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## Pain experience during internal spermatic vein embolization for varicocele: comparison of two cyanoacrylate glues

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**Abstract** The purpose of this study was to evaluate possible pain sensation differences in patients after retrograde varicocele embolization either with n-butyl-(2)-cyanoacrylate (NBCA) or with n-butyl-(2)-cyanoacrylate + methacryloxysulfolane (NBCA-MS). Transcatheter varicocele embolization was performed in 64 consecutive patients (62 left, two bilateral). Embolization was done with NBCA ( $n=32$ ) or NBCA-MS ( $n=32$ ). Immediately after the procedure, patients were asked to evaluate pain during embolization using a visual analog scale (VAS). Statistical analysis was done with Student's *t* test. Mean pain score on VAS was 3.23 (range: 0–8) for NBCA and 3.28 (range 0–9) for NBCA-MS. This difference was not significant ( $P=0.932$ ). Independently of the type

of glue, no difference in pain sensation ( $P$  value 0.421) was found between patients younger than 18 ( $n=29$ ) and patients older than 18 years of age ( $n=35$ ) (younger than 18, mean 3.52; older than 18, mean 3.05). No difference in mean pain experience level ( $P=0.323$ ) was seen in 11 patients with vessel wall perforation (23.4%) during the procedure (3.89; range: 0–8.5) in comparison with those without perforation (mean pain sensation level: 3.13; range: 0–9). No difference in pain experience was found after transcatheter varicocele embolization either with NBCA or NBCA-MS. Age and vessel wall perforation have no influence on pain sensation independently of the type of glue.

**Keywords** Varicocele · Therapeutic embolization · Enbucrilate · Pain

### Introduction

Transcatheter embolization of a variceal and insufficient internal spermatic vein or varicocele is known to be a valuable alternative for surgical spermatic vein ligation [1]. Several embolization materials, such as coils, detachable balloons, or sclerosal agents, are used to occlude the internal spermatic vein [2]. Varicocele embolization by means of glue (isobutyl-2-cyanoacrylate) was introduced by Kunnen in 1980 and 1981 [3, 4] and has been proved to be effective in large series of patients [2]. Although he stated that the procedure was painless [4], in our experience, patients very often mentioned left-sided (or right-sided in case of right varicocele embolization) abdominal pain seconds after injection of n-butyl-(2)-cyanoacrylate

(NBCA) in the internal spermatic vein. This was due to the fact that the polymerization of glue is an exothermic reaction resulting in heat production and that it causes acute inflammatory reactions to the vessel wall and surrounding tissues [5, 6].

NBCA (Histoacryl, B. Braun, Melsungen, Germany) is a cyanoacrylate glue used in surgery, digestive tract endoscopy, and arterial and venous embolizations [7]. N-butyl-(2)-cyanoacrylate + metacryloxysulpholane (NBCA-MS) (Glubran 2, General Enterprise Marketing, Viareggio, Lucca, Italy) is a new cyanoacrylate glue with a longer radical chain (MS) and with the same therapeutic applications as Histoacryl. Experimental studies have shown that equivalent cast homogeneity can be achieved by both NBCA and NBCA-MS in vessels but that NBCA-MS has



a lower temperature of polymerization than NBCA, resulting in a lower histotoxicity/less inflammatory reaction [5, 8]. Because of these differences in biological/biochemical effects between the two cyanoacrylate glues, a lesser pain sensation during the embolization procedure with NBCA-MS could be assumed in comparison with NBCA. The aim of this prospective study was to evaluate the effect of NBCA and NBCA-MS on pain sensation during endovascular varicocele embolization.

## Materials and methods

### Patient population

A total of 64 male patients underwent percutaneous transcatheter embolization of an internal spermatic vein (62 left internal spermatic vein, two left and right internal spermatic veins). Inclusion criteria were clinical varicocele with the request for embolization and an insufficient internal spermatic vein (either directly or via renogonadal collaterals) visible on venography. Indications for embolization were incidental finding of varicocele on clinical examination either by the school physician ( $n=27$ ) or the general physician ( $n=13$ ), subfertility, poor semen quality and varicocele on clinical examination, and color Doppler ultrasound ( $n=22$ ) or recurrent varicocele after transscrotal antegrade sclerotherapy of the spermatic vein ( $n=2$ ). Selection of the type of cyanoacrylate glue was randomized, with use of the envelop method, with two study arms of 32 patients. Mean age of the total group of patients was 23 (age range: 12–49) years. The group of patients treated with NBCA had a mean age of 22 (age range: 12–49) years; those treated with NBCA-MS had a mean age of 24 (age range: 12–38) years. Informed consent was given by the patient, or a legally authorized representative in case of a minor. No approval by the institutional review board was required for this study at our institution at the time.

### Embolization procedure

After puncture of the right common femoral vein under local anesthesia, a 6-F introducer sheath (Terumo Europe, Leuven, Belgium) was placed. Left renal vein catheterization was subsequently performed using a 6-F, 60-cm-long, Cobra-like, formed, braided, guiding catheter (William Cook Europe A/S, Bjaeverskov, Denmark). Then retrograde left renal venography during Valsalva maneuver on a tilt table with the patient in a semiupright position was performed to identify retrograde flow in the internal spermatic vein, either directly or via bypassing collaterals in case of competent proximal valves, which was found in 15 patients (23%). Next, selective catheterization of the cranial portion of the internal spermatic vein with the guiding catheter was done in all cases, even when competent

valves were present. A 3-F, 120-cm-long coaxial microcatheter (modified coaxial infusion set with slip-coat hydrophilic coating; William Cook, Europe) was advanced over a 0.018 in. guide wire (Terumo Europe, Leuven, Belgium) just to the level of the lower half of the sacroiliac joint. All embolizations were performed through the 3-F coaxial microcatheter. A 10% dextrose solution was used to flush the coaxial microcatheter before and after the injection of the glue to avoid immediate glue coagulation in the microcatheter lumen.

Embolization was started below the origin of the lowest (renogonadal or other) collateral, usually at the level of the lower half of the sacroiliac joint, assuring complete thrombosis of the internal spermatic vein and avoiding distal embolization of the pampiniform plexus. The embolization was done by injecting the glue/lipiodized oil mixture under fluoroscopic guidance with the patient in a semi-upright position (table tilted 15–25° in Trendelenburg position) and performing a Valsalva maneuver if necessary. In case of embolization with NBCA, we used a mixture of 1 ml cyanoacrylate glue (Histoacryl L Transparent; B. Braun, Melsungen, Germany) and 0.8 ml lipiodized oil (Lipiodol Ultra-fluid; Laboratoire Guerbet, Aulnay-sous-Bois, France). Whenever NBCA-MS was used, this was done by means of a mixture of 1 ml cyanoacrylate glue (Glubran 2, General Enterprise Marketing, Viareggio, Lucca, Italy) and 0.8 ml lipiodized oil. The volume of glue/lipiodized oil mixture injected varied between 1.5 and 1.8 ml. In all patients, one half to a maximum of two thirds of the internal spermatic vein was filled with the glue/lipiodized oil mixture. In two patients (3.13%), an additional insufficient right internal spermatic vein was found branching from the inferior vena cava. Selective catheterization of the right spermatic vein was performed with a 65-cm-long 5-F Simmons II catheter (Hoogewoud, Cook Europe, Bjaeverskov, Denmark). The same coaxial catheter embolization technique as for the left internal spermatic vein was used. In case of bilateral embolization, the same kind of glue was used for both sides.

At the end of the procedure, a control venography in the left renal vein and/or the inferior vena cava/ostium of the right internal spermatic vein was performed to confirm occlusion of the spermatic vein or veins. Before, during, or immediately after the procedure, no sedatives or pain medication was administered. Immediately after the procedure, the patients were asked to evaluate their pain sensation during the spermatic vein embolization by means of a VAS. The VAS is an instrument consisting of a sliding scale between no pain at one end and worst pain imaginable at the opposite end of the scale without any other verbal descriptors. The patient moves a marker in between these two indicators of pain sensation, which correlates with a numeric score between 0 and 10 (100 mm VAS) at the back of the VAS. If a patient marked no pain at the VAS after the embolization procedure, this correlated with a score of 0. The numeric score was noted in the patient's



record. In case of a bilateral internal spermatic vein embolization, only one pain sensation score was noted. Technical success was defined as absence of opacification of the internal spermatic vein at the control venography at the end of the procedure, without embolization of the pampiniform plexus or renal vein. Complications of the embolization procedure were evaluated following SIR classification system, as mentioned by Sacks et al. [9].

### Statistical analysis

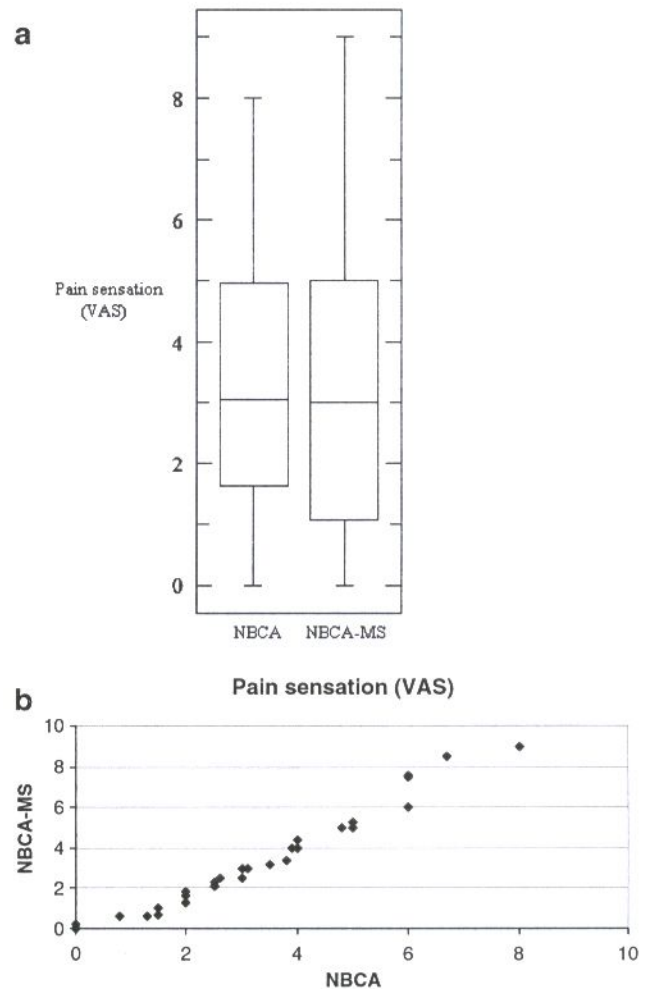
Age distribution and pain scores for both groups were analyzed using the unpaired Student's *t* test. A *P* value of less than 0.05 was considered significant.

### Results

Left renal vein venography and cavography demonstrated 49 directly insufficient internal spermatic veins (47 left and two right), 15 left internal spermatic veins with a competent valve at the internal spermatic vein orifice or in their cranial lumbar subsegment, and two with a competent valve in their caudal lumbar subsegment, according to the classification made by Marsman [10]. The latter 17 internal spermatic veins with competent valves were aberrantly fed by bypassing renogonadal collaterals. In 13 patients with insufficient internal spermatic veins, additional renogonadal or other collaterals were seen.

Thirty-two left internal spermatic veins were embolized by means of NBCA. NBCA-MS was used in 32 left and two additional insufficient right internal spermatic veins. Pain sensation during embolization with NBCA ranged between 0 and 8 (mean: 3.23) on the VAS. With NBCA-MS, varicocele embolization resulted in a VAS pain level range between 0 and 9 with a mean of 3.28. There was no significant difference between the two groups with regard to pain scores ( $P=0.932$ ) (Fig. 1a and b). In these wide ranges of pain sensation, NBCA appears to be less painful in the young patient and more painful in the adult patient while this is the opposite for NBCA-MS (Fig. 2). These differences are, however, not significant ( $P$  value of 0.065 for a pain score  $\leq 3$  on VAS;  $P$  value of 0.108 for a pain score  $\geq 5$  on VAS).

Independent of the type of glue used, no significant difference in pain sensation level was found between the patients younger than 18 years of age ( $n=29$ ) and those older than 18 years of age ( $n=35$ ) (younger than 18, mean 3.52; older than 18, mean 3.05;  $P$  value 0.421). In 11 patients, perforation of the internal spermatic vein occurred during catheterization either by the main catheter or the microcatheter, with extravasation of contrast material. However, in all these patients, superselective catheterization of the internal spermatic vein down to its caudal pelvic subsegment remained possible. Mean pain experience level

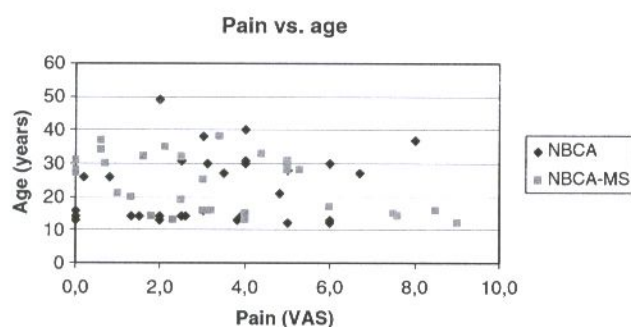


**Fig. 1** **a** Box plot shows VAS scores after varicocele embolization with either n-butyl-(2)-cyanoacrylate (NBCA) or n-butyl-(2)-cyanoacrylate + methacryloxysulfolane (NBCA-MS); 0 means no pain, 10 means worst pain imaginable. Center lines in boxes represent mean values; upper and lower ends of boxes represent 25th and 75th percentile values, respectively. Ends of bars show extreme values for both groups. **b** Scatter plot shows good correlation between the two glues with regard to the wide range of pain sensation level

in patients who presented with perforation during the procedure was 3.89 (range 0–8.5) while in patients without perforation, the mean pain sensation level was 3.13 (range 0–9). With a  $P$  value of 0.323 (unpaired Student's *t* test), no significant difference between these two groups was found.

Successful embolization was obtained in all patients (100%). One patient (1.6%) presented with a recurrent varicocele 1 year after the embolization procedure with NBCA. Control venography of the left renal vein demonstrated occlusion of the internal spermatic vein in its cranial half but opacification of the distal half via multiple renogonadal collaterals, which made repeat transcatheter embolization impossible.





**Fig. 2** Scatter plot demonstrating the distribution of pain in correlation with age for the two cyanoacrylate glues. Young patients mentioned more often low pain levels for n-butyl-(2)-cyanoacrylate (NBCA) and high pain levels for n-butyl-(2)-cyanoacrylate + methacryloxysulfolane (NBCA-MS). For adult patients, this was the opposite. These findings were, however, not statistically significant

## Discussion

Cyanoacrylate glue has been used in endovascular embolization procedures for several decades [6, 11]. Percutaneous glue embolization is usually done in the treatment of brain, spinal cord, and extracranial arteriovenous malformations and arteriovenous fistulas [6, 11]. Nevertheless, NBCA does not have the CE mark for endovascular procedures, and it has FDA approval for embolization of brain arteriovenous malformations only. NBCA-MS, on the other hand, obtained a CE mark, indicating that the product complies with the essential requirements of the applicable European laws or Directives with respect to safety, health, environment, and consumer protection. It has not yet obtained FDA approval for use in the USA, but a premarket approval is being pursued.

Accordingly to the manufacturer, NBCA-MS polymerizes at a lower temperature than NBCA because of the additional methacryloxysulfolane monomer, and Levrier et al. demonstrated that polymerization of NBCA-MS in endovascular embolization procedures resulted in lower histotoxicity and thus less inflammatory reaction [8]. Pain assessment remains difficult and especially in this particular setting where no previous reports on pain originating from glue embolization exist. This study adapted the use of a VAS to quantify pain as reported in studies on patients with cancer pain [12]. The validity of the VAS could be questioned in this setting, but we were not so much interested in the absolute numbers. Our main goal with the VAS was to have a quantification of pain that could be used for comparison. Because in our experience the sensation of pain declined rather fast, no analgesic drugs were administered after embolization.

Our study shows that despite the differences in biological/biochemical findings, the same level of pain experience during varicocele embolization is seen with regard to the two cyanoacrylate glues. For both glues, the embolization procedure was well tolerated, with a mean pain score of less than 4 [12].

The wide range of pain sensation scores—indicating that even with the same glue pain gradation is not predictable—are nearly equal for the two glues, but the distribution with regard to age is different. For NBCA, the low pain scores were more frequently seen in the young patient ( $\leq 18$  years of age) while the adult patients mentioned more intermediate and high pain scores on the VAS. For NBCA-MS the opposite was found for the high and low pain scores (more low scores in adult patients and more high scores in the young patient). These differences were, however, not significant. In addition, age and accidental vessel wall perforation have no significant influence on the pain sensation independently of the type of glue used.

The authors have no explanation for these findings. It could be possible that the difference in exothermic reaction between the two glues is not that large or at least not large enough to reduce significantly the inflammatory reaction of the vessel and the surrounding tissues. It could also be possible that the histotoxicity of the glue is not the main cause for pain after embolization. The latter seems, however, less probable since varicocele embolization with glue is in most cases painful while coil embolization of varicocele is not painful. Thus, pain sensation after varicocele embolization with cyanoacrylate glue appears to be only patient dependent.

We encountered 17 (34.7%) aberrantly fed varicoceles with a competent valve at the ISV orifice or at the lumbar subsegments. This percentage is nearly twice as high as in the study of Marsman where 17–19% of the varicoceles with competent valves were fed by collaterals [10]. Varicoceles with competent valves are more difficult to catheterize, and Marsman had a technical success rate of 73% for left-sided and 57% for right-sided varicoceles [10]. Lenz et al. had an overall success rate of 93.8%, a success rate of 54% for internal spermatic veins with competent valves, and a global recurrence rate of 3.8% [13]. Our technical success rate was 100% for both normally and aberrantly fed varicoceles.

One recurrent varicocele was noted 1 year after the embolization procedure with NBCA. On control left renal venography after 1 year, the internal spermatic vein was still occluded in its lumbar and cranial pelvic subsegments, but more caudally, it was opacified via multiple renogonadal veins. This clinically recurrent varicocele was probably due to the fact that the cast did not extend all the way into the caudal pelvic subsegment where a collateral was partially opacified during the embolization procedure and not because of the type of cyanoacrylate glue. This recurrence rate of 2.1% is in the range of previous studies [2, 13, 14].

In 11 patients (17%), a perforation of the left internal spermatic vein with (self-limiting) extravasation of contrast material occurred during the procedure, which is a much higher number than the study of Lenz et al. where per-



foration was found in 6.22% [13]. This can probably be assigned to the fact that we had also a high percentage of patients with competent valves of the internal spermatic vein. In five of these 11 patients (45.5%) this happened after attempting to pass the 0.035-in. hydrophilic guide wire through competent valves. In the six others, the 0.018-in. hydrophilic guide wire used for superselective catheterization with the 3-F microcatheter perforated the vessel wall. Lenz et al. had 67% of all perforations that occurred in patients with an intact valve of the main trunk of the

internal spermatic vein with bypassing insufficient collaterals [13]. Patients with vessel wall perforation, however, did not mention more pain in comparison with those without perforation.

In conclusion, retrograde varicocele embolization with NBCA-MS causes no decrease in pain sensation in comparison with NBCA. Moreover, age and vessel wall perforation do not have a significant influence on the pain sensation independently of the type of glue that was used.

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