

Study on the Microbial Safety of an Infusion Set for Contrast-Enhanced Imaging

Marlein Miranda Cona, BSc,* Matthias Bauwens, PhD,† Yichao Zheng, BSc,* Walter Coudyzer, BSc,*
Junjie Li, MD,* Yuanbo Feng, MD,* Huaijun Wang, MD, PhD,* Feng Chen, MD, PhD,*
Alfons Verbruggen, PhD,† Raymond Oyen, MD, PhD,* and Yicheng Ni, MD, PhD*

Objectives: Multiple uses of automatic contrast injection systems may impose septic risks on patients. The purpose of this experiment was to verify whether a newly developed replaceable patient-delivery system may allow multiple uses of the system but without such risks.

Methods: Twelve patient-delivery systems were tested according to a multiple-use approach using an automatic contrast injection system consisting of dual syringes and one filling and injecting set. Two protocols with normal saline only ($n = 6$) or contrast media plus normal saline ($n = 6$) loaded in the injection system were performed. Each patient-delivery system was connected through an infusion catheter to the ear vein of a rabbit that was intravenously preinjected with a diffusible radiotracer ^{99m}Tc -dimercaptopropionyl-human serum albumin. Aliquots were sampled from the filling and injecting set, patient line, and animal blood for radioactive analysis after the replacement of each patient-delivery system.

Results: For the protocol performed using only normal saline, radioactivity was found in the blood circulation of the rabbit (1655903 ± 593221 CPM) and in the patient line (52894 ± 33080 CPM), but, virtually, in none of samples from the filling and injecting set (8 ± 3 CPM), relative to the background (7 ± 3 CPM) ($P = 0.726$). Similarly, experimental results attained using contrast plus saline show radioactivity in the blood circulation of the rabbit (1119107 ± 183174 CPM) as well as in the patient line (32991 ± 20232 CPM) but in none of samples from the filling and injecting set (6 ± 6 CPM), relative to the background (6 ± 4 CPM) ($P = 0.955$).

Conclusions: The tested patient-delivery system proves convenient and safe. It allows multiple uses of the contrast injection system and avoids the risk of cross contamination.

Key Words: automatic injector, contrast media, CT, MRI, microbiological contamination

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From the *Radiology Section, Department of Imaging and Pathology, Biomedical Sciences Group, University of Leuven, Belgium; and †Laboratory of Radiopharmacy, Faculty of Pharmaceutical Sciences, University of Leuven, Belgium.

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Reprints: Yicheng Ni, MD, PhD, Radiology Section, University Hospitals, K.U. Leuven, Herestraat 49, B-3000, Leuven, Belgium. E-mail: yicheng.ni@med.kuleuven.be.

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Automatic contrast injection systems are widely used for robotic delivery of contrast media during enhanced imaging procedures with different modalities^{1,2} such as computed tomography (CT), magnetic resonance imaging (MRI), and angiography. However, accidental patient cross contaminations with microbial flora (eg, coagulase-negative staphylococci) and bloodborne pathogenic microorganisms (viruses, bacteria, parasites, etc) associated with infectious diseases such as malaria, acquired immune deficiency syndrome, hepatitis C, and hepatitis B have been reported.^{3–5} Potential outbreak of proteinaceous infectious particles transmission also remains a concern, which can cause incurable neurodegenerative disorders in humans known as transmissible spongiform encephalopathies.^{6–8} To prevent possible nosocomial infections, the injection system including the power syringes and filling and injecting set has to be entirely changed for each patient.

Regulatory authorities such as the Food and Drug Administration in the United States and the Federal Institute for Drugs and Medical Devices in Germany have imposed restrictions over the syringes, tubing, and connectors from contrast injectors as single-use devices^{9,10} in accordance with the instructions from manufacturers' advertisements and clinical uses. However, this implementation proves expensive and time consuming owing to the wasted contrast materials left over in the setup from each examination, the growing consumptions of disposable devices, and the prolonged pauses for replacing the entire set-up with each patient.

To counteract such drawbacks, Canada Health performed a study to assess the safety level and feasibility of multiple patient dosages of the costly contrast materials.¹¹ Results showed that the transfer devices having dedicated check valves can prevent backflow of potentially contaminating body fluids in a multidosing contrast media delivery setting. As cost-effective alternative, the same dual-head injector set-up could be used for up to 4 hours, and just the patient tube needed replacement for each case. After that period the complete set-up should be substituted.¹¹ Gradually more institutions worldwide have been applying multiple usages of the syringes with automatic injectors for serial patients to reduce material and labor costs. Commercially available injection systems containing a special one-way valve tube device have been mostly used. Nevertheless, nosocomial infections among patients have been reported as a result of contamination of the injection system with bloodborne pathogens.¹²

Transflux is a patient-delivery system produced by P&R MEDICAL (Diepenbeek, Belgium)¹³ (Fig. 1). It incorporates a safety zone composed by a length of tubing and 2 one-way valves that permit to flush the delivery system and the vein but prevents blood reflux during contrast-enhanced imaging procedures. This system is replaced for each new patient, while the power syringes need to be changed only once a day after multiple uses for a series of patients. It has been applied for several years in many radiology departments without any contaminative infections reported. To verify the safety of Transflux system and to justify its current clinical use, we conducted this experiment in rabbits with intravenous injection of a diffusible radioactive compound ^{99m}Tc -dimercaptopropionyl-human serum albumin (^{99m}Tc -DMP-HSA). Once injected

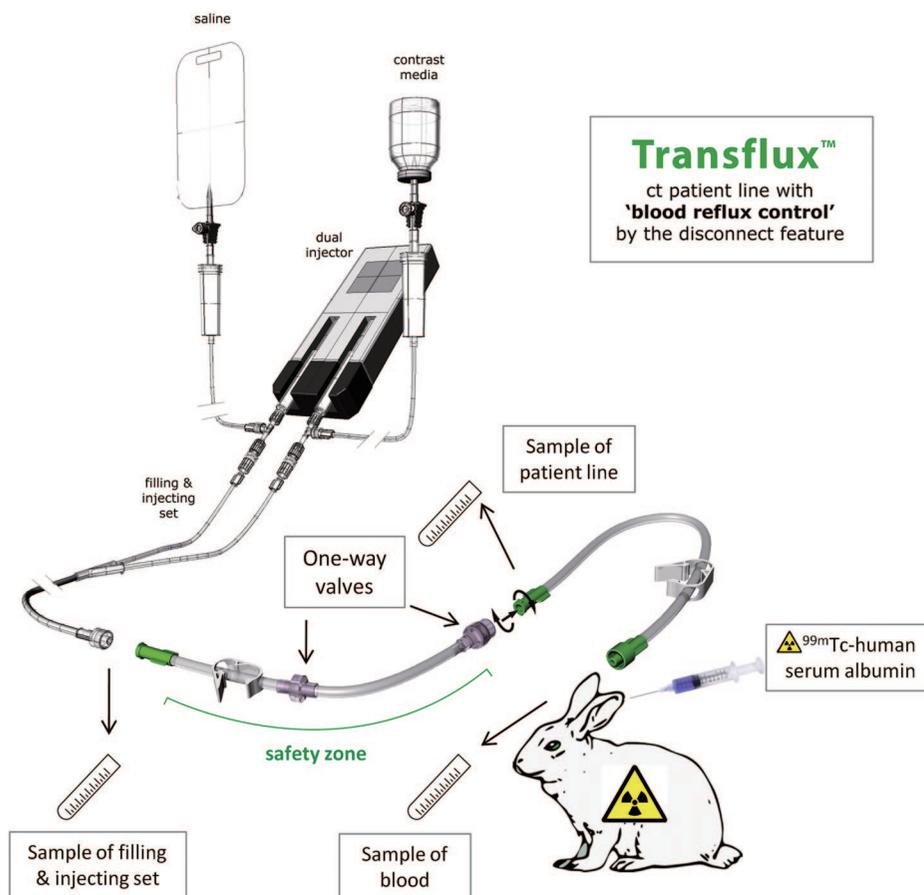


FIGURE 1. Schematic representation of the Transflux CT patient delivery system (P&R Medical company) composed of a “safety zone” tube containing 2 one-way valves, which is connected on one side to the dual-injector system through the injecting and filling set and on the other side to the patient line. In vivo experiments for safety evaluation were done in normal rabbits with intravenous injection of ^{99m}Tc -DMP-HSA as radiotracer. Samples from the filling and injecting set, patient line, and animal blood were collected for radioactive analyses.

in a patient or animal, it remains largely in the blood pool.¹⁴ The tracer was monitored by sampling the delivery system for checking whether the radioactive compound (simulating infectious pathogens) from the patient line in tight contact with animal bloodstream is able to cross the safety zone and reach the dual-syringe injector system.

MATERIALS AND METHODS

This animal study was approved by the institutional ethics and radioprotection committees. To simulate normal clinical scenario, the studies were performed using a power injector (Dual Shot GX; Nemoto Kyorindo, Tokyo, Japan) comprising 2 disposable syringes, one of 200 mL for contrast media infusion and the other of 100 mL for normal saline flushing, both coupled to each other and to a filling and injecting set through a T-connector.

Twelve Transflux CT patient-delivery systems of PR-21414–100 cm type GHB (P&R Medical company, Diepenbeek, Belgium) were tested according to the following 2 protocols:

- Multiple uses of disposable syringes filled with saline solution (Protocol A)—Both disposable syringes were filled with saline solution for further filling of several infusion sets ($n = 6$).
- Multiple uses of disposable syringes filled with contrast agent and saline solution in 2 separate power syringes (Protocol B), taking different viscosity into account—For simulating normal clinical conditions, one syringe was loaded with Iomeron 350 media (Iodinated contrast medium Iomeprol, Bracco, Konstanz, Germany) and the other with saline solution. After filling with media in each delivery system, a volume of 100 mL of saline was pushed through the line ($n = 6$).

The experiments were performed using normal white male New Zealand rabbits ($n = 2$) weighing around 5.0 kg (Animal House, K.U. Leuven, Belgium). The animal was sedated by intramuscular administration of Ketalar (ketamine hydrochloride, Parke-Davis Warner-Lambert, Bornem, Belgium) and Ranpun (xylazine hydrochloride, Bayer AG, Leverkusen, Germany) at 0.5 mL/kg for both. It was kept under sedation during the experiment using pentobarbital (Nembutal; Sanofi Sante Animale, Brussels, Belgium) intraperitoneally at 60 mg/kg. After fixation and restriction of the sedated rabbit in the supine position using a dedicated holder, a 22-G peripheral venous catheter (0.9 mm \times 25 mm, BD Insite-W, Madrid, Spain) was placed in the marginal vein of both ears. One of them was used for administration of the radiotracer solution and the other for connection of the Transflux patient-delivery system to be tested and for blood withdrawal to control the remaining radioactivity in the animal over time.

A single dose of 370 MBq of ^{99m}Tc -DMP-HSA (Fig. 2) was prepared as previously described¹² and administered to the animal. Then, the infusion sets previously filled with saline solution or contrast medium along with saline solution was coupled to the contralateral catheter in such a way as to guarantee a contact between the solution and the animal blood without air in-between. Taking into account that an actual scan only takes a few minutes, the animal was left in connection with the patient line for 10 minutes. After that period, the patient line was carefully disconnected from the animal. After each sampling and installation of a new set, 10 mL was flushed to challenge the valves and to ensure the patency of venous line.

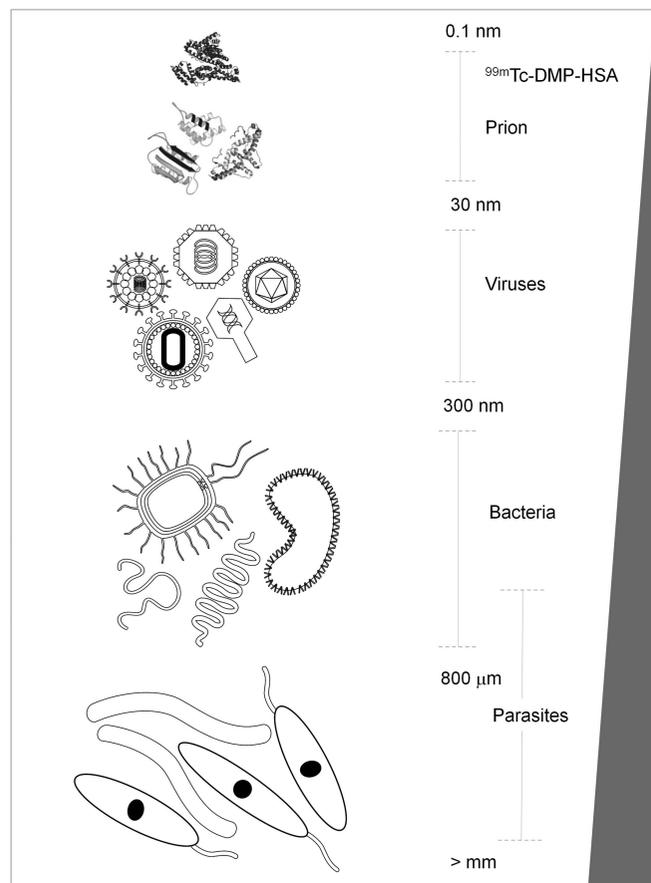


FIGURE 2. Schematic representation of the size and shape of different infectious pathogens including prions, viruses, bacteria, and parasites in relation to the ^{99m}Tc -DMP-HSA radiotracer. Units of length: 1.0 mm = 1000 μm , 1.0 μm = 1000 nm.

An aliquot of 10 mL as well as the whole content of 3.5 mL was collected by tapping from the opening end of the filling and injecting set and patient line, respectively (Fig. 1). Their radioactivities were counted for 1 minute (Counts per minute: CPM). Animal blood samples ($\sim 200 \mu\text{L}$) were withdrawn for controlling the circulating activity during each test. Radioactivity measurements of the collected samples mounted in a sample changer (Wallac 1480 Wizard 3, Wallac, Turku, Finland) were done using a gamma counter (3-in. NaI(Tl) well crystal) coupled to a multichannel analyzer. Rabbits were observed for life signs for 1 week.

Statistical analyses were carried out using GraphPad Prism V.3 software (GraphPad Software Inc., San Diego, CA). Numerical data of measured radioactivities were expressed as mean \pm SD and compared between injector syringe set and natural background radiation using 2-tailed Student *t* test. A statistical significance was considered at a probability value smaller than 0.05.

RESULTS

The rabbits tolerated well the experimental procedures including sedation, anesthesia, catheterization of marginal ear veins, tracer injection, and the multiple samplings over 3 hours per protocol, and recovered to normal status afterward.

The patient delivery systems were tested according to 2 protocols: (1) multiple uses of disposable syringes filled with saline solution, and (2) multiple uses of the 2 disposable syringes one filled

with contrast solution and the other one with saline solution. After connecting each patient line to a rabbit, which was intravenously injected with ^{99m}Tc -DMP-HSA, samples collected from the filling and injecting set and patient line were counted for radioactivity in comparison with natural background.

The results obtained from saline and saline plus contrast protocols are shown in Table 1. For saline protocol, radioactivity detected in the blood circulation of the rabbit (1655903 ± 593221 CPM per 0.2 mL blood) was statistically higher than that (52894 ± 33080 CPM) in the patient line ($P < 0.0001$). Actually there was no radioactivity detected from the filling and injecting set in comparison to the patient line across the safety zone ($P = 0.003$). There were no significant differences between the radioactivity in the samples (8 ± 3 CPM) from filling and injecting set and the natural background radiation (7 ± 3 CPM) ($P = 0.726$).

Likewise, in the contrast agent protocol, there were significant differences between the radioactivity detected in the blood circulation of the animal (1119107 ± 183174 CPM per 0.2 mL blood) and the patient line (32991 ± 20232 CPM); ($P < 0.0001$). No radioactivity was found in any samples from the filling and injecting set (6 ± 6 CPM) in great contrast to the patient line across the safety zone ($P = 0.003$). Statistically, there were no significant differences between samples from filling and injecting set (6 ± 6 CPM) and natural background radiation (6 ± 4 CPM; $P = 0.955$).

DISCUSSION

For avoiding risk of cross-infections when using automatic injectors, a new injector setup for each new patient has to be used for contrast enhanced imaging examinations in daily routine of a radiology department. However, it increases intervals between examinations and hinders the workflow with ever-increasing numbers of patients. The contrast dose received by each patient constitutes often only a small portion of the total amount of contrast agent loaded in the injector system, leading to a great waste of the unused media. Moreover, the growing number of examinations done per day leads to higher expenditure related to the change of the single-use injection device.

Multiple dosages for more than one patient have been a cost-effective alternative implemented for MRI/CT scans. The high capacity of injection syringes allows successive administrations for multiple cases. Only the device or part in direct contact with the patient, the tubing and connector, is replaced between examinations. This practice can not only reduce the waste of contrast agent and injectors or syringes, but also save the time otherwise consumed by assembling injector and reloading syringes.

Nevertheless, although the patient-line set-up dedicated to contrast administration was used just for a short time period (a few minutes); hygiene studies carried out in experimental and clinical practice have reported cross contamination between patients after the fourth injection.¹⁰

The Transflux contrast delivery system is a disposable tubing part, which is directly connected by one hand to the patient (i.e.: the CT patient line) and on the other hand to the main injector unit. This system includes a length of tubing (14.5 cm) that contains 2 high quality one-way valves for establishing a fluid connection from the syringe injector system into a patient line but preventing a fluid reflux from the patient line towards the injector system. Such a system with only 1 valve failed to pass the high pressure (4–10 psi or 200–500 mm Hg) *in vitro* tests (M. M. Cona, personal communication, 2010). In addition, this delivery system is connected with the patient line through a releasable connector. The released position of this releasable connector permits a backflow from the patient during the vein cannulation before connecting to the main injector set, which minimizes extravasations problems. The cost of Transflux

TABLE 1. Results of Measurement of Radioactivity in the Samples From the Experimental Saline and Contrast Plus Saline Protocols as well as the Blood of Experimental Animals

	Before Safety Zone		After Safety Zone	
	Animal Blood (0.2 mL) CPM (n = 6)	Patient Line CPM (n = 6)	Filling and Injecting Set CPM (n = 6)	Natural Background Radiation CPM (n = 6)
Saline protocol				
Samples	2056151	88259	6	6
	2580793	36427	5	5
	1411901	95484	11	13
	1707872	30787	7	5
	1230304	12328	5	4
	948399	54081	12	9
Mean	1655903	52894	8	7
SD	593221	33080	3	3
<i>P</i>	Filling and injecting set vs. natural background radiation			0.726
	Patient line vs. natural background radiation			0.003
	Animal blood vs. natural background radiation			<0.0001
	Filling and injecting set vs. patient line			0.003
	Filling and injecting set vs. animal blood			<0.0001
	Patient line vs. animal blood			<0.0001
Contrast protocol				
Samples	1269190	60928	5	9
	1401743	52357	7	12
	1067618	14303	2	0
	1086509	10062	5	6
	965634	30246	0	3
	923948	30052	16	4
Mean	1119107	32991	6	6
SD	183174	20232	6	4
<i>P</i>	Filling and injecting set vs. natural background radiation			0.955
	Patient line vs. natural background radiation			0.003
	Animal blood vs. natural background radiation			<0.0001
	Filling and injecting set vs. patient line			0.003
	Filling and injecting set vs. animal blood			<0.0001
	Patient line vs. animal blood			<0.0001

SD indicates standard deviation; CPM, counts per minute.

contrast delivery system is approximately only one-tenth of that for the entire injector system.

The introduction of the Transflux delivery system as a “safety zone” avoids the need to change power syringes for each patient procedure by eliminating the risk of contamination of the injector system. For successive patient studies, the “safety zone” and the patient line must be changed but the main injector system can be used for multiple examinations.

To evaluate the safety of the Transflux set, in vivo experiments were conducted based on a multiple dosage approach in combination with radioactive tracer techniques to make highly accurate and sensitive real-time analysis.

According to Stokes-Einstein relation, the diffusion process of a diffusive substance across a certain medium is inversely proportional to its radius and to the viscosity of the solvent at certain temperature. In the current study, we used ^{99m}Tc -DMP-HSA, a diffusible radiotracer whose molecular size (~ 14 nm)¹⁵ is comparable with those of small bloodborne pathogens. For instance, the most infectious units per mass of prions range between particles of 17 to 27 nm.^{16,17} The sizes of the common biologic microorganism can vary from 30 to 300 nm for viruses¹⁸

and from 0.2 to 750 μm for bacteria¹⁹ (Fig. 2). In addition, 2 protocols were performed using different fluids commonly applied for radiology applications to evaluate the influence of the viscosity parameter in the diffusion of such microorganisms through the infusion system.

In the first one, both disposable syringes were filled with saline solution for further successive filling of several Transflux sets. To reproduce more closely the clinical practice, a second protocol was performed, in which one of the syringes was filled with contrast agent (7.5 mPa.s at 37°C) and the other with saline solution (1.0 mPa.s at 37°C) for flushing the delivery system after contrast media infusion. After connecting each patient line to a rabbit intravenously preinjected with ^{99m}Tc -DMP-HSA, samples from the filling and injecting set and patient line were collected and analyzed for checking if the safety zone placed between such tubing segments (Fig. 1) is able to prevent completely the radiotracer diffusion from the animal blood to the automatic injector system. As a representative of all CT and MRI contrast media, we chose Iomeron 350 with a viscosity at a relatively higher level relative to that of normal saline, to cover a full viscosity range, hence results of more general implication.

For each protocol, 6 Transflux sets were tested by replacing the safety zone and patient line but without changing the dual-injector system and the filling and injecting set. Results showed no statistically significant difference in radioactivity between samples from the filling and injecting set and natural background radiation under all conditions tested. Indeed, no radioactivity was detected in any sample from the filling and injecting set after testing each Transflux set in great contrast with the high level of activities present in the patient line as well as in the animal blood. Measurement of radioactivity is a very sensitive and quantitative method, allowing detecting radioactive substances at femtomolar level. To our knowledge, similar *in vivo* studies on the safety of infusion sets for contrast agent administration have not been published in the literature.

The methodology used for validation in this study also appears reliable and accurate and deserves to be applied for validating the safety of other similar devices before it is widely used for multiple patient applications.

CONCLUSION

This study proves the convincing advantage of using the Transflux patient-delivery system in terms of microbial safety and cost-benefits. This system allows safe multiple use of the automatic injector system for several patients without risk of contamination and extravasation but with improved clinical efficiency. In addition, it reduces unnecessary waste of contrast media with each patient procedure and of the costly automatic injector systems.

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