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RADIANT™ LIQUID RADIOISOTOPE INTRAVASCULAR RADIATION THERAPY SYSTEM

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Device

RADIANT™ is manufactured by United States Surgical Corporation, Vascular Therapies Division, (formerly Progressive Angioplasty Systems). The system comprises a liquid β -radiation source, a shielded isolation/transfer device (ISAT), modified over-the-wire or rapid exchange delivery balloons, and accessory kits. The liquid β -source is Rhenium-188 in the form of sodium perrhenate (NaReO_4). Rhenium-188 is primarily a β -emitter with a physical half-life of 17.0 hours. The maximum energy of the β^- particles is 2.1 MeV. The source is produced daily in the nuclear pharmacy "hot lab" by eluting a Tungsten-188/Rhenium-188 generator manufactured by Oak Ridge National Laboratory (ORNL). Using anion exchange columns and Millipore filters the effluent is concentrated to approximately 100 mCi/ml, calibrated, and loaded into the (ISAT) which is subsequently transported to the cardiac catheterization laboratory. The delivery catheters are modified Champion™ over-the-wire, and TNT™ rapid exchange stent delivery balloons. These balloons have thickened polyethylene walls to augment puncture resistance; dual radioopaque markers and specially configured connectors.

Proposed indications

The RADIANT™ system will be evaluated for efficacy to prevent restenosis following balloon angioplasty or stenting patients with *de novo* or restenotic lesions. The planned U.S. trial is called The Radiation Angioplasty Trial (RADIANT). The "RADIANT" Phase-I study is designed as a pilot study to preliminarily evaluate safety/efficacy of intravascular radiation delivery to prevent restenosis. The pivotal study to follow will be a multicenter randomized double blinded placebo controlled design.

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Procedure

Radiation therapy is performed immediately after successful balloon angioplasty or stenting, with the guidewire left in position. A RADIANT™ catheter of the same diameter as the last PTCA balloon used is selected. Prior to insertion, the radiation delivery catheter is tested for integrity to hold air and maintain vacuum. The balloon is positioned in the coronary artery prior to charging it with the radioisotope. Serial inflations at 3 ATM are performed until the prescribed dose has been given (ranging from 6 to 10 minutes total inflation time).

Limitations of current intravascular radiation delivery methods

Current catheter-based radiation systems have limitations that the RADIANT™ system was designed to address. These limitations can be categorized into problems of dose delivery to the target tissue, patient safety, and personnel safety.

Distal and tortuous coronary segments may be untreatable if catheter diameter or stiffness preclude safe access to these locations. The RADIANT™ delivery catheter performs identically to its parent generation PTCA balloons and can reach any portion of the coronary anatomy treatable with balloon angioplasty. Thus vessel segments 20 to 40-mm in length, previously expanded with balloons ranging in diameter from 2 to 4 mm are potentially treatable. Moreover, the device is compatible with 0.064" lumen 6F guiding catheters.

Whether treated with sealed sources or an afterloaded wire, IVUS examination may be needed to specify dose. This approach is expensive and time-consuming. IVUS gives a rough estimate of how far off center the delivery catheter will be, and the distance from the source to the target(s). Dose calculation must also address the problem of cold spots between sources and hot spots due to even small degrees of off centering by as little as 0.5-mm. Even if centered to within 0.5 mm, doses at a prescribed depth will typically vary by a factor of 4. Such variations in dosimetry may limit the therapeutic range of dose specification for these systems.

Dose prescription with the RADIANT™ system is straightforward. The RADIANT™ balloon size is matched to the largest balloon size used for PTCA or stent delivery, guaranteeing that the delivery balloon make contact with the vessel wall or the stent when expanded with isotope. A dose at a prescribed radial distance from the expanded balloon is selected. The total duration of balloon inflation is determined by the activity concentration of the liquid source, the time elapsed after source calibration, and the diameter of the chosen delivery balloon. IVUS guided dosimetry is neither helpful nor necessary. The RADIANT™ balloon is by definition "centered" with respect to the lumen. There are no "hot spots." "Cold spots" due to bubbles or off centered guidewire lumen can cause at worst a 10% reduction in dose to a localized portion of the irradiated tissue. Finally, the dose distribution surrounding a liquid filled balloon is the most homogeneous of any of the currently devised seed or wire type systems.

With respect to patient safety issues there are several concerns: ischemic complications, long term effects at the treatment site, total patient exposure, and embolization of a radiation source. Ischemic complications may result from device trauma, device stimulation of thrombosis, the physical obstruction of flow by the system, the coronary artery dwell time, and the quality of patient monitoring available. The RADIANT™ method consisting of intermittent low-pressure balloon inflations from a low profile, small shaft diameter, PTCA catheter is frequently the standard operating procedure during routine balloon angioplasty.

The incidence and time course of long-term effects at the treatment site, including aneurysm formation or enhanced atherogenesis are not fully known with any intravascular radiation device. To the extent that these sequelae are dose-dependent, the RADIANT™ method offers a potential advantage in eliminating dose "hot spots" and minimizing "cold spots". This has the advantage of extending the therapeutic range for dosing to achieve the desired effect without sequelae due to overdosage.

Source embolization is the most dreaded complication. Although loss of an afterloaded Ir-192 source should be extremely rare, breakage of a wire or a catheter is a known complication of angioplasty. Such a loss would likely be catastrophic and/or represent a considerable exposure risk to personnel attempting to retrieve it. Loss of the RADIANT™ balloon Re-188 liquid source in a coronary artery should also be a rare event for several reasons. Inflation pressures are kept at least four standard deviations below the mean burst pressure, thus the expected frequency of balloon rupture is less than 1 in 30,000 catheters. The chances of balloon rupture are further minimized by the protocol which calls for successful prior full expansion of a PTCA balloon of the same diameter in the same lesion to at least 6 ATM (12 ATM if a stent has been placed). Moreover, every RADIANT™ catheter is pressure tested with air to rated burst pressure immediately prior to insertion and before charging with radioisotope. The worst case scenario is defined as rupture of a 4.0 mm diameter by 40 mm long balloon, discharging its entire isotope contents into the coronary artery. Dilution of the radioisotope in blood is nearly instantaneous resulting in an organ distribution pattern similar to intravenous injection. Organs with the highest exposure are the stomach, large and small bowel, and the thyroid. These exposures are similar to a single fractionated radiation therapy treatment and no short term and only rare long-term stochastic sequelae are expected.

Personnel safety is the final limitation of intravascular radiation therapy. g-Systems such as the Ir-192 expose the radiation oncologist to approximately 10 to 20 mRem per hour. Although these exposure rates have been compared to fluoroscopy during interventional procedures, it should be remembered that standard 0.5 mm-lead equivalent radiation protective devices are virtually worthless in absorbing the high-energy gamma's of Ir-192. Direct handling of a Ir-192 source is exceedingly dangerous.

The staff exposure rates from the RADIANT™ system average less than 2 mR/hr at tablesides when used as directed. These rates are very similar to Sr-90 seeds. A leak inside the isolation/transfer device is prevented from escaping the shield by a system of multiple redundant seals. Radiation surveys will detect such a leak easily due to the low-energy gamma's emitted.

Disposal of liquid Re-188 waste is relatively straightforward. The used catheter and ISAT cartridge syringe insert are stored in a shielded container for 10 half-lives, which is 7 days. Thereafter the remaining material can then be discarded in the regular biohazard waste.

Animal studies with the Radiant™ system

Study design

The efficacy and safety of using the RADIANT™ system was evaluated in the coronary arteries of anesthetized swine over a 4-week period. 34 coronary arteries from 17 pigs were treated over a 20-mm segment with intravascular radiation followed by over-sized stent placement. Each vessel was randomly assigned to receive one of four doses: 0, 14, 18, 22 Gy at a distance of 0.5-mm radial to the outer diameter of the balloon. All investigators except the medical physicist were blinded to the dose until after data analysis was completed. Coronary segments averaging 3.0 to 3.5 mm in diameter were selected by online digital angiographic quantification. After radiation therapy, a 4-mm diameter by 15 mm long ACT-One™ martensitic nitinol stent, mounted on a 20-mm long stent delivery balloon (Progressive Angioplasty Systems), was positioned in the middle of the radiated segment. At 4 weeks the pigs underwent quantitative angiography followed by IVUS. The coronaries were perfusion fixed with formalin immediately following euthanasia.

Results

There was no leakage of the liquid radioisotope either inside or outside of the ISAT, the catheter shaft, the balloon, or into the pig's blood stream in any of the 34 arteries treated. Exposure rates immediately behind the ceiling shield range from 2 to 4 mR/hr. Since the investigator stands some distance behind this shield, and therapy duration (inflation + deflation) lasts less than 20 minutes, we estimate that the exposure outside the lead apron to be considerably less than 2 mR/treatment.

All 17 pigs have completed 30-day follow-up. 33/34 coronary stents were angiographically patent. The single occluded vessel, an RCA, received the medium dose of 18 Gy. The same pig's LAD was treated with 22 Gy. This vessel was widely patent with a MLD of 2.8 mm and -8% diameter stenosis.

Table 1 summarizes the results of QCA in the 33 patent vessels. The mean reference diameter at follow-up was the same between the 4 groups suggesting that radiation delivered to the few millimeters bracketing the stent ends had no effect on normal vessel diameter. All parameters quantifying stenosis severity (MLD, mean diameter within the stent, percent diameter stenosis, mean percent diameter stenosis) improved significantly in a dose-dependent fashion. The increase in MLD from 1.0 mm in controls to 1.9 mm at 22 Gy can be equated into a similar magnitude reduction in late loss.

Table 1. QCA parameters at 4-weeks after treatment

Dose (Gy)	0	14	18	22
n	8	9	8	8
Reference diameter (mm)	2.4±0.3	2.4 ±0.2	2.3±0.2	2.5±0.2
MLD (mm)	1.0±0.7	1.4±0.9	1.5±0.8	1.9±0.8*
Mean instent diameter (mm)	1.7±0.6	2.3±0.4†	2.6±0.4‡	2.8±0.3‡
% diameter stenosis	61±26	39±35	30±34	23±31*
Mean % diameter stenosis	30±20	1±19†	-15±20‡	-13±12‡

*p<.05, †p<.01, ‡p<.001 vs. control

IVUS

IVUS was performed in 31/34 vessels excluding only the totally occluded RCA described above and one additional vessel each receiving 14 and 18 Gy due to failure of the imaging catheter. Table 2 summarizes the IVUS results. Stent area was not significantly different between groups. Lumen area, intimal area and percent area stenosis all improved in a dose-related fashion.

Complete pathology of the swine studies will be presented.

Table 2. IVUS parameters at 4 weeks after treatment.

Dose (Gy)	0	14	18	22
n	8	8	7	8
Stent area (mm ²)	8.3±1.2	9.0±1.5	8.9±0.5	9.3±1.4
Lumen area (mm ²)	4.4±1.2	7.0±1.8†	7.1±1.8†	7.6±1.6‡
Intimal area (mm ²)	3.9±1.9	2.1±1.4*	1.8±1.4*	1.7±0.9†
Percent area stenosis	45±19	23±15*	21±18*	18±10†

*p<.05, †p<.01, ‡p<.001 vs. control

Conclusions

The available data are consistent with the previously reported experience using Sr-90 seeds followed by stent injury in a pig coronary model. They show a substantial and significant dose-related improvement in QCA and IVUS parameters of restenosis at 4 weeks. The results of QCA and IVUS are concordant. Experience using the RADIANT™ in 34 coronary arteries revealed no unanticipated or adverse device handling or safety issues. Similar animal experiments evaluating the RADIANT™ system after balloon over-stretch injury, after stent placement, treatment of serial tandem radiated segments and bifurcation exposures are on going. First human clinical trials are slated for early 1998.

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