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Sclerosis and varicocele embolization with N-butyl cyanoacrylate: experience in 41 patients

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Abstract

Background: Embolization is an established treatment for varicocele. Coils are most frequently used in the procedure. Liquid embolic and sclerosing agents seem to have a number of advantages over coils.

Purpose: To report our experience and explain the technique of using N-2-butyl-cyanoacrylate (N2BCA) in varicocele treatment.

Material and Methods: From January 2010 to July 2011, 42 gonadal veins in 41 consecutive patients (age range, 11–41 years; mean, 18 years) with a diagnosis of varicocele were treated with N2BCA as an embolic agent. The clinical diagnosis was confirmed by Doppler ultrasound in all the patients. Institutional review board approval was obtained, and all the patients signed informed consent for this retrospective review. In all cases, a 4-F hydrophilic catheter was used to catheterize the distal portion of the gonadal vein through which N2BCA, emulsified with lipiodol, was injected.

Results: The technical success was 100%. No complications or non-targeted embolizations were reported. Seven patients reported moderate postembolization pain that required oral analgesic treatment for 7–10 days. After 12-month follow-up, all patients exhibited varicocele resolution in the Doppler ultrasound examination as well as relief of all previous symptoms. We have no fertility-related data for patients treated for this condition.

Conclusion: N2BCA as an embolic agent is a therapeutic alternative for the endovascular treatment of varicocele. This technique is uncomplicated, inexpensive, efficient, and safe.

Keywords

Male varicocele, varicocele sclerotherapy, varicocele embolization, cyanoacrylate, retrograde sclerotherapy

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Introduction

Varicocele is defined as the abnormal enlargement of the scrotal veins in the pampiniform plexus. It occurs by secondary venous reflux caused by a congenital absence of valves in the gonadal vein or by compression of the left renal vein. Left-sided involvement is remarkably more prevalent than right-sided involvement (2%). The incidence of varicocele is 8–23% among young healthy boys/men, reaching 40% in subfertile patients (1).

Peritesticular venous congestion and gonadal vein insufficiency cause an increase in intrascrotal temperature. These factors cause hypoxia and oxidative stress in the testes, and reflux leads to renal and adrenal metabolites reaching the scrotum. For these reasons, varicoceles may cause infertility and/or testicular pain

in adults and testicular growth failure in adolescents (2,3).

Surgical or endovascular treatment can be undertaken. The surgical approach has different modalities: open or laparoscopic retroperitoneal ligation, open inguinal ligation (supra or infrainguinal) and subinguinal microscopic surgery. Varicocele embolization, first promoted in the 1970s, is an effective and consolidated treatment. In the surgical and endovascular approach,

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the presence of collateral veins, which are somewhat developed and are situated parallel to the main gonadal vein, is the major anatomical factor contributing to treatment failure. The overall frequency of recurrence after treatment is 15%, reaching 12% in cases in which embolization is the treatment, and recurrence is equally probable following surgical or embolization treatment (4–7). To date, retrospective studies have shown considerable variability in results, not only between surgery and embolization but also between different surgical options (6). The embolization results have improved as a result of advances in the techniques and materials. The symptom control in the medium-term follow-up is currently approximately 100% (8, 9).

Several techniques and embolic agents have been developed for the embolization of the gonadal veins. Saline and boiling contrast, detachable balloons, gelatin sponge, or alcohol are no longer in use (10, 11).

Among the diverse options and materials currently available for gonadal vein embolization, coils are the most widely used. Liquid agents are less reported, although polydocanol foam and sodium tetradecyl sulphate (STS) have been reported in a number of studies (12, 13). The mechanism of action of polydocanol and STS is a result of the sclerosis of the vein more than of the embolization itself. Cyanoacrylate has been used in treating varicoceles. Glubran2[®], an N-butyl-2-cyanoacrylate co-monomer + metacrylossisulfolane, is a non-toxic biocompatible liquid embolic agent with a density analogous to water. It is transparent, colorless and has a typical odor. One of the major advantages of using liquid agents is that they act not only in the main gonadal vein but expand into the collateral pathways, thus increasing the effectiveness of the procedure (6, 14).

In this retrospective review, we describe the different technical aspects, advantages and results of using an N-butyl-2-cyanoacrylate co-monomer not only as a liquid embolic product but also as a sclerosing agent for varicocele treatment.

Material and Methods

From January 2010 to July 2011, 42 gonadal veins were embolized using N2BCA (Glubran2[®]; Gem, Viareggio, Lucca, Italy) in 41 consecutive patients (age range, 11–44 years, mean, 18 years). In all the patients, left gonadal vein embolization was performed based on an ipsilateral varicocele diagnosis. In one patient, a bilateral varicocele was treated. Varicocele diagnosis and gonadal vein insufficiency were confirmed in all the patients by Doppler ultrasound and physical examination. Institutional review board approval was obtained for this retrospective review, and all patients provided signed informed consent to participate in the study.

Preadolescent or adolescent patients (aged ≤ 18 years, $n=22$) were treated for symptomatic reasons or to prevent testicular atrophy. The indications in adult patients ($n=19$) included symptomatic varicoceles with scrotal pain and heaviness or subfertility in patients with two or more abnormal spermograms.

N2BCA embolization was the first therapeutic approach in 38 of the 41 patients. Three patients had a previous history of non-effective treatment in the preceding 1–3 years, two with surgery and one with coil embolization. All the procedures were performed under local anesthesia, conscious sedation with intravenous midazolam and antibiotic prophylaxis with an intravenous single dose of cefazolin. Vascular access was obtained through the right common femoral vein or through the right jugular vein according to the interventionalist's preference. The gonadal veins were directly catheterized using a 4F hydrophilic cobra or vertebral catheter and a hydrophilic guidewire (Terumo Europe, Leuven, Belgium). We did not use guiding catheters or long vascular sheaths so as to preserve gonadal vein access after the 4F was withdrawn.

Reverse flow in the gonadal vein and valvular incompetence were documented and confirmed by retrograde spermatic venography, obtained at rest and with the Valsalva maneuver. The gonadal vein was selectively catheterized using a 4F hydrophilic catheter and advanced through the distal portion, where the N2BCA injection was performed (Fig. 1).

The Tessari method, using two clean and dry Luer lock disposable syringes and a three-way tap, was used to obtain the Lipiodol (Lipiodol Ultrafluid; Guebert, Aulnay-sous-Bois, France) and N2BCA mixture at a ratio of 1:1 (Fig. 2) (15). Via previous manual injections with iodinated contrast, the velocity and volume of the embolic agent injection was calculated, allowing for the reflux and the collateral distribution to be studied. The catheter dead space was filled with an anionic solution, dextrose 10%, to avoid intracatheter N2BCA polymerization. The lipiodol-N2BCA mixture was injected under strict fluoroscopic control, with continuous manual injection and displaying real-time distribution. The micro catheter technique was not required, and the lipiodol-N2BCA mixture release was performed exclusively through the 4F catheter. If, during the testing injections and prior to embolization, the pampiniform plexus was reached, the inguinal canal was manually compressed just before starting the actual embolization injection. We began the glue injection in the distal intrapelvic segment of the gonadal vein, pulling the catheter while injecting the glue under fluoroscopy guidance. The 4-F catheter was removed when all the venous space selected for filling was occupied by the liquid embolic agent. In the first three consecutive procedures, previous to the N2BCA injection, one or two 8–10 mm

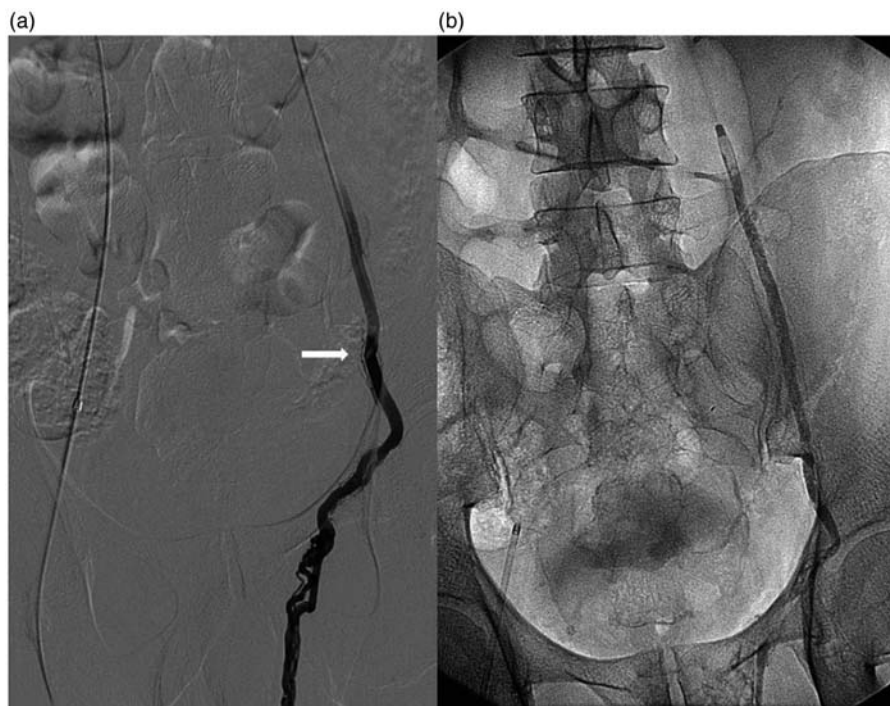


Fig. 1 (a) 4 F hydrophilic catheter within the distal portion of the left spermatic vein (arrow). and (b) Spermatic vein filled with N2BCA after the 4 F catheter removal



Fig. 2 The tools necessary to obtain the mixture between lipiodol and cyanoacrylate. Two clean and dry syringes and a three-way-tap. Non-ionic solution (10% dextrose) to flush the catheter

Gianturco coils (Cook, Bjaeverskov, Denmark) were placed in the proximal gonadal vein to protect against possible cyanoacrylate reflux into the renal vein.

All the patients were discharged after 6–12 h of observation, and they returned to their normal daily activities after 24 h. Ibuprofen 600 mg three times daily was prescribed for 3 days.

All the patients were scheduled for clinical examination in our facility after 1 month and for clinical and ultrasound Doppler examination 12 months after the

embolization. Clinical success was considered to be achieved when two conditions were met: the absence of reflux in the ultrasound Doppler exam and the absence of scrotum pain and heaviness.

Results

All the patients were available for follow-up at 1, 6, and 12 months. All the patients were, therefore, followed-up for 12 months. The physical examination and Doppler

ultrasound showed clinical success after 12 months in all the cases (Table 1). During the 1-month follow-up, a clinical examination without Doppler studies was performed. We asked about post-embolization related pain and pre-embolization scrotal pain relief. At the 6-month follow-up, a scrotal Doppler US examination was performed. At the 12-month follow-up, a clinical examination and scrotal Doppler ultrasound examination were performed. Fertility data were not investigated (Table 2). Pain relief was found in all the patients at the 1-month follow-up, and the data were confirmed after the 12-month follow-up. At the Doppler examination, we found persistence of the pampiniform plexus. The outflow increase and flow inversion during the Valsalva maneuver were no longer present in any patient (Fig. 3).

The procedure was feasible with 100% technical success in all the patients. For the majority of the cases ($n = 34/41$), 2 cc of the embolic mixture (1 cc of N2BCA added to 1 cc of lipiodol) was enough to achieve a satisfactory embolization. In seven patients, because of the large size of the gonadal vein, it was necessary to use up to 3 cc of N2BCA. No major complications were registered after or during the procedure, including undesired embolization or N2BCA migration.

Ibuprofen (600 mg three times daily) was prescribed to all patients for 3 days. A total of 34 of the patients did not report pain, but seven patients returned to the emergency room or phoned our service because of persistent scrotal or left lumbar pain. In these patients, a Doppler US was performed to rule out complications.

Table 1. Features of the patients and their treatment outcomes

Features	$n = 41$
> 18 years	19
≤ 18 years	22
Asymptomatic adolescents	16
Symptomatic adolescents	6
Symptomatic adults	15
Subfertile adults	2
Subfertile and symptomatic adults	2
Embolization: primary/recurrence	38/3
Bilateral embolization	1
Approach: CFV/IJV	34/7
Post-embolization pain	7
Technical success	41
Control Doppler at 6 months	41
Clinical follow-up ≥ 6 months	41
Complications	0
Recurrence during follow-up	0

CFV, common femoral vein; IJV, internal jugular vein

The pain was not disabling and allowed all the patients to perform daily activities.

Discussion

In this retrospective study, we report our experience and explain the technique for varicocele treatment using n-2-butyl-cyanoacrylate. Clinical success after 12 months was 100%, with no immediate or late complications.

More than 30 years ago, coils were shown to be effective in varicocele treatment, and they remain the most widely used method because of safety, ease in handling and wide availability (16). The Amplatzer® nitinol plugs (AGA-Medical St Jude, Plymouth, MN, USA) may be used as an alternative to coils (17). The mechanism of action of the coils and plugs is entirely occlusive and would amount to a surgical ligation of the main gonadal vein without influencing the collateral vein companions.

Another frequently used endovascular option for varicocele treatment is pure sclerotherapy. STS or polidocanol injected as foam induces phlebitis with thrombosis and fibrosis of the vessel. This option is an effective but somewhat painful technique, especially if STS is used (10, 13). The advantage of liquid substances over coils and plugs is that they produce a more extensive effect along the entire gonadal vein, unlike coils or surgery, which cause more focal obstruction of the vein. Liquids proliferate beyond the main gonadal vein through the collaterals, preventing possible relapse (Fig. 4).

Cyanoacrylate is a glue with a high adhesive strength. Its polymerization triggers an exothermic reaction that contributes to the destruction of the vascular endothelium. Cyanoacrylate has a dual mechanism of action. It is an embolic agent that causes mechanical obstruction and thrombosis, and it acts as a sclerosing agent, triggering a chemical phlebitis, which secondarily induces fibrosis and a complete

Table 2. Follow-up schedule

Follow-up (1, 6, and 12 months)
1-month: clinical visit ($n = 41$)
● Post-embolization pain (lasting ≤ 10 days) = 7
● Pre-embolization scrotal pain relief ($n = 23$) = 23*
6-month: scrotal Doppler ultrasound ($n = 41$)
● Varicocele resolution = 41
12-month: clinical visit & Doppler ultrasound ($n = 41$)
● Scrotal pain = 0
● Varicocele resolution = 41

*Only 23 out of 41 patients were symptomatic before embolization

destruction of the gonadal vein in a manner analogous to STS or polidocanol (18).

This cyanoacrylate variant, N2BCA co-monomer, has advantages over classic cyanoacrylate. Classic NBCA (Histoacryl, Braun, Melsungen, Germany) has a polymerization temperature of 90°C and a polymerization rate < 30 s. With Glubran[®], the polymerization rate is slower, making the handling and release easier. The exothermic reaction is weaker (45°C), and it is therefore less painful at the time of injection. The final polymer is more flexible and, unlike conventional cyanoacrylate, does not fragment (6,19). Cyanoacrylate dissolves polycarbonates, and it is important to avoid a long contact time with some types of catheter hubs. N2BCA has a bacteriostatic effect and does not polymerize in contact with air. Glubran[®] has a CE certificate for intravascular use.

Because it is radiolucent, cyanoacrylate should be released under a fluoroscopic control mixed with lipiodol. The mixture with lipiodol also modulates the polymerization rate. We have at all times used a lipiodol-N2BCA ratio of 1:1, thus achieving rapid polymerization that avoids migration into the renal vein.

Another technical aspect is that we experienced no problems when injecting glue through a regular 4 F catheter rather than through a micro catheter as is usual when glue is used.

We performed the preceding catheter flushing step with 10% dextrose solution, always limiting the catheter flushing to the catheter dead space because, if dextrose accumulates in the gonadal vein and comes into contact with the cyanoacrylate, it would polymerize more slowly and create a risk of migration. STS or polidocanol foam are more fluid than cyanoacrylate, and the theoretical risk of backflow is higher. Other authors have suggested that, in the presence of extended collaterals, STS, or polidocanol foam should not be used (12). In our first three cases, we used a proximal “ancillary” coil to prevent backflow of cyanoacrylate (Fig. 5). Cyanoacrylate is more viscous than foam and polymerizes quickly, and the possibility of significant reflux and massive diffusion through the collaterals is unlikely. The primary disadvantage of liquid embolization agents compared to coils or nitinol plugs is that their release is not 100% controllable. Possible complications of cyanoacrylate varicocele embolization

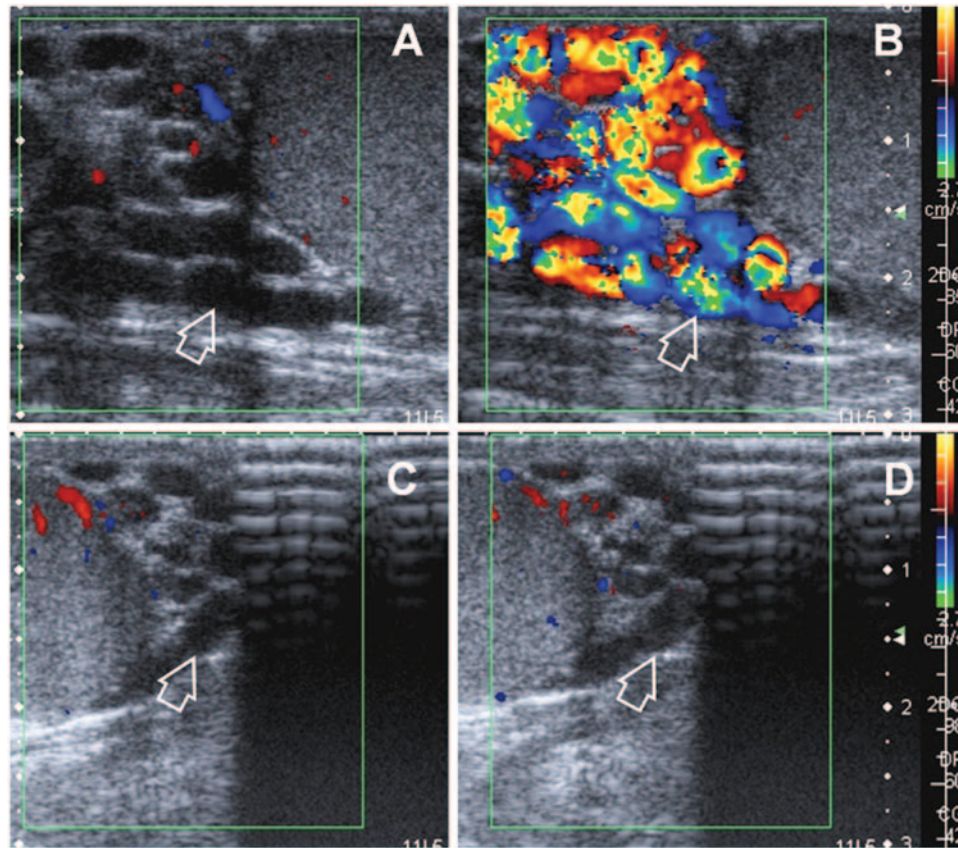


Fig. 3 Color Doppler US examination. Pre-treatment (A-B) and 12 months post-embolization (C, D). At rest (A, C) and during Valsalva (B, D). Pampiniform plexus color Doppler signal during valsalva (B) that is no longer appreciated after the embolization (D)

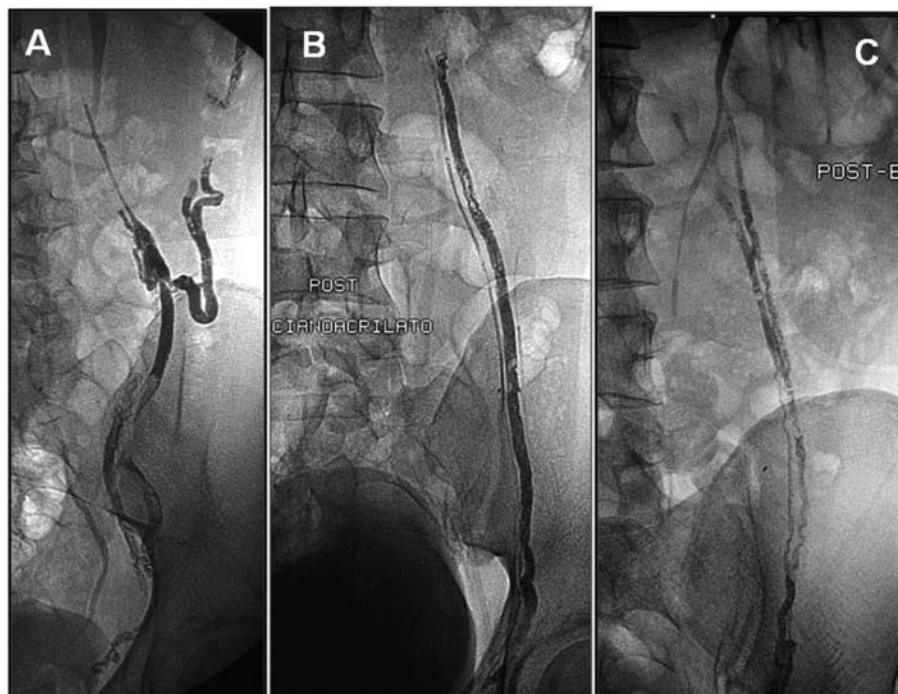


Fig. 4 Three different cases that show how the cyanoacrylate not only fills the main spermatic vein but also fills the collateral and accessory spermatic veins regardless of size



Fig. 5 Case 2: a Gianturco coil (arrow) was deployed proximal to the glue injection point to prevent glue migration

are glue migration into the pulmonary circulation, a glued catheter and severe phlebitis of the gonadal vein or pampiniform plexus (6). The occurrence of post-embolization pain seems to be more frequent when

using cyanoacrylate and sclerosing agents rather than coils, and this symptom is related to the secondary phlebitis that they cause (6,12,18).

Embolization with Glubran® is cost-effective. One cc is comparable in cost to a single conventional pushing coil and is sufficient for successful treatment in the majority of cases. If using controlled-release coils or nitinol plugs, the cost is significantly higher.

N2BCA has a cosmetic advantage, as cyanoacrylate is absorbed over time by hydrolysis. The coils will appear in imaging tests throughout the patient's lifetime.

A limitation of this study is that it is a retrospective review of a small cohort from a single center. It would be beneficial to conduct a comparative study with the standard treatment using coil embolization or surgery.

In conclusion, the use of N2BCA as an embolic agent for percutaneous treatment of varicoceles is a therapeutic alternative that is effective, safe, simple and inexpensive. N2BCA triggers a local inflammatory reaction that promotes sclerosis and thrombosis. The liquid nature of the embolization product allows diffusion through the gonadal vein and their collaterals, which appears to reduce recurrence and improve results.

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