Prospective Randomized Crossover Pilot Study of the Safety and Efficacy of Carbon Dioxide versus Iodinated Contrast for Peripheral Angiography[1]

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RATIONALE AND OBJECTIVES

There are certain inherent drawbacks and limitations to iodinated contrast agents (1–3). These include rare severe and life-threatening reactions, less frequent mild and moderate reactions which lead to discomfort, and adverse effects in patients with compromised renal function. Alternatives to iodinated contrast, then, are desirable. One such alternative is carbon dioxide, which has been widely used for angiography by hand injection for many years (4–7). Because of the characteristics of carbon dioxide, however, hand injection also has significant limitations. Further, objective comparisons between the utility and safety of carbon dioxide and iodinated contrast agents have been very limited. This study was undertaken as a pilot investigation to compare the safety and efficacy of carbon dioxide, as administered with a specially designed injector, to that of an iodinated contrast agent.

MATERIALS AND METHODS

Two hospitals were involved in this pilot study. The study was approved by the Human Studies Committee at both, and each patient gave informed consent for participation in the study. All patients recruited required angiography of abdominal or lower-extremity vessels for clinical reasons. After routine completion of the clinically indicated arteriogram, each patient underwent eight additional injections, four with carbon dioxide utilizing the injector (AngioDynamics, Glens Falls, NY) and four with ioversol 320 (Optiray; Mallinckrodt, St. Louis, Mo) with imaging of the same four anatomic areas with each contrast. Patients were randomized to CO_2 first or iodine first. Two image sets of four identical sites, one set with CO_2 and one set with ioversol, were produced, utilizing digital subtraction angiography. These image sets were all subsequently evaluated by two readers, blinded to clinical setting and the contrast agent which was utilized. Image sets were divided so that each reviewer received the CO_2 images and the iodinated images for each patient at different times, at least 2 weeks apart. Image sets were evaluated for diagnostic adequacy, diagnostic quality and efficacy, and, by the investigators on site, for consistency with clinical outcome. Patients evaluated heat and pain with each injection on a scale of 0 (none) to 3 (severe). Patients were also secondarily evaluated for adverse events, changes in vital signs, and changes in blood gases or other serum measurements. Diagnostic quality was rated on a scale of 1–4 (1 = excellent, 4 = inadequate). Diagnostic adequacy was classified as either adequate or inadequate.

RESULTS

A total of 41 patients were recruited into this phase of the study. Seventeen patients received carbon dioxide first, followed by ioversol. Eighteen patients received ioversol first, followed by carbon dioxide. Six patients who had a serum creatinine of 2 mg/dL or greater received only carbon dioxide.

Demographics showed no significant difference between the three groups of patients. In the patients who received ioversol first, the mean dose of ioversol was 65

Acad Radiol 1998; 5(suppl 1):S58–S59

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mL, with a mean dose of carbon dioxide of 292 mL. In the patients who received carbon dioxide first, the mean dose of ioversol was 61 mL and the mean dose of carbon dioxide was 265 mL. In the patients who received carbon dioxide alone, the mean dose was 388 mL. In regard to diagnostic outcome, as evaluated by the investigators at each institution, the findings with both contrast agents were consistent with the discharge diagnosis in 100% of the cases. The findings were consistent with the treatment subsequently given in 100% of the cases, and in all cases the findings with both contrast agents were thought to affect decision making.

In regard to the blinded evaluation, both readers rated the ioversol studies as diagnostically adequate in all cases. With carbon dioxide, reader A rated cases as diagnostic in 100% of the cases and reader B rated them as diagnostic in 97% (40/41) of cases. In regard to diagnostic efficacy the mean score with ioversol for reader A was 1.91 and for reader B, 1.12. With carbon dioxide the mean efficacy rating for reader A was 2.04 and for reader B, 1.91. These results are statistically significantly different for both readers ($P < .01$). For the patients receiving carbon dioxide alone, the diagnostic adequacy was 100% by the assessment of both readers. The efficacy was 2.13 by reader A and 1.96 by reader B. There was no major diagnostic disagreement between the two image sets for any of the patients. There was minor disagreement, not thought to affect the final diagnosis, in 12% of the cases. There was, then, complete agreement in 88% of the cases.

Regarding adverse events, there were no statistically or clinically significant changes or trends overall in vital signs, blood gases or other laboratory studies. Adverse events which were thought to be drug related occurred in 22% of patients who received ioversol first, none of the patients who received carbon dioxide first, 20% of patients who received only carbon dioxide, and in 12% of patients overall. These adverse events were nausea, vomiting, chest pain, chills and urticaria. Serious reactions occurred in two patients (sepsis and death in one patient, prolonged angina in one patient), and neither of these reactions was thought to be related to either contrast agent.

In regard to discomfort during injection, average rating for pain was 0.45 for ioversol and 1.34 for carbon dioxide. The average rating for heat was 1.18 for ioversol and 1.30 for carbon dioxide. When CO_2 alone was used, the average rating for pain was 1.31 and for heat, 0.94. Thus, heat and pain were less with ioversol but were minimal to mild with both.

CONCLUSION

Based on this limited experience with the use of carbon dioxide injected by specifically developed injector as compared to a nonionic contrast agent, the pain and heat experienced with carbon dioxide are mild and slightly greater than with the iodinated contrast. No serious drug-related adverse events occurred. There were no significant effects on vital signs, blood gases, or other serum measurements. The diagnostic quality of the images, as evaluated in a blinded fashion, was slightly better for the iodinated contrast agents than for carbon dioxide. The diagnostic adequacy, however, was equal for both agents.

Despite certain limitations, utilizing a specialized injector and standard digital subtraction equipment, carbon dioxide appears to be a safe and effective contrast agent for the evaluation of peripheral vascular occlusive disease. The quality of images may be expected to improve with increased experience and with improvement in the digital-imaging chain. Because of inherent advantages (no evidence of adverse renal effects, no evidence of immune-mediated adverse events, first-pass pulmonary elimination with no osmotic load) and because of diagnostic efficacy which is equivalent to that achieved with an iodinated contrast agent, carbon dioxide, administered by a specially designed injector, deserves further, broader investigation.

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