Original Article

Innovative Approach to Preparing Radial Artery Cocktails in Response to Manufacturer Shortages of Nitroglycerin and Verapamil

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Abstract

Background: Transradial access has gained popularity over transfemoral access for cardiac catheterization, because of the decreased risk of bleeding, time to ambulation, and length of stay leading to improved patient satisfaction. One disadvantage of the radial artery approach is vasospasm, which can be prevented with the administration of verapamil and nitroglycerin in a pre- and postradial cocktail. Unfortunately, there have been manufacturer shortages for both of these medications.

Methods: The utilization of radial artery cocktails and other nitroglycerin compounding practices were evaluated in response to cost containment and waste reduction initiatives and to medication shortages.

Results: A modified process for supplying verapamil and nitroglycerin for the transradial approach via separate syringes enabled physicians to have quick access to the medications and to customize the cocktail based on the patient's needs. This process also decreased costs and minimized waste. The change in practice decreased waste from 44% for preradial cocktail syringes and 66% for postradial cocktail syringes to 8.7%.

Discussion: This process for supplying the medications necessary to perform a radial artery catheterization and intracoronary nitroglycerin has allowed for conservation of commercial product supply.

Key Words—verapamil, cardiac catheterization, drug shortage, nitroglycerin, radial artery spasm, stability, transradial

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At The Ohio State University Wexner Medical Center (OSUWMC), 4,000 diagnostic catheterizations and 1,500 percutaneous coronary interventions (PCI) are performed annually. Until September 2010, the transfemoral approach accounted for more than 80% of the access sites used

for patients undergoing cardiac catheterization procedures. The transradial approach has gained popularity as a way to decrease the number of post-PCI bleeding complications, access site hematomas, and transfusions as well as to decrease the time to ambulation and length of stay.¹⁻⁴

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In comparison to the femoral artery, the radial artery is significantly smaller, which predisposes the vessel to vasospasm. One of the most frequent complications of patients undergoing the transradial approach is radial artery spasm; this can cause discomfort for the patient during the procedure and can require that the procedure be stopped or the access site changed. There is no standard definition for radial artery spasm and there are differences in techniques used to perform the procedure, but the incidence of vasospasm is estimated to be between 2% and 51.3%.¹⁻⁴ Factors other than radial artery spasm can lead to the procedure being stopped or the access site being changed, so the incidence attributable to radial artery spasm alone is not well-established.

Intra-arterial administration of vasodilating agents with differing mechanisms of action (ie, verapamil and nitroglycerin) prior to inserting the sheath has been shown to reduce the incidence and severity of radial artery spasm.^{3,4} Verapamil works by inhibiting calcium influx and contractility of smooth muscles through selective blockade of the L-type voltage-gated calcium channels; nitroglycerin works by releasing nitric oxide, raising cGMP levels, and reducing the calcium concentration to cause relaxation in the smooth muscle. In addition to vasodilating agents, heparin may be used in the preradial cocktail to prevent thrombus formation that may lead to radial artery occlusion when the wire is inserted.

Up to 2012 at OSUWMC, the interventional cardiologists could administer a preradial cocktail con-

taining nitroglycerin 200 mcg, verapamil 2.5 mg, and heparin 2,500 units and a postradial cocktail containing nitroglycerin 200 mcg and verapamil 2.5 mg (see **Table 1**) to prevent vasospasms and thrombus formation.³ Both syringes were diluted with normal saline to a total volume of 10 mL; they had an arbitrary refrigerated 24-hour default expiration date due to the lack of data showing detrimental degradation within this time period or supportive data extending the storage time. This expiration dating falls within the sterility dating as established by the US Pharmacopeia (USP).⁵ For predrawn syringes, the beyond-use dating for a medium risk level would permit 30 hours at room temperature or 9 days refrigerated without additional sterility testing.

The main objective for predrawn syringes is to have the radial cocktails readily accessible, so the transradial approach can be used without delays. The Joint Commission and other accrediting organizations have established quality measures for door-to-balloon within 90 minutes for primary PCI in patients with an ST-elevation myocardial infarction.⁶ Prior to 2013, at OSUWMC the syringes were stocked in automated dispensing cabinets (ADCs) in the catheterization lab in anticipation of an order instead of compounding the syringes once an order was received, which would delay therapy and the procedure. The goal of this article is to review the methods used at OSUWMC to minimize waste and decrease cost while maintaining rapid physician access to the medications for the transradial approach and to manage multiple manufacturer shortages.

Table 1. Baseline recipe for pre- and postradial cocktails^{3,4}

Preradial cocktail: combined in 1 syringe		
Ingredients:	Commercial product:	Final syringe contents:
Heparin	5,000 units/mL, 1 mL vial	2,500 units (0.5 mL)
Nitroglycerin	5 mg/mL, 10 mL vial	0.2 mg (0.04 mL)
Verapamil	2.5 mg/mL, 2 mL vial	2.5 mg (1 mL)
0.9% sodium chloride		QS to 10 mL
Postradial cocktail: combined in 1 syringe		
Ingredients:	Commercial product:	Final syringe contents:
Nitroglycerin	5 mg/mL, 10 mL vial	0.2 mg (0.04 mL)
Verapamil	2.5 mg/mL, 2 mL vial	2.5 mg (1 mL)
0.9% sodium chloride		QS to 10 mL
Expiration dating	24 hours refrigerated	

Note: QS = quantity sufficient.

COST-CONTAINMENT EVALUATION

Beginning in late 2012, the Department of Pharmacy began looking critically at current practices to identify cost-containment opportunities. All individuals in the department were asked to evaluate current practices and submit ideas. A pharmacy technician questioned the waste of radial cocktail syringes, thus an audit was performed to assess the use of these syringes.

From March through May 2013, a 10-week audit was conducted at the main campus location. The practice at that time was to prepare 11 preradial cocktail and 7 postradial cocktail syringes daily Monday through Friday, 3 of each for Saturday, and 6 of each for Sunday. There were a total of 607 preradial cocktail syringes and 419 postradial cocktail syringes compounded and a total of 268 (44%) preradial cocktail syringes and 275 (66%) postradial cocktail syringes wasted. A discussion with the physicians revealed that a preradial cocktail could be given without a postradial cocktail. The preradial cocktail is used to prevent vasospasm when inserting the catheter, and a post-radial cocktail is used to prevent vasospasm when removing the catheter; thus, the cocktails are not always used together. This finding resulted in a decision to separate the heparin from the other ingredients and compound nitroglycerin and verapamil in one prefilled syringe. The heparin component for the preradial cocktail would be obtained from the 10,000 unit/mL vial concentration of heparin stocked in the ADC. This vial size was selected because patients often require multiple doses of heparin during the procedure to maintain therapeutic anticoagulation. In addition, another cost-containment strategy occurring around the same time was to decrease utilization of bivalirudin in our catheterization lab, requiring a change in our heparin dosing. The decision to separate heparin from other ingredients would allow physicians to administer heparin 50 units/kg (maximum of 5,000 units) in those patients who receive heparin only. Medication errors from the use of heparin were avoided by stocking only one concentration in the procedure area ADC and requiring verbal confirmation and appropriate labeling of syringes during transfer of medications into the sterile field.^{7,8}

VERAPAMIL SHORTAGE ISSUED

On April 17, 2013 (during the data collection period for the audit), verapamil was added to the US Food and Drug Administration's (FDA) Drug Shortages Index. As a result, we re-evaluated and modified our procedures to conserve the verapamil supply.

During the discussion of the audit results, the physicians expressed concerns about the potential for hypotension and bradycardia associated with verapamil. A review of the limited literature found studies with small sample sizes and inconsistent dosing of verapamil in radial cocktails. Chen et al⁴ studied the use of a lower dose (1.25 mg) of verapamil in more than 400 patients and determined that the verapamil dose could be decreased from 2.5 mg and still significantly prevent radial artery spasm. At this time, OSUWMC made the decision to change the verapamil dose in the syringe to 1 mg, which would allow 5 syringes to be made from a 2.5 mg/mL, 2 mL vial instead of just 2 syringes; this further conserved the manufacturer supply.

The next step in modifying our verapamil use process was to engage the physicians and observe their usage of these syringes during cardiac catheterization. During the procedure, the contents of the pharmacy-compounded syringe are transferred to another syringe in the field to maintain sterility.^{7,8} Because of this practice, we were able to consider pre-drawing the correct dose of nitroglycerin and verapamil into separate syringes; the physicians could combine these ingredients into the same syringe with heparin (if desired) when the drugs were transferred to the sterile field at the time of administration. The use of separate syringes presented an opportunity to re-evaluate the length of stability for single-ingredient pharmacy-prepared syringes versus the arbitrary 24-hour stability assigned to the multiple-ingredient syringes as previously mentioned. In addition, separate syringes would allow physicians to customize the radial cocktail. This may be necessary for patients who are receiving concurrent medications that may interact with a component of the radial cocktail or who may experience adverse effects from a component of the radial cocktail.

STABILITY AND STERILITY

General practice has been to use a default 24-hour expiration for medications dispensed in a hospital setting unless there are definitive data stating loss of potency or unsafe decomposition during this time. For the combination of heparin, nitroglycerin, and verapamil in the same syringe, there are no data in the literature to support long-term storage. **Table 2** provides the limited stability information available for combining 2 of the 3 drugs in the preradial cocktail syringe, which does not offer extended stability beyond the time that the medications would be combined just prior to administration.

Table 2. Compatibility and stability of ingredients in radial cocktails¹⁴

	Heparin	Nitroglycerin	Verapamil
Heparin	NA	Syringe – at least 5 min	Additive – 24 hours Syringe – at least 5 min
Nitroglycerin	Syringe – at least 5 min	NA	Additive – 24 hours
Verapamil	Additive – 24 hours Syringe – at least 5 min	Additive – 24 hours	NA

Note: additive = additive compatibility of both drugs in the same intravenous bag; NA = not applicable; syringe = compatibility of both drugs in the same syringe.

(approximately 5 minutes).⁹ As previously mentioned, we next investigated the stability information regarding predrawing and diluting each drug separately.

Two studies reported at least 24-day stability for nitroglycerin diluted in 0.9% sodium chloride or dextrose 5% in water stored at room temperature or refrigerated.¹⁰⁻¹² Another study demonstrated a 24-hour room temperature stability and 7-day refrigerated stability for nitroglycerin stored in polyethylene syringes.¹³ Additionally, 2 studies demonstrated no loss of stability for nitroglycerin in polyethylene syringes at 24 hours^{14,15} and 1 study at 24 days.¹² Adsorption has been noted with polyvinyl chloride containers, but has not been noted extensively with plastics such as polyethylene or polypropylene.⁹ There is a study reporting dilutions of verapamil in 0.9% sodium chloride or dextrose 5% in water to be stable for 7 days at room temperature.^{9,16} Given that verapamil solubility is 7 g in 100 g of water, we concluded that refrigeration of the diluted solution would likely not pose a risk for precipitation.¹⁷

After determining the stability data for each medication diluted separately, our next focus was on sterility dating as established by the USP.⁵ For pre-drawn syringes, the beyond-use dating for a medium risk level would permit dating of 30 hours at room temperature or 9 days refrigerated without additional sterility testing. Thus based on the combined stability and sterility data, OSUWMC decided to dilute nitroglycerin and verapamil and dispense each in separate syringes with a 7-day refrigerated expiration and compound both syringes at the same time for ease of inventory management (see Table 3).

RESULTS

An evaluation was performed of the preparation of single drug-containing syringes (one of verapamil and

another of nitroglycerin) from November 5, 2013 to April 30, 2014. During this time, 1,539 sets of syringes were prepared and 134 were documented as having been wasted. Thus the change in compounding practice described here contributed to a decrease in waste from 44% for preradial cocktail syringes and 66% for postradial cocktail syringes to 8.7% for the single drug-containing sets of syringes.

On December 20, 2013, nitroglycerin was added to the FDA Drug Shortages Index. With this notification, our supply of both the 50 mg/250 mL premix bottles and the 5 mg/mL, 10 mL concentrated vials had to be assessed. Despite the shortage, the commercial supply of the premix bottles was larger than the concentrated vials. Therefore, the recipe for the radial cocktail syringes was changed to compound from the premix bottles versus the concentrated vials (see Table 4). The base diluent difference between the single syringes would now be in dextrose 5% in water for nitroglycerin and 0.9% sodium chloride for verapamil; there was no expectation that combining these 2 syringes in the sterile field would pose a compatibility issue since both medications are compatible in both base diluents.

Some other considerations for nitroglycerin use during this time were the compounding of nitroglycerin syringes for the operating rooms (50 mcg/mL, 10 mL) and for intracoronary administration (1 mg/mL, 5 mL) in the catheterization lab. Changing the recipe for the radial cocktail to be compounded from the dilute commercial premix bottles of nitroglycerin allowed simultaneous compounding of the syringes for the operating room; this maximized the use and limited the waste of the large 250 mL premix bottle during compounding. However, the syringes used for intracoronary administration cannot be compounded from the larger more dilute premix bottles of nitroglycerin; these syringes must be compounded from the concentrated nitroglycerin vials. After a brief chart audit, the volume of the more concentrated

Table 3. Reformulated radial cocktail recipe in response to the verapamil shortage

Heparin vial	5,000 units/mL, 1 mL vial	2,500 units (0.5 mL)
Syringe 1:	Commercial product:	Final syringe contents:
Nitroglycerin	5 mg/mL, 10 mL vial	0.2 mg (0.04 mL)
0.9% sodium chloride		QS to 5 mL
Syringe 2:		Final syringe contents:
Verapamil	2.5 mg/mL, 2 mL vial	1 mg (0.4 mL)
0.9% sodium chloride		QS to 5 mL
Expiration dating ⁵⁻¹⁴	7 days refrigerated	

Note: QS = quantity sufficient.

Table 4. Radial cocktail recipe in response to the nitroglycerin shortage

Heparin vial	5,000 units/mL, 1 mL vial	2,500 units (0.5 mL)
Syringe 1:	Commercial product:	Final syringe contents:
Nitroglycerin	50 mg/250 mL premix bottle	0.2 mg (1 mL)
Dextrose 5% in water		QS to 5 mL
Syringe 2:		Final syringe contents:
Verapamil	2.5 mg/mL, 2 mL vial	1 mg (0.4 mL)
0.9% sodium chloride		QS to 5 mL
Expiration dating ⁵⁻¹⁴	7 days refrigerated	

Note: QS = quantity sufficient.

intracoronary nitroglycerin syringes (1mg/mL) was decreased to 1 mL; most cases required no more than 1 mg. This change further contributed to conservation of the manufacturer supply.

DISCUSSION

There have been several challenges in addressing the compounding of radial cocktail syringes, including multiple drug shortages and the need for cost containment. OSUWMC optimized the utilization of available commercial nitroglycerin and verapamil supplies by evaluating what the optimal doses are to prevent radial artery spasm and modifying the compounding processes throughout the health system. The new process allows the physicians to customize the radial cocktail based on the patient's need. For example, if a patient is bradycardic, nitroglycerin could be used alone. Conversely, if a patient currently receives a phosphodiesterase type-5 inhibitor, the nitroglycerin could be omitted and verapamil

could be used alone. Once the manufacturer shortages resolve and market availability is no longer an issue, a cost analysis will be performed to determine whether the recipes presented in Table 3 or 4 will be used.

CONCLUSION

There has been no resistance from physician staff with regard to the new process of combining heparin from a vial and preparing multiple single-drug syringes in the catheterization lab. Additionally, clinical efficacy of the use of the heparin vial and single-drug syringe method for nitroglycerin and verapamil administration has not been questioned. This is supported by minimal reports of radial artery spasm requiring administration of a postradial cocktail, the increase in activated clotting times when the cocktail containing heparin is administered, and relief of vasospasm and chest pain with the administration of intracoronary nitroglycerin.

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