An Improved Radiolabeling Technique of Ivalon and Its Use for Dynamic Monitoring of Complications During Therapeutic Transcatheter Embolization

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Transcatheter embolization by Ivalon particles for treatment of arteriovenous malformations has been an accepted therapeutic technique for many years. We describe a new and efficient radiolabeling technique of Ivalon particles using \[^{99m}\text{Te}\] sulfur colloid. Continuous and dynamic monitoring of injected radiolabeled Ivalon particles is made possible by viewing the persistence scope of a portable gamma camera whose head is positioned over the patient undergoing therapeutic embolization. Therefore, if inadvertent pulmonary embolism or reflux migration of radiolabeled Ivalon particles has occurred, the angiographer is immediately aware of this potentially serious or fatal complication and can take corrective action. We describe two patients, each with an arteriovenous malformation, who had therapeutic embolization with radiolabeled Ivalon particles, one resulting in reflux migration and the other resulting in inadvertent pulmonary embolism.


The technique of transcatheter therapeutic embolization with Ivalon has been in use since 1975 (1–5). Ivalon is made of polyvinyl alcohol that is an inert, nonbiodegradable substance. Ivalon particles are sponge-like in shape with jagged edges and large interstitial spaces (1). Because the Ivalon particles are radiolucent and on the order of 1 mm in size, they cannot be directly visualized by fluoroscopy.

Inadvertent pulmonary embolization and reflux migration of Ivalon particles are two serious and potentially fatal complications of therapeutic embolization that may go unheeded. When the Ivalon particle size is smaller than the tumor vasculature, internal shunting of Ivalon particles through the tumor may occur resulting in inadvertent pulmonary embolism. When preferential blood flow to the tumor is inadequate to carry the Ivalon particles into the tumor, reflux migration of Ivalon particles may occur. A recent report has documented two fatalities from inadvertent pulmonary embolism during therapeutic embolization of Ivalon (6).

Dynamic scintigraphic detection of radiolabeled Ivalon particles using a portable gamma camera positioned in the angiographic suite permits precise localization of radiolabeled Ivalon particles. Intermittent repositionings of the gamma camera head over the tumor, the chest, and distal to the tumor while constantly viewing the persistence scope of the gamma camera permits dynamic monitoring of inadvertent pulmonary embolism and reflux migration of radiolabeled Ivalon particles. When the distance from the image intensifier of the fluoroscopic tower to the patient’s chest is large, the gamma camera head can be left in position over the patient’s chest thereby permitting continuous monitoring of possible inadvertent pulmonary embolism of radiolabeled Ivalon particles.

In 1986, Jack et al. described a technique for radiolabeling Ivalon particles with technetium-99m sulfur colloid \((^{99m}\text{Te})\text{SC}) (7). In his radiolabeling method, \(^{99m}\text{Te}\) SC was first produced in the standard manner and then Ivalon particles were subsequently labeled by heating them in a suspension with the \(^{99m}\text{Te}\) SC.
mechanism of labeling of Ivalon by $^{99m}$TcSC, whose particle size is <200 nm, is by physical adsorption of $^{99m}$TcSC to exposed surfaces of the Ivalon particles. Heated Ivalon particles do not change size or shape upon boiling (7).

We describe a new method of radiolabeling Ivalon particles with $^{99m}$TcSC that is 2.3 times more efficient than the method described by Jack et al. We also demonstrate in vitro stability of $^{99m}$TcSC Ivalon particles. We show the clinical utility of $^{99m}$TcSC Ivalon in two patients undergoing a total of three separate therapeutic embolization procedures of arteriovenous malformations (AVM). Dosimetry estimates from $^{99m}$TcSC Ivalon particles obtained from kinetic modeling with Monte Carlo simulations on a Cray S/MP supercomputer are also presented.

MATERIALS AND METHODS

To prepare the $^{99m}$TcSC Ivalon particles, we used sterile Ivalon particles and radiolabeled them with $^{99m}$TcSC (Mediphysics, Inc., Richmond, CA) by the following method. The unlabeled Ivalon particles were placed into a closed and shielded SC reaction vial containing 0.5 ml 1.0 N hydrochloric acid. We then added 1.1 ml aqueous solution of 1.9 mg sodium thiosulfate anhydrous and 20–50 mCi $^{99m}$TcSodium pertechnetate in normal saline. The reaction vial supplied by the manufacturer was placed in boiling water for 5 min. After removal from the boiling water bath, 5.3 mg of gelatin in 2.1 ml of aqueous acetate buffer solution was quickly added. The reaction vial was cooled and the $^{99m}$TcSC Ivalon particles were removed by decanting. Technetium-99m SC Ivalon particles were rinsed with normal saline, transferred by syringe to a sterile glass beaker, and placed in a lead container which was carried to the angiographic suite.

In order to measure the labeling efficiency of $^{99m}$TcSC Ivalon particles, the following procedure was performed. A magnifying lens and tweezers were used to carefully separate 53 groups of 1.0-mm Ivalon particles, each group containing 30 particles. Twenty-seven groups of 30 Ivalon particles were radiolabeled using the Jack method and 26 groups of 30 Ivalon particles were radiolabeled using our modified radiolabeling method. After radiolabeling of Ivalon, each group of particles were rinsed with normal saline and then placed in 10 cc of normal saline. At various times over a 6-hr interval, the groups of 30 radiolabeled Ivalon particles were removed from the normal saline, rinsed, and placed in a gamma well counter for measurement of activity. Labeling efficiency per $^{99m}$TcSC Ivalon particle was then calculated by dividing the total activity of each group by 30. All measurements were corrected for physical decay of $^{99m}$Tc.

The stability of the $^{99m}$TcSC Ivalon particles in various suspending media was assessed in the following manner. Unlabeled 1.0-mm sized Ivalon particles were separated into 45 groups of particles, each group containing 30 individual Ivalon particles. The Ivalon particles were then radiolabeled using our modified radiolabeling method. The $^{99m}$TcSC Ivalon particles were then rinsed with normal saline and then gently mixed in 10 cc solutions of normal saline, nonionic (Iopamiro, Squibb Diagnostic, New Brunswick, NJ), or ionic (Diatrizoate meglumine, Berlex Laboratories, Wayne, NY) contrast medium. The $^{99m}$TcSC Ivalon particles were allowed to stand without agitation at room temperature for variable periods of time up to 4 hr. This procedure essentially duplicates the conditions of actual clinical handling of the Ivalon particles in the angiographic suite, where Ivalon particles might be allowed to stay in solution for several hours before embolization. The labeling efficiency per $^{99m}$TcSC particle was measured using the same technique as described above and data were corrected for physical decay of $^{99m}$Tc.

Dosimetry for Patient 1 was performed using the MABDOS software of Johnson (8–10). The patient’s AVM was modeled as an ellipsoid with the major/minor axes of dimensions 20 cm and 10 cm, respectively. The ellipsoid was centered at the knee and offset from the right leg central axis. The dosimetry model assumed that $^{99m}$TcSC dissociates from the $^{99m}$TcSC Ivalon particles at the same rate as measured in vitro, ~15% per 6 hr. The model further assumed $^{99m}$TcSC sulfur colloid to distribute itself after dissociation according to normal sulfur colloid kinetic pathways. Hence, uptake was assumed in the same proportions as reported in MIRD Dose Estimate Report No. 3: liver (85%), spleen (8%) and whole body/red marrow (7%) (11). This model is summarized in Figure 1.

RESULTS

Because of only one transfer of Ivalon particles, the typical preparation time for our radiolabeling technique was ~15 min compared to 25 min for the labeling method described by Jack (7).

The labeling efficiency and stability of $^{99m}$TcSC Ivalon particles in normal saline solution is shown in Table 1. Using the radiolabeling procedure of Jack et al., the mean labeling efficiency per $^{99m}$TcSC Ivalon particle immediately after radiolabeling was 0.047 ± 0.013%. The mean labeling efficiency per $^{99m}$TcSC Ivalon particle for our radiolabeling technique was 0.110 ± 0.027%, a 2.3 times increase in labeling efficiency. Both radiolabeling methods have a 6-hr dissociation rate in normal saline of ~15%. There is no statistical difference between the rate of dissociation of $^{99m}$TcSC from $^{99m}$TcSC Ivalon particles using our modified method and the method of Jack et al (7).

The labeling efficiency of $^{99m}$TcSC Ivalon particles in solutions of normal saline, nonionic and ionic contrast were measured at 2, 4, and 6 hr. The 2-hr percent dissociation of $^{99m}$TcSC from $^{99m}$TcSC Ivalon particles in saline, nonionic, and ionic contrast was 9.9 ± 4.6%, 9.6 ± 4.0%, and 14.0 ± 6.4%, respectively. The 4-hr percent dissociation of $^{99m}$TcSC in saline, nonionic, and ionic contrast was 13.7 ± 3.9%, 24.2 ± 12.0%, and 24.6 ± 5.3%, respectively. The 6-hr percent dissociation of $^{99m}$TcSC in saline, nonionic, and ionic contrast was 13.4 ± 1.6%, 24.5 ± 7.6%, and 26.4 ± 5.3%, respectively. There is no statistical significant difference between the amount of dissociation of
A 37-yr-old woman with known congenital hemangioma of the distal thigh and upper calf of the right leg complained of increasing pain and swelling with ulceration of her right leg. An angiogram performed prior to therapeutic embolization demonstrates a large AVM supplied by multiple branches of both the superficial and deep femoral arteries. A lung perfusion scan using 2.5 mCi $[^{99m}Tc]$MAA performed ~8 hr before therapeutic embolization was normal. Prior to therapeutic embolization of the AVM, 1.0 g of sterile Ivalon particles 1.0 mm in size were radiolabeled with 104 mCi $[^{99m}Tc]$pertechnetate using our modified radiolabeling technique. The $[^{99m}Tc]$SC Ivalon particles, total activity of 11.0 mCi, were then placed in normal saline and carried to the angiographic suite.

A portable gamma camera (Picker Dyna Mo) with a LEAP collimator was maneuvered into the angiographic suite and positioned close to the angiographic table. A sterile plastic drape was placed over the gamma camera head to ensure sterility of the field. The persistence scope of the portable gamma camera was set on high intensity. In order to diminish exposure of radiation to the angiographer and technologists by the radioactive Ivalon particles, the particles were surrounded by a 3-mm lead shield.

After the initial embolization of $[^{99m}Tc]$SC Ivalon particles to the AVM using a 9 French catheter, the gamma camera head was periodically repositioned between the lower extremity and the chest permitting monitoring of reflux embolization to the distal lower extremity and for inadvertent pulmonary embolism. During most of the embolization procedure, the gamma camera head was left in position over the chest permitting continuous monitoring of inadvertent pulmonary embolism. At no time during the entire embolization procedure was a solitary focus of radioactivity activity seen within the lungs. A repeat angiogram performed after therapeutic embolization demonstrated obliteration of much of the tumor bulk.

After the completion of therapeutic embolization, the patient was taken to nuclear medicine to confirm our impression that no pulmonary emboli or reflux migration occurred. A whole-body scintigram and gamma camera images of the right knee showed numerous $[^{99m}Tc]$SC Ivalon particles within the AVM. No $[^{99m}Tc]$SC Ivalon particles were seen within the lungs or distal to the knee. Next, a lung perfusion scan using 2.5 mCi $[^{99m}Tc]$MAA was performed which was normal, also confirming that no Ivalon particles embolized to the lung.

The patient returned to the hospital after 1 yr because of increasing knee pain and swelling. A femoral artery angiogram revealed at least four small clusters of AVM which had increased in size from the post-therapeutic embolism angiogram of 1 yr earlier. A repeat therapeutic embolization $[^{99m}Tc]$SC Ivalon was then performed using a 9 French catheter.

The portable gamma camera with a LEAP collimator was positioned next to the angiographic table. The gamma camera head, covered with a sterile plastic drape, was initially positioned over the chest to monitor for inadvertent pulmonary embolism of the first injected Ivalon particles. No focus of abnormal lung activity was noted and the gamma camera head was then repositioned over the AVM where multiple foci of increased activity where seen within the AVM. The gamma
camera head was then repositioned over the lungs while more radioactive Ivalon particles were injected. At no time during the entire procedure was a focus of increased activity seen within the lungs. However, after embolization of one of the small AVM clusters, the gamma camera head was repositioned over the lower extremity distal to the AVM where multiple foci of increased activity were immediately seen on the persistence scope by the angiographer and technologists. Reflux migration of injected Ivalon particles was then diagnosed and the catheter was then immediately repositioned. Remaining AVM clusters were embolized without evidence of inadvertent pulmonary embolism or more reflux migration. During embolization, the gamma camera head was frequently repositioned over the chest and distal to the AVM. At no time during therapeutic embolization was a solitary focus of increased activity detected with the lungs.

In order to document the reflux migration of $[^{99m}Tc]SC$ Ivalon particles, imaging of the lower extremity was performed within the nuclear medicine department $\sim 8$ hr after completion of the embolization procedure (Fig. 2). The gamma camera image verifies the multiple foci of activity in the calf and foot seen initially on the persistence scope as representing reflux migration.

The MABDOS dosimetry for Patient 1 is shown in Table 2.

**TABLE 2**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Cumulative Organ Dose (mrad)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenals</td>
<td>59.6</td>
</tr>
<tr>
<td>Marrow red</td>
<td>23.2</td>
</tr>
<tr>
<td>AVM</td>
<td>3449.8</td>
</tr>
<tr>
<td>Bladder wall</td>
<td>3.7</td>
</tr>
<tr>
<td>Oth tiss musc</td>
<td>41.5</td>
</tr>
<tr>
<td>Bone total</td>
<td>69.3</td>
</tr>
<tr>
<td>Ovaries</td>
<td>9.5</td>
</tr>
<tr>
<td>Gl stom wall</td>
<td>32.8</td>
</tr>
<tr>
<td>Pancreas</td>
<td>72.7</td>
</tr>
<tr>
<td>Gl si</td>
<td>19.9</td>
</tr>
<tr>
<td>Skin</td>
<td>37.5</td>
</tr>
<tr>
<td>Gl uli wall</td>
<td>31.9</td>
</tr>
<tr>
<td>Spleen</td>
<td>341.6</td>
</tr>
<tr>
<td>Gl ili wall</td>
<td>5.7</td>
</tr>
<tr>
<td>Testes</td>
<td>7.7</td>
</tr>
<tr>
<td>Kidneys</td>
<td>52.9</td>
</tr>
<tr>
<td>Thyroid</td>
<td>2.5</td>
</tr>
<tr>
<td>Liver</td>
<td>470.8</td>
</tr>
<tr>
<td>Uterus nongrv</td>
<td>9.1</td>
</tr>
<tr>
<td>Lungs</td>
<td>31.8</td>
</tr>
<tr>
<td>Total body</td>
<td>85.2</td>
</tr>
</tbody>
</table>

### Case 2

A 45-yr-old woman with a known pelvic AVM complained of worsening discomfort. An angiogram demonstrated a very large AVM involving the right pelvis including the right buttock. Using the modified radiolabeling technique, 1 g of 1.0-mm-sized Ivalon particles was labeled yielding 8.5 mCi of $[^{99m}Tc]SC$ Ivalon particles. The portable gamma camera was maneuvered into the angiographic suite and the gamma camera head was covered with a sterile plastic drape. With the gamma camera head positioned over the patient’s chest, several 1.0-mm-radiolabeled Ivalon particles were injected through a 9 French catheter. An intense solitary focus of radioactivity in the lung was immediately seen on the persistence scope of the gamma camera. A 60-sec portable gamma camera image was then taken for documentation of inadvertent pulmonary embolism (Fig. 3). The catheter was repositioned and embolization proceeded without complication. An angiogram performed at the termination of the embolization procedure showed decrease of AVM size.

At no time during the therapeutic embolization of either Case 1 or 2 with radiolabeled Ivalon particles was activity diffusely seen within the catheter delivering the Ivalon particles. No thyroidal activity was noted by gamma camera in either Patient 1 or 2.

### DISCUSSION

Ivalon particle transcatheter embolization has been used in a wide variety of therapeutic procedures including embolization to control acute hemorrhage, tumor embolization, and embolization of arteriovenous malformations (12–18). In order to achieve a satisfactory therapeutic endpoint, it is not uncommon for the angiographer to use many hundreds or even thousands of Ivalon particles. Dynamic monitoring of $[^{99m}Tc]SC$ Ivalon particles with a portable gamma camera during therapeutic embolization permits continuous and precise localization of each $[^{99m}Tc]SC$ Ivalon particle. Potentially serious or life-threatening complications such
as inadvertent pulmonary embolism and reflux migration may be immediately detected.

Unlabeled Ivalon particles are very small and radiolucent and therefore they are impossible to detect by fluoroscopy. Recently, a commercial Ivalon impregnated with barium became available for transcatheter embolization (Ingenor, Paris, France). However, because of overlying soft tissue, bone, and vasculature, the small barium impregnated Ivalon particles may go undetected by fluoroscopy. In addition, there is a more serious problem—this commercial Ivalon preparation contains ~80,000 particles from 4 to 50 nm in size, which may result in pulmonary embolism, as has been demonstrated by Repa et al. They have concluded that embolization with barium impregnated Ivalon is dangerous and may be fatal (6).

Our modified radiolabeling technique differs from the method previously described by Jack et al. because the $^{99m}$Tc]SC formation and the Ivalon labeling proceed simultaneously in a single reaction vessel. This simplifies the preparation of $^{99m}$Tc]SC Ivalon particles and results in a 2.3 times higher labeling efficiency. We postulate that this increase in labeling efficiency is the result of physical adsorption of $^{99m}$Tc]SC not only on the exposed external surface of each Ivalon particle, but also within the interstitial spaces of each particle. While the overall labeling efficiency is not high for either radiolabeling technique, a 2.3 times increase of labeling efficiency yields many more $^{99m}$Tc]SC Ivalon particles for a given amount of $^{99m}$Tc]pertechnetate. This is clinically important because our modified radiolabeling technique produces more $^{99m}$Tc]SC Ivalon particles to be used by the angiographer who is performing the therapeutic embolization. We have demonstrated that $^{99m}$Tc]SC Ivalon particles are stable in normal saline, ionic, and nonionic contrast media and may be kept for several hours prior to therapeutic embolization without significant loss of the radiolabel. Compared to the Jack radiolabeling technique, the modified technique takes less time and requires only one transfer thereby decreasing the likelihood of microbial contamination.

Because of the relatively small attenuation for the 140-keV photons of $^{99m}$Tc in lung parenchyma and the nearly complete lack of background activity from the patient at the time of therapeutic embolization, the detection of inadvertent pulmonary embolism of radiolabeled Ivalon particles using a modern portable gamma camera is very sensitive.

The method of use for the radiolabeled Ivalon particles depends upon the total number of radiolabeled
particles available for use by the angiographer and the
extent of the AVM. If only a few hundred radiolabeled
Ivalon particles are produced, the “hot” particles can
be embolized intermittently between a series of “cold”
Ivalon particles. If a large number of radiolabeled Ivalon
particles are produced, most, if not all of the embolized
Ivalon particles can be radiolabeled. A small AVM
requires a relatively smaller number of Ivalon particles
to be embolized for a successful outcome.

A potential problem of an artificial “hotspot” exists
from the common practice of many angiographers to
shake off the last droplet of fluid from the syringe tip
before injection. If a radiolabeled Ivalon particle is
accidentally flipped onto the sterile cloth sheet covering
the patient, the potential for misdiagnosing inadvertent
pulmonary embolism or reflux migration exists. An-
giographers should be warned not to shake off the last
droplet from the syringe tip.

We believe that the postulated mathematic model
used for estimation of dosimetry for the kinetics is valid
for thrombosed radioactive Ivalon particles embolized
to an AVM. This approach makes the assumption that
the rate at which the sulfur colloid leaves off embo-
lized radiolabeled Ivalon particles within the AVM is the
same as the in vitro dissociation rate. Other than the
fraction of seconds needed for the Ivalon particle to
move through the vessel feeding into the AVM, the in
vitro environment and the thrombosed environment
embedding the radioactive Ivalon particles embolized
within an AVM are roughly equivalent.

The dosimetry of $^{99m}$Tc Ivalon embolization is
comparable to many other diagnostic examinations in
nuclear medicine and radiology. The typical radiation
dose from fluoroscopy is ~5 rad/min of fluoroscopic
time. Therapeutic embolization procedures are com-
monly 10 or more minutes in fluoroscopic length.
Therefore, the added radiation burden to the patient
from $^{99m}$TcIvalon particles appears reasonable.
Also, we believe that the added radiation risk is bal-
anced by the benefit of detecting the potentially serious
or fatal complications of inadvertent pulmonary em-
bolism and reflux migration of radiolabeled Ivalon par-
icles.

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