Physical Compatibility of Norepinephrine-Dobutamine with Common Medication in Critical Care: Visual and Microscopy Evaluation

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Abstract. Intravenous (IV) incompatibility is one of the obstacles in achieving the intended therapeutic goals. Norepinephrine-dobutamine is common inotropes that often meet with other injections and somehow cause incompatibility risk. Aim: This study aims to evaluate the compatibility of norepinephrine-dobutamine with common IV medications in critical care using the naked eye, black-white background, and microscope. Methods: Inotropic solution (dobutamine and norepinephrine) was prepared in a triplicate by adding D5W to a syringe to a final concentration of 1.4 mg/mL for dobutamine in which 30 μg/mL of norepinephrine was achieved. The solution was set up as a typical y-site infusion with the three-way connector. The inotropes are infused through the infusion set, and the other medications (acyclovir, ampicillin, cefotaxime, chloramphenicol, dexamethasone, furosemide, gentamicin, meropenem, phenobarbital, phenytoin, and ranitidine) are injected through the three-way orderly. The compatibility has been investigated in the tubing with the naked eye. Then, aliquot samples are collected to see discolouration, gas, and precipitate formation under black-white background and microscope. By using the naked eye, colour changes and precipitation were seen on meropenem and phenytoin injection, respectively. Under a black and white background, a slight precipitate was observed in acyclovir injection. Incompatibility was detected on acyclovir, ampicillin, gentamicin, meropenem, phenobarbital, and phenytoin under microscopy observation. Norepinephrine-dobutamine is incompatible with acyclovir, ampicillin, gentamicin, meropenem, phenobarbital, and phenytoin. The visual inspection resulted in the detection of a small amount of incompatibility (13,3%), compared to visual inspection against black and white backgrounds and with light (20%), and optical microscopy (40%).

Keywords: intravenous compatibility · norepinephrine-dobutamine · visual inspection · microscopy

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1 Introduction

The combination of inotrope medication such as dobutamine and norepinephrine is often used, particularly for patients with septic shock [1]. This combination is superior as an inopressor for cardiogenic shock [2]. Dobutamine was familiarly combined with norepinephrine to ensure the myocardial perfusion achievement. The addition of dobutamine builds up the cardiac performance index in patients with septic shock compared to norepinephrine on its own [1]. To achieve a precise dose, dobutamine and epinephrine need dose manipulation by dilution, and titration through micro infusion. Even though both medications are administered through the different syringes, they may meet in the three way or connector [3]. Inotropes medication such as dobutamine-epinephrine not only may meet with one and another but also may interact with other medications in the tubing. This may induce incompatibility. To prevent incompatibility, a protocol about compatibility amongst co-administered medication should be provided. However, in the condition which has no information of the compatibility, to prevent incompatibility, inspection of the tubing by the naked eye is customary in practice; this is the only way for practitioners to monitor possible incompatibility [3]. Identification of incompatibility while at the bedside during the patient's hospital stay is difficult. To the best of our knowledge, there is no study yet comparing the accuracy of visual inspection of naked eye. This study aims to compare the result of the visual inspection and microscopy as a gold standard for compatibility testing.

2 Method

2.1 Material

The characteristics of medication used in this study are seen on Table 1..

2.2 Design Study

This study used "a typical patient model" to mimic how the IV medications are co-administered in the patients. Figure 1 shows a diagram of the arrangement of the "typical patient model".

2.3 Compatibility Justification

Three assessment techniques were applied; visual inspection with naked eye, under consistent light-with black and white backgrounds, and using microscopy. 1. Visual inspection was undertaken of the precipitate in the connector/extension line to mimic the monitoring of IV drug compatibility as done by practitioners in the ward. Each 2 mL sample in the test tube was also subjected to visual inspection under consistent light and with black and white backgrounds. Visual inspection also included visual checks for clarity, colour change, gas formation and precipitation. Two different assessors performed the visual inspection for each sample. 2. Colour change was determined visually against a white background while clarity was decided visually against white and

Table 1. The medications used for study

Medication	Manufacturer	Concentration[a]
Acyclovir 50 mg/mL	Glaxo SmithKline	10 mg/mL
Ampicillin 1000 mg	Indofarma	200 mg/mL
Cefotaxime sodium 1000 mg	Dexa Medica	200 mg/mL
Chloramphenicol sodium succinate 1000 mg	Phapros	200 mg/mL
Dexamethasone sodium phosphate 5 mg/mL	Indofarma	1 mg/mL
Dobutamine HCl 250 mg/5 mL	Novell Pharm. Lab	1.4 mg/mL
Furosemide sodium 20 mg/2 mL	Indofarma	10 mg/mL
Gentamicin sulfate 80 mg/2 mL	Indofarma	40 mg/mL
Meropenem 500 mg	Kalbe Farma	50 mg/mL
Norepinephrine Bitartrat 4mg/4mL	Novell Pharm. Lab	30 μg/mL
Phenobarbital sodium 200 mg/2 mL	Mersifarma	10 mg/mL
Phenytoin sodium 100 mg/2 mL	Indofarma	10 mg/mL
Ranitidine HCl 50 mg/2 mL	Hexpharm Jaya	25 mg/mL

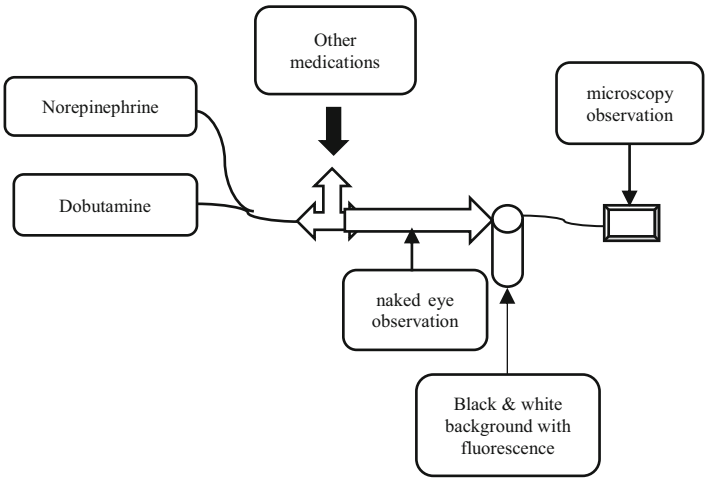

Fig. 1. A typical patient model to administer norepinephrine-dobutamine with other medications

black backgrounds. 3. a 25 μL (microlitre) sample was taken for microscopic testing. Justification of incompatibility was based on the particle of a size >10 μm numbered more than 12 per mL or when any particle >25 μm numbered at least two [2] per mL [4].

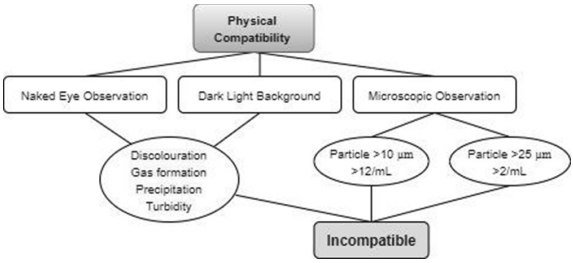

Fig. 2. Incompatibility Justification

3 Result and Discussion

3.1 The Compatibility Result

Table 2. shows that there are only 2 incompatibilities of 11 samples tested based on naked eyed evaluation. Using additional background and fluorescence light, three incompatibilities are examined of 11 samples. However, there are 7 incompatibilities that were detected under microscopy testing.

Incompatibility was observed for all groups with precipitation of phenytoin and discoloration of meropenem as shown in Table 2. Visual inspection under consistent light with black and white backgrounds revealed more particulate matter. Precipitation was seen clearly in samples with phenytoin, meropenem and acyclovir. Meanwhile, the incompatibility was detected as well in some of the ampicillin, cefotaxime, gentamicin, meropenem, and phenobarbital.

4 Discussions

This study shows that naked eye results in a lot of undetected incompatibilities. This finding serves as a reminder that it is hard to identify clarity with visual inspection, as a clear background does not give sufficient contrast against the fluid in the tubing. Even-though, visual inspection is often undertaken as the main way to monitor incompatibility when no other protocol is available, this finding suggests that assessment based only on observations and experience of health personnel during routine hospital practice was not adequate for identifying incompatibility problems. Therefore, this study is a reminder to provide a protocol that informs compatibility with sufficient methods.

This finding supports the work of Staven et al. which indicated that visual detection cannot be applied as the sole technique for incompatibility detection [5]. Visual inspection has limitations in terms of sensitivity and reproducibility. Sadeghipur et al. noted that the reliability of visual inspection was no higher than 85% with wide variability (RSD 32%; $n = 19$). Furthermore, some approaches to optimise the results from visual inspection are recommended.

Table 2. Compatibility observed with naked eye in the tubing

Methods	**IV Medications**											
	Control	Acyclovir	Ampicillin	Cefotaxime	Chloramphenicol	Dexamethasone	Furosemide	Gentamicin	Meropenem	Phenobarbital	Phenytoin	Ranitidine
Naked eye observation	C	C	C	C	C	C	C	C	**D**	C	**P**	C
Black and white with fluorescence	C	**S**	C	C	C	C	C	C	**D**	C	**P**	C
Black and white and microscopy	C	**I**	**I**	**I**	C	C	C	**I**	**I**	**I**	**I**	C

Note: C=compatible, I=incompatible based on USP, D=colour changes, S=slightly turbid, P=precipitation

Visual inspection against black and white backgrounds with sufficient illumination was more sensitive than direct eye inspection in determining incompatibility. Observation of the tubing against a black background makes it easier to distinguish clarity and turbidity [5]. This supports the viewpoint that the capacity of physical examination using the naked eye was enhanced by the intensity of the light used and the nature and size of the particle Rothrock. Furthermore, distinguishing between a gas bubble and a particle is also often confused in visual examination [6].

Vegeland found that a strong focused light from a pocket laser pointer enhances the ability of visual inspection, with this light scattering by particles called the Tyndall effect [7]. This is a promising valuable tool that provide a better result. However, a recent study concluded that the validity and reliability of the Tyndall effect were low and that it was suitable only for particles larger than 5 μm [5].

Furthermore, Sadeghipur et al. demonstrated that training improved the ability of the inspector to produce better quality assurance for visual inspections [8]. The results of visual inspection are thus subjective as they are influenced by the experience of the operator [8]. Taking into consideration the limitations of the visual detection of incompatibility, it is essential that a protocol is made available. Smulders stated that the inspector/operator and the frequency of inspection both have roles that affect the result of visual inspection [9].

The visibility of particles seems to be influenced by their size in terms of the current threshold of particle size. Likewise, when considering particle size, acicular (needle-shaped) precipitates >100 μm, such as phenytoin, were visible in the tubing. This is in line with the European Pharmacopeia's wider threshold that determines that 100 μm is the limit for detection by examination with the naked eye [10]. In addition, this corroborates with other scholars who found that a particle size of 100 μm was the minimum size for detection, providing better reliability and reproducibility [11]. However, the current study has shown that size was not the only parameter for visibility when under observation in the tubing. Some particles in acyclovir were longer than 100 μm; however, the particles were very soft and thin, and even though they also formed acicular crystals, this was not detected as being turbid.

Black and white backgrounds and light illumination will enhance visibility; thus, precipitates of 50 μm or larger can be detected, such as meropenem, acyclovir, ampicillin and furosemide. Although the Filter Manufacturers Council has established 40 μm as the visibility limit capable of being seen by the human eye, as cited by Knapp, their own work has suggested that particles larger than 80 μm can be detected by visual inspection [11]. Thus, this finding is in agreement with most opinions that state that the limits for visual detection are particles larger than 50 μm if using adequate lighting [7].

Phenytoin and acyclovir solution is a good example of a basic drug (pKa = 8.3 and pKa = 10.9), as it has very poor aqueous solubility that is readily precipitated by an acid drug or acid solution. Thus, precipitation occurred when it came into contact with a 5% glucose solution. As the precipitation is affected by solubility, the amount of precipitation depends upon the initial pH of medication and the pH of the solution for reconstitution [12]. Meanwhile, the duration before precipitation occurs depends on the length of time to when the solution creates supersaturation and induction to form the precipitates, with the latter influenced by retarded nucleation and crystal growth [13].

In comparing the three methods (visual with and no light also microscopy), this study demonstrates that optical microscopy is the most sensitive, able to detect more precipitation and incompatibility than the other approaches. Microscopy is the best choice for the qualitative observation of particles as, through microscopy, it is possible to identify size and shape; however, it is limited when it comes to calculating particle numbers [14].

5 Conclusion

This study sums that the naked eyed visual inspection observed 13,3% incompatibility. Visual inspection against black and white backgrounds and with light identified 20% incompatibility while optical microscopy detected 40% incompatibility.

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