METHODS

Morphological Assessment of Arteries Occluded by Hydrogel with Enhanced Hemostatic Effect

N. D. Skuba, N. A. Goryukhina, A. A. Adamyan, N. V. Panova, O. S. Voronkova, M. I. Titova, and N. V. Trostenyuk

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny,* Vol. 125, No. 2, pp. 237-240, February, 1998
Original article submitted May 13, 1997

Dicinone-saturated emboli switch off pathological bloodflow and arrest bleedings upon endovascular embolization of blood vessels. Dicinone emboli exert a potent hemostatic effect and promote more rapid and expressed (in volume) thrombogenesis.

Key Words: *endovascular occlusion; embolus; dicinone*

Endovascular embolization of blood vessels has been widely used in vascular surgery for switching off pathological blood flow. Blood loss during surgical intervention is reduced and bleeding is sooner arrested [2-5,7-9].

Today the main embolizing material in Russia is hydrogel based on poly-2-hydroxyethylmethacrylate. This gel was developed at the A. V. Vishnevskii Institute of Surgery in cooperation with the Institute of Macromolecular Chemistry of Czech Academy of Sciences and Institute of Chemical Physics of Russian Academy of Sciences. Emboli formed from this material cause no injuries or inflammatory reactions in the vascular wall, stimulate blood clotting, swell in a vessel lumen, and produce good and rapid obturating effect. Hydrogel emboli consisting of biologically inert material are not resorbed. Despite these properties of pure hydrogel, there are clinical cases requiring still more rapid thrombogenesis. It is especially important in arterial bleeding from trophic ulcers at sites where extensive cavernous hemangiomas are localized or in angiodysplasias when there are arteriovenous fistulas involving the bone. In such situations, hemorrhages can be arrested only by embolization, and the rate of blood clotting is of paramount importance in such cases.

We tried to modify the hydrogel by rendering it a more potent hemostatic effect.

Dicinone is a drug that stimulates blood clotting by predominantly activating tissue thromboplastin and enhancing platelet adhesion [1,6]. Moreover, this drug stimulates the production of high-molecular-weight mucopolysaccharides in capillary walls, thus decreasing vascular permeability. These effects and minimal side effects account for the choice of dicinone for the development of new material with a potent hemostatic effect.

MATERIALS AND METHODS

Dicinone was added to hydrogel without chemical bonds between the emboli. Hydrogel was soaked in sterile dicinone solution for at least 24 h. The content of dicinone per gram dry substance was 0.05 g (1 g of emboli 0.5 mm in diameter is equivalent to a length of 350 cm). This dose is equivalent to 1/10 therapeutic dose for an adult.

In order to investigate the effect of emboli with a high hemostatic potency on thrombogenesis and vascular walls, emboli were implanted into the femoral arteries of 20 rabbits. Hydrogel emboli without

A. V. Vishnevskii Institute of Surgery, Russian Academy of Medical Sciences, Moscow

0007-4888/98/0002-0209$20.00

dicinone were used in control experiments. The arteries were examined 20 min-3 months after implantation.

RESULTS

Histological studies of transverse sections of arteries occluded with dicinone emboli show that on day 1 the embolus substance is homogeneous and occupies lesser part of the lumen. The remainder of the lumen is filled with thrombotic mass: red thrombi with small sites of white thrombi. The components of white thrombi were identified on the embolus surface. Vascular wall was stretched at the site of embolus and thrombus localization, as evidenced by smoothing of the internal elastic membrane folds. A

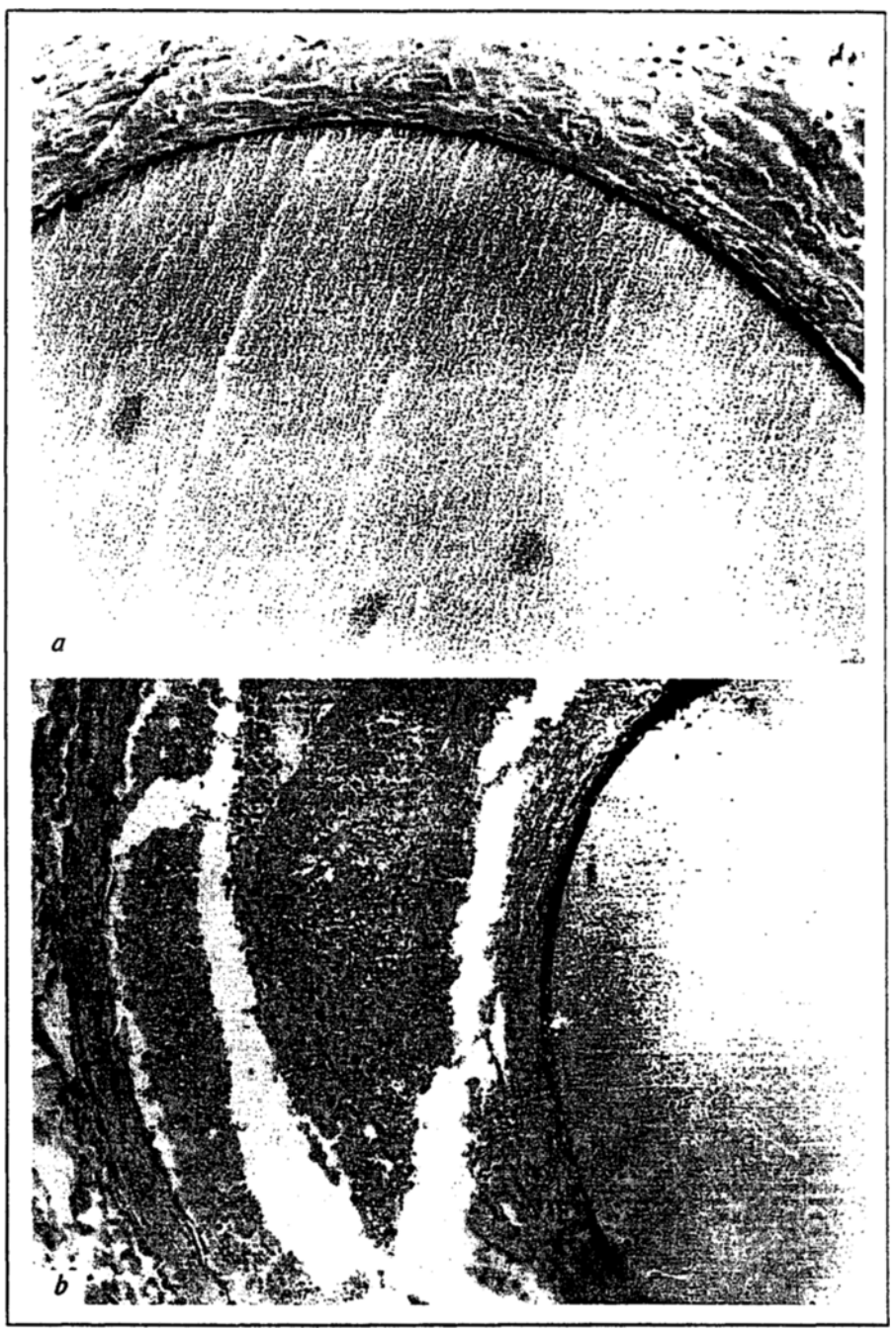

Fig. 1. Transverse section of an artery with a hydrogel embolus without dicinone (control, *a*) and with dicinone (*b*). *a*) embolus material fills the entire vascular lumen; arterial wall is stretched. *b*) thrombotic mass with initial signs of organization (penetration of fibroblasts into thrombotic mass) occupies the greater part of the lumen; arterial wall is stretched (left). Here and in Fig. 2: exposure 25 days; hematoxylin and eosin staining. ×63.

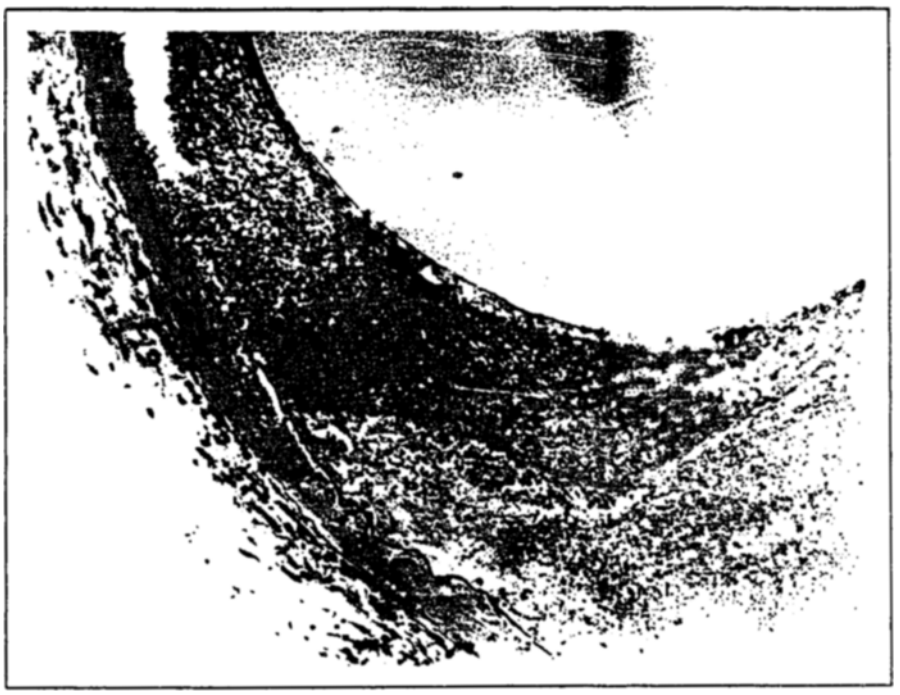

Fig. 2. Hydrogel embolus saturated with dicinone in the arterial lumen. Embolizing material fills small part of vascular lumen, the greater part of which is occupied with thrombotic mass; vascular wall is stretched.

segment of the artery distal from the embolus looked shrunk. The lumen was shrunk and filled with red thrombus. Arterial wall was thickened; the internal elastic membrane formed deep folds. There were no signs of inflammation or injury to vascular wall. Such a picture allows a conclusion that hydrogel emboli saturated with dicinone stimulate thrombogenesis, which is proven by a much larger volume of the thrombus compared with that of the embolus. Moreover, accumulation of platelets and leukocytes at the surface of emboli indicates that thrombogenesis starts near the surface of embolizing material. None of such features of thrombogenesis was observed in the control.

On day 5, a similar picture was observed, except that erythrocyte hemolysis started in thrombi, this process consisting in penetration of fibroblasts into the thrombus. Vascular wall was intact, without signs of injury or inflammation.

On day 16, the lumen of femoral arteries was filled mainly with hydrogel emboli material and partially with arranged thrombi. Arterial walls were stretched and their membranes thinned. Thinning of vascular walls was caused by stretching due to hydrogel swelling and rapid thrombogenesis at the site of embolus impregnated with dicinone. The presence of hydrogel in thrombotic mass indicates that dicinone accelerates thrombogenesis: thrombus is formed sooner that hydrophobic hydrogel swells. This indicates a higher rate of thrombogenesis (like on day 1), as a result of which the thrombus replaces the embolus material. In the control, the lumen of femoral arteries was generally filled only with embolus material; this confirms our previous hypothesis about dicinone stimulation of thrombogenesis.

On day 25, transverse section of arterial lumen was twice as large as transverse section of embolus which was surrounded by thrombotic mass (Figs. 1 and 2). Arterial wall was stretched, thinned, without any signs of inflammation or injury in it. Thrombi in the lumen of arteries were of a mixed nature. Accumulations of leukocytes and platelets — elements of initial thrombogenesis — were sometimes seen near the surface of hydrogel emboli. There were signs of thrombi formed by penetration of fibroblasts. Therefore, there are good grounds to assert that extension of the lumen of an artery at this term, like at the previous, is caused by two factors: rapid thrombogenesis and swelling of emboli. In the control, hydrogel emboli were not surrounded by thrombotic mass or were small (Fig. 1, *a*).

Later, organized red thrombi were seen in the lumen of femoral arteries occluded with dicinone emboli; this was additional evidence of rapid thrombogenesis. Histological picture was supplemented by thinning, atrophy, and sclerosis of arterial walls but no signs of inflammation or injury.

In control animals the volume of thrombogenesis and degree of arterial wall stretching were much lower both at remote and immediate terms.

Thus, hydrogel emboli saturated with dicinone promote a more rapid and extensive thrombogenesis that emboli without dicinone. Impregnation of emboli with dicinone did not lead to arterial wall inflammation or injury.

REFERENCES

1. A. I. Vorob'ev, *Manual of Hematology* [in Russian], Moscow (1985).
2. V. N. Dan and B. N. Varava, *Khirurgiya,* No. 8, 127-131 (1986).
3. V. S. Dudaruv and A. A. Adamyan, *Zdravookhr. Belorussii,* No. 7, 19-21 (1987).
4. G. G. Zelenov, N. D. Skuba, and V. A. Vishnevskii, *Arkh. Patol.,* No. 12, 23-28 (1989).
5. M. I. Kuzin, Yu. D. Volynskii, A. A. Vishnevskii, and F. I. Todua, *Endovascular Therapy and Surgery for Pulmonary Hemorrhages* [in Russian], Irkutsk (1981).
6. M. D. Mashkovskii, in: *Drugs* [in Russian], Moscow (1993), Vol. 1, pp. 566-567.
7. N. D. Skuba, A. A. Adamyan, and V. N. Dan, *Byull. Eksp. Biol. Med.,* **107,** No. 1, 379-382 (1989).
8. N. D. Skuba and F. I. Todua, in: *Endovascular Therapy and Surgery for Pulmonary Hemorrhages* [in Russian], Irkutsk (1981), pp. 120-125.
9. M. I. Kuzin and Yu. D. Volynsky, *Endovascular Lung Surgery,* Moscow (1985).