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Five percent dextrose maximizes dose delivery of Yttrium-90 resin microspheres and reduces rates of premature stasis compared to sterile water

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Abstract. Resin Yttrium-90 (Y90) microspheres have historically been infused using sterile water (H_2O). In 2013, recommendations expanded to allow delivery with 5% dextrose in water (D_5W). In this retrospective study, we hypothesized that D_5W would improve Y90 delivery with a lower incidence of stasis. We reviewed 190 resin Y90 infusions using H_2O (n=137) or D_5W (n=53). Y90 dosimetry was calculated using the body surface area method. Infusion was halted if intra-arterial stasis was fluoroscopically identified prior to clearing the vial. Differences between H_2O and D_5W groups were calculated for activity prescription, percentage of cases reaching stasis, and percentage delivery of prescribed activity using z- and t-test comparisons, with α=0.05. Thirty-one of 137 H_2O infusions developed stasis compared to 2 of 53 with D_5W (z=3.07, p=1.05E-03). D_5W also had a significantly higher prescribed activity than H_2O [28.2 millicuries (mCi) vs. 20.4 mCi, respectively; t=5.0, p=1.1E-6]. D_5W had a higher delivery percentage of the prescribed dose compared to H_2O (101.5 vs. 92.7%, respectively; t=3.8, p=1.92E-4). In conclusion, resin microsphere infusion utilizing D_5W has a significantly lower rate of stasis than H_2O and results in more complete dose delivery. D_5W is preferable to H_2O for resin microsphere infusion.

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Abbreviations: Y90, Yttrium-90; Bq, Becquerel; H_2O, water; D_5W, 5% dextrose in water; BSA, body surface area; V_{tumor}, volume tumor; V_{liver}, volume liver

Key words: radioembolization, metastatic disease, liver, locoregional therapy, yttrium-90, palliative therapy

Introduction

Yttrium-90 (Y90) microspheres are used to treat patients with primary hepatic and liver-dominant metastatic cancer. The glass and resin Y90 products differ significantly in the density of radionuclide per bead. Glass microspheres have a higher density [2,500 Becquerel (Bq)/bead] of Y90 than resin (50 Bq/bead) (1). The higher Y90 concentration in glass beads allows the delivery of prescribed activity without feeding artery occlusion, a known issue with resin microspheres. From the time of government approval in 2002, the standard technique for infusion of resin microspheres used sterile water (H_2O) alternating with small aliquots of contrast to evaluate for arterial stasis prior to delivery of the entire dose vial (2,3). While clinical outcomes have resulted in excellent control of hepatic disease, a previous review using H_2O to inject resin microspheres identified a 20% early stasis rate (4-6).

Delivering less than the prescribed Y90 activity has the potential to reduce treatment efficacy or result in earlier time to progression. Therefore, investigation of other injection methods for resin microspheres is required. In 2013, our group began to use 5% dextrose in water (D_5W) as an alternative to H_2O (7).

The aim of the current study was to measure the incidence of premature stasis using D_5W in comparison to H_2O. We hypothesized that D_5W induces stasis less frequently than H_2O in a clinical cohort of patients with primary or secondary hepatic malignancy.

Materials and methods

Clinical setting and patients. Our Institutional Review Board approved this retrospective study. All the procedures performed were in accordance with the ethical standards of the Vanderbilt University School of Medicine and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

We retrospectively reviewed laboratory, radiology and nuclear pharmacy reports of all resin Y90 infusions performed between July, 2013 and July, 2014. Consecutive patients treated after September, 2013, were treated with

Table I. Breakdown of infusion regimens and stasis events by tumor type.

Variables	H_2O patient	H_2O infusions	Stasis events	Stasis (%)	D_5W patients	D_5W infusions	Stasis events	Stasis (%)
Total	78	137	31	22.6	34	53	2	3.8
Uveal melanoma	43	78	12	15.4	0	0	N/A	N/A
Neuroendocrine	5	9	6	67	14	23	0	0
Colorectal carcinoma	14	22	9	40.9	8	11	1	9.1
Breast carcinoma	3	7	1	14.3	3	4	0	0
Hepatocellular carcinoma	5	7	1	14.3	0	0	N/A	N/A
Cholangio-carcinoma	2	4	0	0	3	4	1	25
Other	6	10	2	20	6	11	0	0

H_2O, sterile water; D_5W, 5% dextrose in water; N/A, not applicable.

D_5W. A previous data set of 128 infusions using H_2O was included as well (4). Patients in the comparison group were treated using an identical technique, as one of the current investigators (DBB) was involved with the previous study (4). Thus, 112 patients were treated as follows: 78 with H_2O and 34 with D_5W. Thirty-seven of the 78 H_2O patients and 14 of the 34 D_5W patients were male.

Patients were scheduled for treatment after clinic assessment, including review of relevant cross-sectional imaging (computed tomography and/or magnetic resonance imaging). Mapping arteriography was performed as described previously (1). Criteria for treatment with Y90 microspheres included: i) Confirmed unresectable liver-dominant disease; ii) an East Coast Oncology Group performance status of 0-2; and iii) adequate liver function (bilirubin of <1.8 mg/dl).

Patients were excluded from treatment if there was: i) A life expectancy of <3 months, ii) side branch flow to the gastrointestinal tract that could not be avoided or embolized, and iii) the estimated lung dose was expected to exceed 25 Gray.

Y90 treatment. Y90 infusion was performed 7-10 days after mapping. The dose was prescribed using the body surface area (BSA) method and calculated as: A Gigabecquerel (GBq) = (BSA-0.2)+V_{tumor}/V_{liver}, where A represents prescribed activity in GBq and V_{tumor} and V_{liver} represent the volume of the tumor and total infused liver volume, respectively. BSA in square meters was calculated as: 0.20247 x height in $m^{0.725}$ x weight in $kg^{0.425}$.

Patients were treated with lobar therapy. In the setting of bilobar disease, sequential infusions were performed 5-6 weeks apart.

A standard infusion protocol was followed for all resin microsphere infusions. These infusions were performed off label as non-colorectal metastases were treated. For the patients with colorectal cancer metastases, infusions were off label as intra-arterial chemotherapy was not used. Two interventional radiologists with 5 and 19 years experience performed the infusions (AJL, DBB). No anti-reflux devices or occlusion balloon techniques were used. The proprietary delivery kit was used in all the cases with the microspheres pushed into the delivery tubing with small aliquots of H_2O or D_5W. After the line was cleared, 2-3 ml of non-ionic contrast (Optiray 350-Ioversol 74%, Mallinckrodt Pharmaceuticals, Dublin, Ireland) was injected to evaluate for stasis. The process was repeated until the delivery vial was clear to vision. At this point, the vial was emptied by filling the priming line with air.

Stasis. Stasis was defined as a lack of antegrade arterial flow leading to procedure cessation prior to delivering the final air purge of the vial. Post-infusion assessment of residual activity was measured using a Ludlum Model 3 Survey Meter (Ludlum Measurements, Inc., Sweetwater, TX, USA).

Statistical analysis. The primary outcome variable was the incidence of stasis. The stasis incidents between H_2O and D_5W cases were compared using a z-test, with α=0.05. Secondary measures included differences in prescribed activity and the percentage of prescribed activity that was delivered between the H_2O and D_5W groups. The secondary variables were evaluated using t-tests.

Results

A total of 112 patients were treated: 78 with H_2O and 34 with D_5W. Thirty-seven of the 78 H_2O patients and 14 of the 34 D_5W patients were male. The group underwent 190 infusions: 137 were performed with H_2O and 53 with D_5W. Infusions and stasis events broken down by tumor type are shown in Table I. Thirty-one of the 137 (23%) H_2O infusions developed stasis compared to 2 of the 53 infusions (4%) with D_5W (z=3.1, p=1.1E-3) (Fig. 1). The H_2O group had a significantly lower prescribed dose than that of the D_5W cohort [0.75 vs 1.04 millicuries (mCi), respectively; t=5.0, p=1.1E-6] as demonstrated in Fig. 2A. Finally, the H_2O group had a significantly lower percentage delivery of the prescribed dose compared to D_5W, as seen in Fig. 2B (92.7 vs. 101.5%, respectively; t=3.8, p=2.2E-4). Over 97% of completed infusions with H_2O and D_5W achieved >90% delivery of prescribed activity while none of the infusions with early stasis reached 90% delivery (Table II). No patients in either group developed gastrointestinal signs/symptoms of ulceration.

Table II. Percent delivery of resin Y90 with and without early stasis.

Delivery percentage (%)	Early stasis (%)	No stasis (%)
<50	12/33 (36)	0/157 (0)
50-75	10/33 (30)	0/157 (0)
76-90	11/33 (33)	4/157 (3)
90-100	0/33 (0)	153/157 (97)

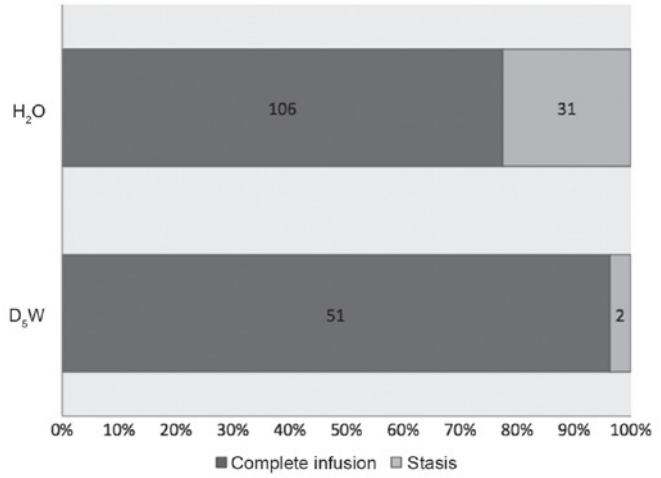

Figure 1. Percentage of infusions resulting in stasis for H_2O (23%) vs. D_5W (4%). This difference was statistically significant (p=1.1E-3).

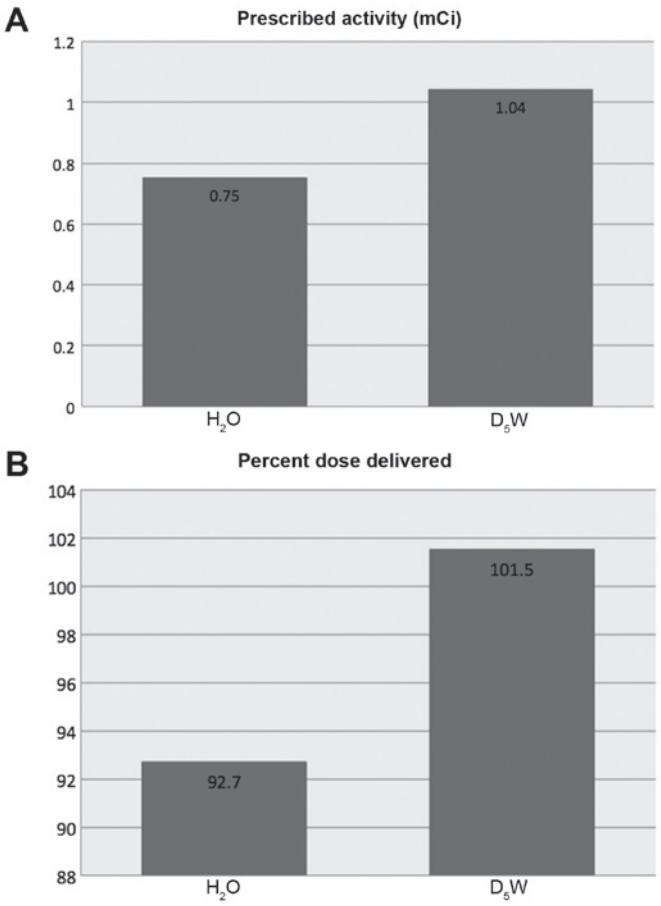

Figure 2. (A) The amount prescribed for D_5W cases (1.04 GBq) was significantly higher than that for H_2O (0.75 GBq, p=1.1E-6). (B) The mean percentage of the prescribed activity that was infused was significantly higher for D_5W (101.5%) than for H_2O (92.7%, p=2.2E-4). GBq, Gigabecquerel.

Discussion

Delivery of resin Y90 microspheres with D_5W rather than H_2O significantly reduces the rates of early arterial stasis. Improved delivery was achieved despite the D_5W group being prescribed significantly greater activity, which could have actually increased the risk of stasis. We also achieved more complete delivery of resin Y90 microspheres with D_5W compared to H_2O. In all the stasis events using either D_5W or H_2O, administered activity was ≥10% less than the prescribed activity. Although both glass and resin microsphere have been used to palliate patients with common metastatic tumors such as colorectal and breast cancer, the efficacy of glass microspheres was significantly decreased with the increasing tumor burden (5,8,9). The number of microspheres in a 3 GBq resin vial can be ≤80-fold greater than the same activity of glass spheres based on the time from calibration (1). Potentially, resin Y90 can better saturate larger tumors and improve outcomes given the greater number of microspheres with preferential clustering in the viable, hypervascular portion of target masses (10). However, the theoretical benefit of more complete tumor coverage has been incompletely realized as incomplete delivery of the prescribed activity potentially decreases efficacy or the result in earlier time to progression.

Although there is a known 21% incidence of early stasis with H_2O, the etiology remains largely unexplained (4). *In vivo* use of H_2O can result in intravascular hemolysis (11). The Food and Drug Administration reported 10 hemolysis cases in 1999, following dilution of 25% albumin to 5% using H_2O for plasmapheresis (11). The hypotonicity of the resulting infusion resulted in acute renal failure in five patients and death in one patient. Red blood cells lyse in hypotonic solutions such as those created with H_2O (12). The release of intracellular contents following hemolysis expends endothelial nitric oxide, which increases the vasomotor tone (13-15). The end result of these events could include increased vascular spasm resulting in early stasis or *in situ* thrombosis, which is seen in other entities associated with hemolysis such as paroxysmal nocturnal hemoglobinuria or esophageal dysmotility (16,17).

Previous research evaluated other potential risk factors contributing to early arterial stasis without finding a significant correlation (4). Considerations included relative tumor vascularity at cross-sectional imaging and previous intra-arterial therapy. However, neither of these factors affected stasis rates. Notably, the main limiting factor in the majority of stasis events with resin microspheres is use of H_2O. Tumors that appear hypovascular on computed tomography or magnetic resonance imaging are frequently hypervascular at angiography (18). We also perform chemoembolization using techniques associated with maximal long-term arterial patency (19). The findings of Chao *et al*, support the limitations of H_2O (20). They described a reduction in early stasis from 15% with H_2O to 4.5% with dilute contrast [Chao *et al* (20) presented at the 2014 Society

of Interventional Radiology Annual Scientific Meeting]. Direct comparisons of D_5W and dilute contrast have not been reported. While dilute contrast allows real-time monitoring of vascular patency and possible reflux into non-target arteries, we did not have any gastrointestinal toxicities using D_5W with intermittent contrast injection in our group.

There are several important limitations to this study. First, our data are retrospective and include a variety of tumor types. However, as patients were treated consecutively with each delivery vehicle, the potential for selection bias is unlikely to have altered results in either direction. Furthermore, previous findings have has not shown any difference in stasis based on treatment/tumor history (4). Second, our sample size reflects that of a single approach to prescribing and infusing resin Y90. A multi-center study is necessary to substantiate these findings. Finally, the impact of early stasis on efficacy remains uncertain, and should be explored in future studies.

In summary, D_5W performs superiorly to H_2O to deliver resin microspheres with lower rates of early arterial stasis and greater delivered activity. Future research may evaluate differences between D_5W and dilute contrast. Based on our findings, practitioners should eliminate use of H_2O when performing resin microsphere infusion.

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