiting period of 3 months is usually required. On the other hand, the efficacy of nonsurgical treatments is directly related to precocity. Generally when surgical repair of the fistula is needed, the waiting period leads to social and psychological distress for patients.

Fibrin glue is the injectable biological surgical sealant with the longest followup with regard to the nonsurgical management of fistulous disease, as it has been used since the late 1980s for the treatment of bronchopleural fistulas, perineal, anal and colorectal fistulas, as well as urinary tract fistulas.[5–12] A small amount of topically injected fibrin glue is usually used. Morita and Tokue achieved the closure of a neovesicocutaneous fistula using topical fibrin glue.[8] Tostain reported on 4 cases of urinary fistulas (2 ureterovaginal and 2 vesicovaginal) successfully plugged with fibrin sealant.[11] Schneider et al reported a 66% closure rate in 6 cases treated with endoscopic fibrin sealing of iatrogenic vesicovaginal fistulas.[12] Welp et al reported 3 cases of vesicovaginal fistulas successfully treated with topical application of fibrin glue.[13] Evans et al used fibrin sealant with a direct injection technique in 19 patients, 5 of whom were affected by complex urinary fistulas. They reported successful fistula repair after a single application of fibrin glue in 4 patients (80%). This approach failed in 1 case of vesicovaginal fistulas.[14]

More recently, synthetic cyanoacrylic sealants have been introduced in urology for the nonsurgical management of iatrogenic urinary tract fistulas. The main differences between fibrin glue and cyanoacrylic glue are reported in Appendix 2. We have already reported our initial favorable experience with this glue through the endoscopic plugging of 3 persistent iatrogenic lower urinary tract fistulas complicating major pelvic surgery.[15]

Other positive experiences using this synthetic glue were recently published in other medical fields.[16,17] Mechanical and biological properties of cyanoacrylic sealants seem suitable for endoscopic or percutaneous use, having a crucial role in healing urinary fistulas with this approach.

More recently the usefulness of this sealant was also evaluated at urethral and upper urinary tract levels. Lapointe et al assessed the efficacy of n-butyl cyanoacrylate for the early repair of fistulas after hypospadias surgery in 8 children, attaining fistula closure with good cosmetic and functional outcome in 62.5%.[18] Tekin[19] and Riera Canals[20] et al performed upper urinary tract fistula embolization with n-butyl 2-cyanoacrylate under fluoroscopic guidance with a percutaneous approach and urinary drainage, and fistula repair was reported in both experiences. In our current series we assessed the value of cyanoacrylic glue for endoscopic, percutaneous and endovaginal use, confirming its adaptability and versatility along with its safety and efficacy.

However, regarding safety, some concern was raised about the postoperative risk of infertility with vesicouterine fistulas since uterine adherences or tubal occlusion may occur as a result of intraluminal cyanoacrylic sealant polymerization. In the single case reported in our series, occlusion therapy failed and the fistula was repaired with a conventional surgical approach. However, because of the previously mentioned risk we are not in favor of using this procedure for the management of vesicouterine fistulas.

Finally, based on our experience, to optimize the efficacy and predict the probability of cure with this approach, several key points should be noted. 1) The length and width of the fistulous tract are decisive factors. The probability of sealing the fistulous tract is directly related to the length and inversely related to the width. Thus, narrow and long tract fistulas have a higher probability of being sealed because the glue has a narrow passage with the greatest possible surface connection. Thus, we used an oxidized regenerated cellulose strip and a vaginal approach to maintain the glue in the vesicovaginal fistulas. 2) The exact location of the fistulous hole and accurate sealant injection are mandatory. This phase could be much more complex in nephrocutaneous fistulas as the maneuver must be performed under fluoroscopic guidance with a simultaneous retrograde or antegrade pyelogram. 3) The injection of an unnecessary amount of cyanoacrylic glue must be avoided. Usually 1 to 3 ml are enough for this purpose. Excess sealant does not improve the results and, at the same time, it creates glue clots whose clearance might require ancillary maneuvers. 4) The speed of execution is important. Cyanoacrylic glue polymerization time is short (less than 90 seconds), thus it is crucial to remove the endoscope along with ureteral catheter as soon as the sealant is injected. This will prevent entrapment of the ureteral catheter and damage to the endoscope. Therefore, it is useful to keep the endoscope 3 to 4 cm away from the glue injection. 5) Cyanoacrylate sealant appears to be safe. However, its use in vesicouterine fistulas in fertile women is not recommended as there is a high risk of occluding the uterine cavity and uterine tube. 6) Regardless of the fistula location, the use of this technique does not seem to affect later conventional surgical repair of the fistula (as noticed in our series).

CONCLUSIONS

In our experience this kind of glue is suitable for endoscopic, percutaneous and endovaginal use. Cyanoacrylic sealant successfully healed 11 of 13 (85%) urinary fistulas of different locations and etiology of lower and upper urinary tracts. Hospital stay and time to recovery were also favorably influenced. Occlusion therapy represents a safe and minimally invasive approach that might be offered as a first line option for the treatment of urinary fistulas, especially of narrow (width less than 1 cm) and long tracts. Wide and short tract fistulas might be treated, taking into consideration, however, that in these cases occlusion therapy is also highly prone to failure as it does not affect subsequent surgical reparation.

Andrew M. Garvey provided editorial assistance.

APPENDIX 1

Diagnosis	Symptomatology Before Treatment	Diagnostic Imaging	Followup Imaging
Vesicovaginal fistula	Urinary incontinence	Cystography	Cystography at 3 months
Vesicovaginal fistula	Urinary incontinence	Cystography	Cystography at 1 month
Vesicovaginal fistula	Urinary incontinence	Cystography	Cystography at 3 months
Vesicouterine fistula	Urinary incontinence	Cystography	Cystography at 1 month
Neobladder-ileal fistula	Abdominal pain-Nausea-Diarrhea	Neocystogram	Neocystogram and CT at 1 month
Neobladder-ileal fistula	Abdominal pain-Diarrhea	CT and Neocystogram	CT and Neocystogram at 1 month
Vesicosigmoid fistula	Pneumaturia-Cystitis	Cystography and CT	Cystography at 2 months
Prostato-perineal fistula	Urinary leakage from perineal wound	Cystourethrogram	Cystourethrogram at 2 months
Neobladder-urethral fistula	Urinary leakage from pelvic drain	CT	CT at 3 months
Neobladder-urethral fistula	Urinary leakage from pelvic drain	CT and Neocystogram	CT and Neocystogram at 3 months
Neovesicocutaneous fistula	Urinary leakage from cutaneous hole of the drain	CT and fistulography	CT and Neocystogram at 2 months
Vesicosigmoid fistula	Pneumaturia-Cystitis	Cystography	Cystography at 3 months
Nephrocutaneous fistula	Urinary leakage from lumbar drain	Urography and percutaneous pyelography	Urography at 3 months

APPENDIX 2: CYANOACRYLIC GLUE VS FIBRIN GLUE

Cyanoacrylic Glue	Fibrin Glue
Synthetic glue	Biological glue
High adhesive property (strength film in vitro 5 kg/F)	Not well documented
High hemostatic property (enter in the extrinsic way of coagulation process)	High hemostatic property (enter in the intrinsic way of coagulation process)
High antibacterial property (suitable for application in infectious areas)	Not suitable
Elimination process: hydrolytic degradation (after 1 to 6 mos)	Elimination process: resorption
Works well in wet environment	Poor performance
Low quantity to be applied	High quantity to be applied

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