Abstract

Background and Objectives: Complete surgical excision of vascular anomalies is technically difficult and seldom possible, prompting interest in other treatment options, especially sclerotherapy. We decided to study the results of intralesional injection of n-butyl cyanoacrylate (NBCA) and autologous fibrin glue (FG) in hemangioma and vascular malformations (VMs). Materials and Methods: This prospective study was conducted in fifty consecutive patients of hemangioma and VMs. Frequency of injections was decided according to size and injections were given at the interval of 4 days to complete the treatment in 30 days. Postinjection reduction in size of the lesion was assessed. Lesions which did not disappear or those having complications were taken for surgery and amount of blood loss during excision was estimated. Results: In NBCA group, the mean reduction in size of hemangioma and low flow VM was 63.85%–73.3%; in FG Group, it was 51.9%–53.80%, respectively. In FG group, the mean blood loss was 37.5 ml for a mean size of 3.6 cm² hemangioma and 79.55 ml for low flow VM with a mean size of lesion 2.23 cm². In NBCA group, the mean blood loss was 37.5 ml for mean size of 4.4 cm² hemangioma and 37.5 ml with a mean size of 3.55 cm² low flow VM. Conclusion: Repeated intralesional injections of NBCA and FG in hemangioma and VMs are associated with significant reduction in size and blood loss during excision. Small vascular lesions (<2 cm) disappeared completely, and excision of remaining lesions becomes technically easy.

Keywords: Fibrin glue, hemangioma, intralesional injection, n-butyl cyanoacrylate, sclerotherapy, vascular malformations

INTRODUCTION

Vascular anomalies are commonly seen in clinical practice. Studies of the incidence of IH suggest that it ranges from 4%–5% of infants to 2.6%–9.9% of older children are affected.¹² These are classified embryologically into hemangioma and vascular malformations (VMs).¹ High-flow VMs are arteriovenous malformations which are usually treated by embolization/surgery or combination of both.¹⁴⁻⁶ Unresolved hemangiomata and low-flow VMs (capillary, lymphatic, and venous malformations) usually require surgical excision.¹⁷ However, irregular growth of vascular anomalies into the surrounding soft tissue makes complete surgical excision difficult and may lead to incomplete excision/recurrence, local nerve damage, and severe blood loss during surgery. This has prompted interest in other treatment options, especially sclerotherapy.¹⁸⁻⁹ The present study was conducted to study the results of intralesional injection of n-butyl cyanoacrylate (NBCA) and autologous fibrin glue (FG) in hemangioma and low-flow VMs.

MATERIALS AND METHODS

This prospective study was conducted in Plastic Surgery Unit, Department of Surgery, in a tertiary referral center in Central India over a period of 1 year. The Institutional Ethical Committee approved the study protocol. Written and informed consent was obtained from all patients.

Patients younger than 2 years and older than 50 years, patients with hemangioma/A-V malformations in periorbital,
orbital, ear canal, nose region, high-flow VMs, and lymphatic malformations were excluded from the study.

The diagnosis of the lesion was made on the basis of the history and clinical examination. MR angiography or ultrasound was done to confirm the type and extent of the lesion. Patient’s hemogram and coagulation profile were tested. Measurement of size and clinical photographs were taken at the time of first visit and subsequent visits after sclerotherapy or excision.

Commercially available NBCA (Endocryl [Samarth Life Sciences Pvt. Ltd., India], or Histacryl [B. Braun Surgical S. A., Spain]) was used, while FG was prepared in the following manner. Fibrogen was prepared according to the technique of Hartman et al.\(^\text{[10]}\) 10 ml of patient’s venous blood was drawn a day before sclerotherapy in a heparinized syringe. It was centrifuged at 3000 rpm for 10 min and the separated plasma was then aspirated with spinal needle. The whole procedure was performed with strict sterile precautions. This plasma served as a source of fibrogen and was stored in a syringe at \(-20^\circ\text{C}\). Thrombin was prepared by the technique of Quick\(^\text{[11]}\). Thrombin was obtained from fresh frozen plasma (FFP) of healthy donors (which were screened negative for HIV and Hepatitis B). A volume of 10 ml of FFP was thawed to 2°C–4°C and was 10 times diluted with distilled water, making 100 ml of solution. In this, 1 ml of 1% acetic acid was added to make the pH 5.8 and this resulted in the formation of precipitate. This was kept for \(\frac{1}{2}\) h and then centrifuged at 3000 rpm and titrated with sodium bicarbonate to bring the pH at 7. This was put in water bath (37°C) and 0.1 ml of CaCl\(_2\) (calcium chloride) was added. The clot that formed in 45–120 s was removed by wrapping it around a stirring glass rod. The thrombin solution thus prepared was stored in a syringe at \(-20^\circ\text{C}\). Before injection, 0.5 ml of each component was mixed with each other making 1 ml.

Alternate patients were allotted for NBCA or FG sclerotherapy. NBCA or FG was injected intraluminally through percutaneous or through the mucosa after compressing the lesion. One milliliter insulin syringe was used with four intramuscular 26-gauge needles. One needle was used to draw NBCA/FG and other three were used for subsequent injections because the needle got occluded rapidly. NBCA and FG were used in the dose of 1 ml/2 cm\(^2\) areas at the interval of 4 days. Technique of injection was same for both hemangioma and VMs. Injections were given according to palpating and compressing the lesion, and after injection, pressure was applied for 5 min to prevent bleeding from injection site. Injections were given according to size, one injection for lesion <2 cm\(^2\), two injection for 3–5 cm\(^2\) lesion, four injections for 6–10 cm\(^2\) lesion, and six injections for >10 cm\(^2\) size lesion. All these injections were given at the interval of 4 days and size of the lesion was assessed. The aim was to complete the treatment within 30 days.

Complications such as ulceration, bleeding, or eczema were noted. The end point was complete disappearance of lesion or reduction in size. If the lesions did not disappear, then excision of the lesion was performed, and the amount of blood loss was assessed intraoperatively by weighing the gauze piece and pads. The excised mass was sent for histological assessment to assess biological reaction to sclerotherapy.

The data were analyzed using SPSS-20 software (IBM Corp, Armonk, NY) for windows. Appropriate univariate and bivariate analysis were carried out using the Student’s \(t\)-test for a continuous variable (age) and two-tailed Fisher’s exact test or “Chi-square” test for categorical variables. All means were expressed as mean \(\pm\) standard deviation. The critical levels of significance of the results were considered at 0.05 levels.

**Results**

A total of 62 patients were assessed for sclerotherapy. Twelve patients with high-flow VMs were excluded from the study and 50 patients of unresolved hemangiomata and low-flow VMs were enrolled. Fourteen of 50 (28%) patients had unresolved hemangiomata, while 36 patients (72%) had low flow VMs. NBCA group included 25 patients (6 unresolved hemangiomata and 19 low-flow VMs) and FG group included 25 patients (8 unresolved hemangiomata and 17 low-flow VMs).

Mean age of patients was 15.21 years (range: 2–60 years). Vascular anomalies were most common in head and neck region (52%) followed by extremities (38%) and trunk (10%) [Table 1]. In hemangiomata group, female-to-male patient’s ratio was 2:1, while in VM, male to female ratio was 1:1. None of the patients had received any medical treatment for these lesions previously.

All lesions were superficial therefore obviating the need to localize these lesions with the help of USG. The local anesthetic was not required for injection. However, radiological size of the lesion could not be calculated because of nonavailability of sonologists at all the times.

In 11 patients (7 in NBCA Group and 4 in FG Group), lesion <2 cm in size completely disappeared after the first injection. Excision of lesion was required in 39 patients.

| Table 1: Demographic details of patients |
|------------------------------------------|
| **Type of lesion** | **Age (years)** | **Sex** | **Site** |
| | 0-10 | 10-20 | 20-30 | 30-40 | >40 | **Male** | **Female** | **Head/neck** | **Truck** | **Extremity** |
| Hemangioma (n=14; 28%) (%) | 7 (14) | 1 (2) | 5 (10) | 1 (2) | 0 | 5 (35.7) | 9 (64.3) | 9 (18) | 4 (8) | 1 (2) |
| VM (n=36; 72%) (%) | 15 (30) | 10 (20) | 4 (8) | 4 (8) | 3 (6) | 16 (44.4) | 20 (55.6) | 17 (34) | 2 (4) | 17 (34) |
| Total | 22 | 11 | 9 | 5 | 3 | 14 | 36 | 26 | 6 | 18 |

VM: Vascular malformation
Significant reduction in size of hemangioma (FG Group 52.61%, NBCA Group 53.80%) and low flow VMs (FG Group 63.85%, NBCA Group 73.3%) was seen after sclerotherapy [Table 2 and Figures 1-4].

The mean size of all lesions in FG group was 3.13 cm². In this group, a total of 49 sessions of sclerotherapy (average 1.59 sessions/lesion) of FG were given. The mean size of all lesions in NBCA Group was 4.22 cm². In this group, a total of 59 sessions of sclerotherapy (average 1.78 sessions/lesion) were given.

In FG group, the mean blood loss was 37.5 ml for a mean size of 3.6 cm² hemangioma, whereas in low flow VMs, the mean blood loss was 79.55 ml for a mean size of lesion 2.23 cm². In NBCA group, the mean blood loss was 37.5 ml for mean size of 4.4 cm² hemangioma ($P > 0.05$) and 37.5 ml with a mean size of 3.55 cm² low flow VM ($P < 0.001$) [Table 3].

In FG group, six patients developed complications (eczema in 3, pigmentation in 2, and ulceration in 1 patient), while in NBCA group, three patients developed complications (facial nerve paresis, ulceration, and pigmentation in one each). The rate of complication was more in FG group than NBCA group (24% vs. 12%; $P > 0.05$).

On histological examination, the use of NBCA and FG was associated with fibrous thickening of blood vessels and chronic inflammatory reaction around the vessels. In some cases, foreign body giant cell reaction was present with the use of NBCA. The patients were followed up for 2 years. There were no recurrences.

**Discussion**

Absolute indications for treatment of the hemangioma and VMs include hemorrhage, hemodynamic problems such as high-output cardiac failure, or secondary ischemic complications caused by high-flow AV shunting. Other indications include pain, ulceration, and deformity. Surgical excision of vascular lesions is associated with technical difficulty, incomplete excision, recurrence, intraoperative blood loss, and postoperative scar formation. Addition of sclerotherapy is a welcome addition to the armamentarium of vascular surgeons.

Most hemangioma undergo involution by the age of 10 years; therefore, a wait-and-watch policy is adopted. If unresolved, sclerotherapy can be used to reduce the morbidity of surgery. High-flow arteriovenous malformations are not suitable for percutaneous sclerotherapy as high flow will lead to dilution of sclerosant leading to decrease efficacy. In addition, there is definite feeding vessel which can be embolized followed by, if required, surgical excision of the lesion. Capillary malformations and lymphatic malformations are often treated

| FG | Hemangioma | Percentage reduction |
|----|------------|----------------------|
|    | Mean initial size ± SD ($n$ = 8) | End size ($n$ = 8) | 52.61±32.9035 |
|    | 2.23±0.6346 | 1.16±0.9870 | $P < 0.05$ |
|    | VM Significance | 3.55±1.608 | 1.9±1.257 | 53.80±26.544 | $P < 0.05$ |

| NBCA | Hemangioma | Percentage reduction |
|------|------------|----------------------|
|      | Mean initial size ± SD ($n$ = 6) | End size ($n$ = 6) | 63.85±22.1718 |
|      | 3.60±2.3925 | 1.30±0.9055 | $P < 0.05$ |
|      | 4.42±2.614 | 1.18±1.592 | $P < 0.0001$ |

| FG | Hemangioma | Mean blood loss ml |
|----|------------|--------------------|
|    | 2.23±0.6346 | 37.5±13.69 |
| NBCA | 3.60±2.3925 | 37.5±17.68 |

| Low flow VM | Mean blood loss ml |
|-------------|--------------------|
| 3.55±1.608 | 79.55±29.19 |
| 4.42±2.614 | 37.5±13.36 |
The use of NBCA showed greater reduction.

Left arm arteriovenous malformations preoperative with magnetic resonance angiography and postoperative result following n-butyl cyanoacrylate injection.

Many sclerosing agents are used for the treatment of hemangioma and VMs: pingyangmycin, ethanol, bleomycin, ethanalamine oleate, polidocanol, and sodium tetradeacyl sulfate, but it is unclear which sclerosing agent is superior in terms of safety and effectiveness. These sclerosants were compared in a meta-analysis, but this review failed to identify an optimal sclerosant agent.[16] In general, all these sclerosants have an excellent overall response between 71% and 100%; the difference in complication rates and personal preference of physician is the deciding factor in the choice between sclerosing agents.[17]

Complications such as skin necrosis and nerve injury are often reported with the use of ethanol sclerotherapy; rare complications include brain embolism, hemoglobinuria, deep venous thrombosis, pulmonary embolism, pulmonary hypertension, and cardiac collapse.[18-20] Hemolytic disorders (ethanolamime oleate), reversible cardiac arrest (polidocanol), and hypersensitivity reactions (sodium tetradeacyl sulfate) have been observed with other sclerosants.[21,22]

Considering these complications, we decided to use NBCA or autologous FG. Upon injection, NBCA undergoes an exothermic hydroxylation reaction that results in polymerization and stripping of endothelium over a considerable distance and exposing highly thrombogenic endothelium in the process. NBCA permanently occludes the vessel and they do not recanalize.[23,24] This leads to cessation of blood flow and whole mass turns into solid polymer which then may be excised without much blood loss. FG is a biological tissue adhesive which consists of two separate solutions of fibrinogen and thrombin when mixed together these agents mimic last stage of clotting cascade to form fibrin clot. When injected, the glue hardens and forms a mechanical barrier, which reduces the size of hemangioma/VM.[25] Intraoperative blood loss is decreased due to the development of pseudocapsule around the lesion.[26]

In the present study, both FG and NBCA reduced the size of hemangioma and VMs, which was similar to previous studies.[27] The use of NBCA showed greater reduction in size of VMs and less mean blood loss as compared to FG (P < 0.001) [Table 2]. On histological examination, the use of NBCA and FG was associated with fibrous thickening of blood vessels and chronic inflammatory reaction around the vessels. In some cases, foreign body giant cell reaction was present with the use of NBCA.

In NBCA group, the complication rate was 12%. One patient developed facial nerve paresis but improved after excision of lesion. In another case, the patient with a lesion affecting left arm experienced skin necrosis over the lesion, which was due to superficial injection of NBCA in the dermis. The necrotic skin was resected and wound was closed primarily. One patient developed hyperpigmentation. In FG group, complications occurred in six patients (24%). Eczema developed in three patients, hyperpigmentation in two patients, and ulceration in one patient. All patients responded to conservative treatment and did not require any intervention. FG group had more (P > 0.05) complications.

Serious complications such as systemic embolization and anaphylactic reaction have been reported with the use of FG,[28] but these were not seen in the present study. These complications are seen more commonly with commercially available FG which is expensive, has a risk of transmission of HIV and HbsAg, may not be readily available, and has problems with its storage.[29,30] Use of NBCA has been shown to be associated with skin necrosis, nontargeted embolization, hyperpigmentation, transient bacteremia, facial nerve palsy, and rarely anaphylactic reaction.[31]

There is limited evidence in literature about the safety and efficacy of percutaneous sclerotherapy for VMs. Majority of the studies demonstrated substantial variability in lesion characteristics, type and dose of sclerosant used, and treatment details and outcome methods used to measure lesion response. In a recent European Guideline on sclerotherapy, foam sclerotherapy is recommended over liquid therapy for the treatment of venous malformations as it is more effective and has fewer complications.[32,33] To avoid complications associated with sclerotherapy, Odyninde et al.[34] advised precautions such as the use of fine long needle, small volume of sclerosant in multiple sessions, avoidance of alcohol as sclerosant, use of steroids in cases of nerve injury, inject saline in cases of superficial injection of sclerosant, use of USG for localization, and three-way needle for injection.
CONCLUSION
Intralesional injections of NBCA and FG in unresolved hemangiomata and VMs are associated with significant reduction in size and blood loss during excision. Their use is inexpensive and leads to effective devascularization with few complications and can be done immediately before surgery. Small vascular lesions (<2 cm) disappeared completely and postsclerotherapy excision of lesions becomes technically easier. Therefore, we recommend the use of NBCA/FG in unresolved hemangiomata and VMs before surgical excision. Sclerotherapy is a simple, safe, inexpensive, and effective treatment for patients with hemangiomata and VMs as a stand-alone treatment or pretreatment for surgery.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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