European Journal of Radiology 83 (2014) 559–563

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Tolerance of glue embolization under local anesthesia in varicoceles: A comparative study of two different cyanoacrylates

Peter Vanlangenhove [a,*], Karel Everaert [b], Georges Van Maele [c], Luc Defreyne [a]

[a] Department of Vascular and Interventional Radiology, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium
[b] Department of Urology, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium
[c] Department of Statistics, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium

ARTICLE INFO

Article history:
Received 17 July 2013
Received in revised form 8 October 2013
Accepted 15 November 2013

Keywords:
Varicocele
Embolization
n-Butylcyanoacrylate

ABSTRACT

Purpose: To find out whether in varicocele embolization the copolymer cyanoacrylate glue (NBCA-MS) has a better patient tolerance compared to the monomer n-butyl-2-cyanoacrylate (NBCA).
Materials and methods: $N = 112$ insufficient spermatic veins (left sided $N = 84$, right sided $N = 28$) diagnosed in $N = 83$ adult males were prospectively randomized for blinded embolization with either NBCA $N = 54$ (Histoacryl) or with NBCA-MS $N = 58$ (Glubran2). Before, during and up to one week after embolization, patient discomfort was assessed by a standardized pain scale. Type, location and side of discomfort were noted.

Statistical analysis was performed with the Mann–Whitney *U*-test, the McNemar test and the Fisher's exact test.
Results: Embolization caused discomfort in $N = 48/112$ (43%) spermatic veins, comprising $N = 26/54$ (48%) in the NBCA group and $N = 22/58$ (38%) in the NBCA-MS group. During the week after embolization, the overall number of discomfort reports rose to $N = 62/106$ (59%), with an increase to $N = 30/53$ (57%) in the NBCA group and to $N = 32/53$ (60%) in the NBCA-MS group. The number of immediate grade 2 to 4 pain reactions was $N = 22/112$ (20%), and rose to $N = 37/106$ (35%) after one week. No difference in discomfort during embolization and at 1 week after treatment was noted. Characteristics, severity grading, and location of discomfort were similar in both NBCA groups, regardless the time point of observation.
Conclusion: Discomfort after glue embolization of varicocele is a common side effect, which might evolve to pain. The assumed lower inflammatory reaction on NBCA-MS was not translated in an improved tolerance.

1. Introduction

A varicocele is an abnormally dilated cluster of veins in the pampiniform plexus, caused by reflux of blood through insufficient valves in the internal spermatic vein (ISV) [1]. The incidence is rare before the age of 10 years, rises to 15% in the adolescent population and increases up to 45% in infertile males [2,3]. Treatment is indicated to relieve local discomfort and to improve male fertility [4]. Percutaneous embolization has the advantage over surgery because it is an outpatient procedure under local anesthesia with a faster return to normal activities and a considerable lower cost [4]. Recurrence rates for both techniques vary between 1.6 and 13% [5–9]. Although many materials have been proposed and used for embolization of varicoceles, it remains unclear whether coil placement has a lower recurrence rate than for instance the injection of an sclerosing agent. The concept that the complex venous network found in many cases of spermatic vein insufficiency should be completely obliterated was the principal reason for the use of a tissue adhesive [10,11]. Kunnen et al. already reported in 1980 a high success rate with IBCA (isobutyl-2-cyanoacrylate, bucrylate, Ethicon) [10]. Later on IBCA was replaced by NBCA (n-butyl-2-cyanoacrylate or embucrilate; Histoacryl transparent, Braun, Tuttlingen, Germany) by reasons of possible carcinogenicity [12–14]. NBCA causes an acute and chronic inflammatory reaction expressed clinically in varicoceles by local pain and discomfort. The Food and Drug Administration (FDA) refused subsequently to approve NBCA for intravascular application, untill Trufill demonstrated recently its value for embolization of intracranial arterio-venous malformations [15]. In Europe, the company never applied for or received a CE-label for intravascular use.

For many years research was concentrated on extension of the carbon group of the NBCA, however it was only after introduction of the copolymer NBCA-MS (Glubran 2) that a glue component with a lower exothermic reaction and a higher stability became

* Corresponding author. Tel.: +32 93322933; fax: +32 93324112.
E-mail addresses: peter.vanlangenhove@uzgent.be, pvanlangenhove@pandora.be (P. Vanlangenhove).

0720-048X/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejrad.2013.11.018

commercially available. The company General Enterprise Marketing (Viareggio, Lucca, Italy) received a CE label for intravascular use after animal studies demonstrating a lower histotoxicity and inflammatory reaction [16–18]. According to the manufacturer, NBCA-MS should have the same embolic capacities as NBCA, which was confirmed by two randomized controlled trials [11,19].

Concerning the side effects of NBCA-MS the issue is less clear. Heye et al. did not reveal any difference between NBCA and NBCA-MS, but their study had several shortcomings [19]. In Heye's study, the investigator was not blinded for the glue. Pain sensation was only evaluated at the end of the procedure, while continuous registration during the procedure might be more accurate. Heye et al. investigated only the acute pain reaction and not the post inflammatory pain during the week after embolization. They included also children in the trial, who might be less reliable in reporting pain sensation. Therefore we initiated a blinded comparative prospective randomized study with the varicocele as a model to find out whether NBCA with the co-monomer (MS) is clinically better tolerated than the classical NBCA.

2. Materials and methods

2.1. Patients selection criteria

We prospectively randomized 112 spermatic veins in 83 adult patients to be treated either by NBCA or by NBCA-MS. In the same patient, the left varicocele could be randomized to a different embolic agent than the right one. A similar number of left ($N = 40$ and $N = 44$) and right ($N = 14$ and $N = 14$) spermatic veins were treated with either NBCA or NBCA-MS.

Reasons for treatment consisted of impotence, clinical inconvenience with or without infertility, primary or secondary infertility and prophylactic embolization. The study was approved by the ethical board of our hospital. All participating patients signed the informed consent to participate the study (ethical board number 2003/081).

2.2. Technical aspects

Phlebographies of the renal vein and the ISV were performed using 6 French (F) diagnostic catheters (Cook Europe, Bjaeverskov, Denmark) after local anesthesia with Lidocaine 1% (Xylocaine NV Astra Zeneca, Brussels, Belgium). Technical aspects of embolization with glue were described extensively elsewhere [11,19].The 3F Microferret microcatheter (modified coaxial infusion set with slipcoat hydrophilic coating) (Cook Europe, Bjaeverskov, Denmark) was then positioned suprainguinal or as low as possible to perform a superselective distal venography in supine position.

The injection of glue was started from above the inguinal region. The cyano-acrylate was delivered during slow withdrawal of the microcatheter up to the level of the renal vein. We aimed at occluding the spermatic vein along with parallel veins or all relevant side-branches or renospermatic bypasses. The embolization was performed as an outpatient procedure.

2.3. Randomization and blinded set-up

Randomization was done by a computer random generator producing a continuous list of "0" (NBCA) and "1" (NBCA-MS) numbers. Each insufficient spermatic vein was connected to one number on the list and was embolized with the allocated glue. The interventional radiologist and the patient were blinded for the type of glue used. A technical assistant prepared the glue in a separate room. In a 3 ml syringe, either 1 cm^3 of NBCA or 1 cm^3 NBCA-MS was mixed with 1.2 cm^3 or 1.0 cm^3 of Lipiodol Ultra-fluide (Liopidol Ultra-fluide, Laboratoire Guerbet, Roissy, France) respectively. The decision to utilize a mixture with a higher concentration of NBCA-MS was empirical based on the supposed slower polymerization rate of Glubran2 [18]. The blinded operator received the 3 cm^3 syringe always filled with 1.8 cm^3 of the allocated glue mixture. As both glues have the same odor and color, it was not possible for the operator to guess which one he was using. All embolizations in the study were done by the same experienced operator well acquainted with tissue adhesives.

Table 1
Adapted pain scale.

	Left hand movements	Pain scale	Visual analog scale
0	Does nothing	Patient feels nothing	0
1	Shows 1 finger	Patient feels something but has no pain	1–3
2	Shows 2 fingers	Patient has pain but bearable	4–6
3	Shows 1 hand	Patient has a clear pain	7–8
4	Shows 1 moving hand	Patient has a severe and unbearable pain	9–10

2.4. Patient's comfort and side-effects during and after embolization.

Discomfort and the degree of discomfort are subjective parameters, which might differ between patients. Patients with a lower pain threshold will indicate discomfort more rapidly. Comparing measurements with the same painscale can make these parameters more objective, easier to assess and it has the advantage to detect the most painful period of the procedure. During the procedure patients can suffer or they can feel nothing and this can be indicated as discomfort "yes" or as discomfort "now". As an additional evaluation, patients were instructed to score on a painscale (Table 1) from 0 to 4, where 0 means "feel nothing" and 4 is associated with severe pain. No sedatives or pain medication were administered before embolization.

2.4.1. Pain reference test during local anesthesia

Local anesthesia was performed with 8 cm^3 xylocaine 1% (NV Astra Zeneca, Brussels, Belgium) through a 21 G intramuscular needle (BD Medical Systems, Drogheda, Ireland) and standardized by the same operator in all procedures. We know that local anesthesia caused some discomfort and by analysing this discomfort on the same painscale we could detect low pain threshold patients.

2.4.2. Discomfort during and after embolization

"During embolization" is defined as the period between the start of glue injection until the withdrawal of the microcatheter. Patients were instructed to score pain by standardized hand movements based on a visual analog scale score (VAS) as shown in Table 1. The use of a classical VAS score during the embolization was not workable. The highest score during the procedure was taken into account as well as the characteristics of the pain (immediately or later). "After embolization" means the period between the end of the procedure and the moment the patient left the hospital. Intake of analgesic or non-steroid anti-inflammatory drugs (NSAID) was noted.

2.4.3. Discomfort during 1 week after embolization

This evaluation was done by completing a questionnaire at home where patients could indicate persisting or late onset discomfort. Patients were asked to localize the discomfort on a drawing, presenting the groin, the testicles, the scrotum, the penis and the hypochondrium. Other inconveniences, duration of pain (hours or days) or the intake of drugs could be written on the questionnaire.