The Use of Technetium-99m Sulfur Colloid as a Marker for Experimental Venous Thrombosis: Concise Communication

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The binding of technetium-99m sulfur colloid to in vivo thrombi was studied in a rat model of deep vein thrombosis. After thrombosis was induced by mechanical traumatization of a right femoral vein segment, technetium-99m sulfur colloid was injected into the peripheral veins of different experimental groups at intervals of 30 min and 1–7 days. Ratios of mean activity in traumatized right femoral vein segment to activity in control segments of left femoral vein (R/L ratios) ranged from 2.97–11.0 for all in situ venous thrombi studied. There was no relation between clot size and R/L ratios. The significant uptake ratios observed by us for venous thrombi up to 1 wk in age suggest that in vivo thrombus detection may be feasible by imaging with a gamma camera after technetium-99m sulfur colloid injection in a peripheral vein.


The clinical diagnosis of deep-vein thrombosis is characterized by its relative inaccuracy. Kakkar and coworkers have shown that clinical signs of venous thrombosis were absent in 50% of patients who had demonstrable thrombi in lower extremity veins by venography or at autopsy (7).

Work done by several investigators has suggested the in vitro and in vivo utility of technetium-99m sulfur colloid (Tc-99m SC) as a labeling agent for thrombi. George et al. observed that Tc-99m SC accumulated in both experimental and human renal transplants that were undergoing rejection (2,3). Freeman and coworkers found that Tc-99m SC concentrated in clots caused by indwelling central-venous catheters (4). Klingensmith et al. demonstrated an increased renal uptake of Tc-99m SC in experimental endotoxemia (5). More recently, Vieras et al. reported high thrombus-to-blood ratios in electrically induced venous thrombi that varied in age from 4–72 hr (6,7). Our experiment was designed to expand these observations by studying the time-dependent uptake of Tc-99m SC in artificially induced venous thrombi in rats.

MATERIALS AND METHODS

Forty male Sprague–Dawley rats weighing 275 g were anesthetized with ether and subjected to ligation of the proximal right femoral vein for 5 min. One rat from the 5-day group died during the course of the study, leaving 39 rats in the experimental group. During the 5-min interval of stasis, the femoral vein distal to the ligature was cross-clamped three times; the ligature was then released. After release of the ligature, Ts-99m SC* was administered at time intervals of 30 min, 24 hr, and daily for a total of 7 days.

In a pilot study performed previously, it had been determined that injection of Tc-99m SC in the femoral vein distal to the site of trauma resulted in a higher clot uptake than injection in a peripheral vein, but injection in a peripheral vein was sufficient to produce a significant thrombus uptake.

The rats were injected in the dorsal penile vein with a dose of 100 μCi Tc-99m SC in a total volume of 0.25 ml and after 15 min, they were killed. A 1.0-cm segment of traumatized right femoral vein that included the intact
clots was isolated from each animal along with an intact segment of equal length from the left femoral vein, and the segments were removed and weighed. Specimens of blood and liver were also obtained in order to check the adequacy of the venous injection. All of the tissue specimens were placed in an automatic gamma counter and the radioactivity in each sample was measured. The vessels were then fixed in formaldehyde, and histological sections were prepared to confirm the presence of thrombi.

The size of each induced femoral-vein thrombus was estimated independently by two observers (P.A.B. and J.R.) who had no prior knowledge of clot age.

The clots were graded according to the following system: 0 = no gross clot evident, 1+ = clot less than 25% of vessel length, 2+ = clot 25–75% of vessel length, 3+ = clot 76–100% of vessel length.

The clot grading system is diagrammed in Fig. 1.

RESULTS

Blood and liver counts demonstrated intravascular injection of radiolabeled colloid in all of the animals.

The ratios of mean activity in right femoral vein segments to that in left over a 7-day period are shown in Table 1 and are plotted in Fig. 2. It is evident that there was a significant uptake of Tc-99m SC in the thrombus-containing vascular segments. In addition, during the time course of these experiments we found that there was no significant difference in the uptake ratios for clots ranging in age from 30 min to 7 days.

The transient depression in the mean R/L ratios of Day 3 rats may have been due to a single animal in which it was suspected that the right femoral vein was not adequately traumatized and no gross clot was evident at the time of death.

In order to determine whether there was any relation between clot size and right-to-left ratios, these parameters were plotted graphically using standard linear regression equations (Fig. 3). The correlation coefficient (r) was 0.217.

DISCUSSION

All of the methods for diagnosing deep-vein thrombosis, including venography, fibrinogen uptake, radionuclide venography, and impedance plethysmography,
suffer from problems. Several lines of evidence suggest that Tc-99m SC may offer a more favorable alternative to the tests currently available for thrombus detection.

The efficiency of Tc-99m SC in detecting renal transplant rejection was presumed by George et al. to be caused by a binding of this radiopharmaceutical to fibrin in the glomerulus (2). Some experimental support for this theory was provided by an in vitro study that showed Tc-99m SC incorporation into whole blood and into platelet-rich plasma (3). We have shown that Tc-99m SC will bind to platelet-poor plasma, thus indicating that binding occurs to some component in plasma and not to platelets (P. A. Bardfeld and J. Rand, unpublished data).

Additional support for the binding properties of Tc-99m SC came with a clinical report that it could localize in clots associated with venous catheters and with the observation that Tc-99m SC uptake is increased in the kidneys of animals with experimental endotoxemia (4, 5). Vieras et al. later demonstrated significant thrombus-to-blood ratios in a canine model of induced thrombi with ages ranging from 4–72 hr (7). Heparin caused only a partial depression of Tc-99m SC uptake in the clots, and imaging of the deep-vein thrombi with a gamma camera was found to be feasible (7). We note that thrombi were induced in the inferior vena cava for the tissue uptake studies and in the femoral vein for the imaging experiments. Injections of Tc-99m SC were made in veins of the hind limb in the former studies and in the hind-limb veins distal to the thrombi in the latter.

Our data have permitted an expansion of these observations in two directions that have clinical relevance. We have shown that there are no major differences in Tc-99m SC uptake in thrombi ranging in age from 30 min to 7 days. Thus, the clinical utility of Tc-99m SC imaging of deep-vein thrombi may be extended from 3 to at least 7 days.

Secondly, we have administered Tc-99m SC in peripheral veins that were not in the direct venous pathway of the induced thrombus. In a pilot study, we showed that injection in such a vein results in a lower thrombus uptake than injection in a vein distal to a thrombus. Although extraction by the reticuloendothelial system will lead to a smaller concentration of Tc-99m SC in the venous blood delivered to the induced deep-vein thrombus, injection by this method will more closely approximate the situation likely to be encountered if Tc-99m SC venography is introduced as a noninvasive test in patients with suspected deep-vein thrombosis. Intravenous injection distal to a thrombus, on the other hand, would offer little advantage over radionuclide venography.

We failed to find any correlation between thrombus size and uptake of Tc-99m SC in the thrombosed vein relative to uptake in a nonthrombosed vein. Vieras et al. have also noted a lack of any relationship between thrombus weight and Tc-99m SC activity in the clot (6).

The work described in this study, as well as the reports of Vieras and his coworkers, suggest that the time is now appropriate for clinical trials of Tc-99m SC injected by the peripheral route to localize deep-vein thrombi (6, 7). The thrombus uptake ratios observed by us and by Vieras indicate a target-to-nontarget ratio in excess of 4:1, which is within the range of feasible detection with a gamma camera (7).

We are aware that bone-marrow uptake may be a source of problems in interpretation. However, experience with the total-body bone-marrow scan has shown that there is minimal uptake in the adult beyond the proximal third of the femur. Clinical studies would be necessary to determine whether this would indeed be a problem. We have already begun a study in humans designed to establish the efficacy of Tc-99m SC venography in comparison with conventional venography and impedance plethysmography.

FOOTNOTE

* Tesuloid, E. R. Squibb & Sons, Princeton, NJ.

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