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The influence of flushing on reducing precipitation of intravenous (IV) drug compatibility

Suci HANIFAH [1] *, Patrick A. BALL [2], Ross A. KENNEDY [3]

1 Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Universitas Islam Indonesia, Yogyakarta, Indonesia.
2 School of Pharmacy, Worlverhampton University, Wolverhampton WV1 1NA, United Kingdom.
3 School of Biomedical Sciences, Charles Sturt University, Bathurst, NSW, Australia.
* Corresponding Author. E-mail: suci.hanifah@uii.ac.id (S.H.); Tel. +62 856-4395-8700.

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ABSTRACT: Simultaneous delivery of incompatible IV medications may produce a very large amount of precipitation as a result of incompatibility. This study aims to evaluate the influence of flushing to reduce precipitation. To study the effect of flushing, we examined flushing with various volumes before and after injection of drug combinations which resulted in incompatibility. A series of infusion and injection drug were delivered using "a typical patient model". Flushing of pre-and post-drug delivery was administered for each of the incompatible drug combination. The influence of the different flushing volumes was analyzed qualitatively by comparing the particle images of each sample. The benefits of flushing was analysed from the precipitation images in the samples compared to the sample control. Amongst five co-infusion groups and one co-injections administrations, two mililiters flushing was effective for the prevention of incompatibility in co-infusion A with acyclovir; coinfusion B with meropenem; co-infusion C with chloramphenicol; and co-infusion D with cefotaxime. However, phenytoin precipitation with co-infusion C could not be avoided even though a higher volume (up to 5 mL of flushing) was used. A flushing of 1.5 mL pre and a 2 mL post-drug delivery effectively reduce the precipitation of drug incompatibilities except for the phenytoin.

KEYWORDS: Intravenous; incompatibility prevention; flushing;

1. INTRODUCTION

Co-administration of some intravenous (IV) medications often cannot be avoided in the intensive care unit (1, 2). Administration of infusion with another injection drug incompatible through the same Y-site may produce a large amount of precipitation or a larger globule in emulsion (3, 4). Physical incompatibility results in precipitation which is more dangerous than chemical one. Chemical incompatibility commonly causes concentration changes (5). However, the precipitation may result in a technical problem such as blockage of infusion set blockage which can lead to death (6). Therefore, strategies to prevent physical incompatibility are important to relieve the negative consequences emerging from the formation of precipitates. Precipitates that can block the IV-line cause non-thrombotic occlusion, resulting in 42% occlusion (7, 8). Non-thrombotic embolism is often less common, unspecific, and unpredictable, and thus is unwittingly fatal (9).

To date, flushing is the only method used to avoid non-thrombotic occlusion. Practioners routinely flush the IV line with fluid or salin to avoid non-thrombic occlusions. However, this practice brings consequences for the patient to get a larger volume of fluid which can cause hypervolemia. Thus, a minimal volume of flushing would be valuable for critically ill patients who may have rigid limitations regarding their intake of fluids or sodium (10). Unfortunately, there is limited evidence of flushing to prevent incompatibility. The practice of flushing to reduce incompatibility varies among hospitals, since the required flushing volume can vary significantly depending on the patients, the type of catheter, or the medication used. Recent evidence commonly studies about the type of fluid for flushing comparing saline and heparin to maintain IV-line patency. Even though there are many studies in the literature about the flushing method, but those studies are not based on flushing volume itself, unlike this study (11).

Based on the above problems, there are two research questions: shall flushing diminish the particles or precipitates that were seen on the microscopic image, and what volume of flushing is effective reducing

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incompatibility? It is necessary to corroborate whether the use of flushing is effective when precipitation of incompatibility result occurs. Moreover, this study also investigates the minimum volume required to prevent precipitation. Therefore, this study primarily addresses the benefit of flushing to reduce particulate because of incompatibility. Then, it calculates the minimum volume, effectively reducing precipitation.

2. RESULTS

Based on microscopy detection, the incompatibility amongst medications (infusion and injections) results in a lot of precipitations with the specific shape and size. Macro-precipitates larger than 50 µm were seen on acyclovir, phenytoin, and meropenem. Micro-precipitates were identified on chloramphenicol and cefotaxime. The effectiveness of flushing was noted with the absence of particulate matter or clarity after 1.5 mL pre-dose flushing and 2 mL post-dose flushing in all groups except infusion group V-phenytoin (sample 5). The test results are presented in tables 1 and 2.

Table 1. The number of particles after flushing of 0.9% saline solution pre-injection.

Samples No	Particle Images	Number of particles after pre-dose flushing				
		0 mL	0.5 mL	1 mL	1.5 mL	2 mL
1	acicular macroprecipitates	>100/mL	<12/mL	<12/mL	Clear	Clear
2	irregular macroprecipitates	>12/mL	<12/mL	<12/mL	Clear	Clear
3	irregular microprecipitates	>12/mL	<12/mL	Clear	Clear	Clear
4	irregular microprecipitates	<12/mL	<12/mL	Clear	Clear	Clear
5	acicular macroprecipitates	>100/mL	>100/mL	>100/mL	<12/mL	<12/mL
6	irregular microprecipitates	>100/mL	>12/mL	Clear	Clear	Clear

Table 2. The number of particles after flushing of 0.9% saline solution post-injection

Samples No	Particle Images	Number of particles after pre-dose flushing				
		0 mL	0.5 mL	1 mL	1.5 mL	2 mL
1	acicular macroprecipitates	>100/mL	>100/mL	>100/mL	<12/mL	Clear
2	irregular macroprecipitates	>12/mL	>12/mL	>12/mL	<12/mL	Clear
3	irregular microprecipitates	>12/mL	>100/mL	>12/mL	Clear	Clear
4	irregular microprecipitates	>12/mL	>12/mL	>12/mL	Clear	Clear
5	acicular macroprecipitates	>100/mL	>100/mL	>100/mL	>100/mL	>100/mL
6	irregular microprecipitates	>100/mL	>12/mL	>12/mL	Clear	Clear

3. DISCUSSION

This study identified that flushing is quite effective in avoiding incompatibility. In general, flushing in a 1.5 mL pre- and a 2 mL post drug delivery using Normal Saline (NS) can avoid precipitation as a result of incompatibility. Even though, there are differences in the exact volume needed to clear precipitation. Precipitations from incompatibility of phenytoin with co-infusion C seem problematic. A 2 mL NS flushing is disabled to clear the precipitates. However, phenytoin is practically insoluble in water solutions. This is why the phenytoin tends to make crystallization when facing the water solution. In addition, phenytoin also has extremely basic pH (pH=12). Therefore, it is easy to precipitate with acid pH medications. A study reported

that phenytoin needs 50 to 100 mL of normal saline to dilute, with the final concentration in NS should not exceed 10 mg/mL (12).

The effective volume of flushing resulted in this current study was far lower than used in common practice (i.e., 3-10 mL). Although this volume is higher than the suggested volume by other scholars, it is similar to the common guidance in European or Australian hospitals (13). In addition, the Infusion Nurses Society (INS) suggests that the flushing volume should be double the size of IV line (14). Considering the characteristics of cannula or IV-line, the current research model would require 1.2 mL NS (i.e., 2 x 0.6 mL=1.2 mL). The result is similar to this current finding that 1.5 mL pre-dose flushing is effective. Therefore, this study validated the formula of INS for calculating the optimal volume for pre-dose flushing.

Furthermore, this study found that the volume requires for pre-dose and post-dose NS flushing seem to differ. The precipitation number resulted from pre-dose flushing diminished with an increasing volume of flushing solvent used. In contrast, the precipitates of phenytoin were still identified when the volume of pre-dose flushing was larger than 1.5 mL or 2.0 mL post-dose flushing. Our data addresses a tendency for a greater volume required of post-dose flushing than pre-dose flushing. This is possibly influenced by the flow rate of post-dose flushing to clear precipitation is higher (1–5 mL/min) than the infusion (1–5 mL/hr). However, this does not mean we need a faster rate for post-dose flushing. As far as can be identified, there is no study published the differences in the volume before or after flushing.

Flushing can minimize precipitates by reducing the interaction between the co-solutions. In theory, when a flushing solution is delivered between medications, it will avoid drug-to-drug contacting (13). However, de-separation has been established in loops, in archways, and in dead space volume in the IV line where the drug solution can stay beyond the running stream (13).

This current data validate recent studies that indicated that saline is effective for flushing (11). Furthermore, a scoping review has found that flushing with NS solution improved the quality of care by maintaining patency and avoiding adverse events compared with heparin (11). This study confirmed the effectiveness of flushing and the optimal volume. However, this would probably need to be done further on a case-by-case basis owing to different tubing diameters and drug characteristics. Further study is needed to confirm the other medications, combinations, and situations.

4. CONCLUSION

The current study has addressed the findings that 1.5 mL pre and 2 mL post-dose normal saline avoid the precipitation of the incompatible drugs, except for the incompatibility of Infusion group V with phenytoin.

5. MATERIALS AND METHODS

We used a dynamic infusion system as a typical patient model to mimic real practice as closely as possible (15). A flushing pre-and post-delivery with various volumes from 0.5 mL up to 5 mL was applied for incompatible medications as seen in Table 3. Choosing these combinations was based on the common co-infusions used in critical care unit. Meanwhile, choosing the injections considered the incidence of precipitation in practice.

Table 3. Combination of medications for flushing test

Sample	Co-infusion	Injection from Three-way
1	Co-infusion A of ketamine, midazolam, morphine	Acyclovir
2	Co-infusion B of dobutamine, fentanyl, norepinephrine	Meropenem
3	Co-infusion C of fentanyl, morphine, midazolam	Phenytoin
4	Co-infusion D of dobutamine, morphine, fentanyl	Chloramphenicol
5	Co-infusion E of dobutamine, midazolam, norepinephrine	Cefotaxime
6	-	Furosemide-Gentamicin*

**sequential administration*

Pre- and post-dose flushing was administered between each infusion/injection. The procedure was conducted following the steps as seen in Figure 1. below with the duplicate replication. The effectivity of flushing and ideal volume was analyzed qualitatively based on the changes of particles of each sample.

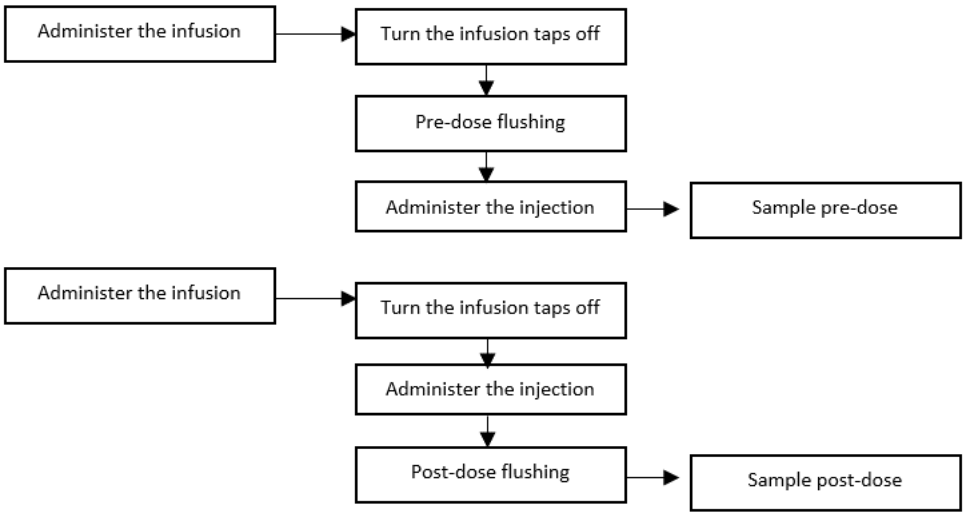

Figure 1. Procedure of sample drawing for identification of flushing

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