약학박사 학위논문

재구성과 희석 과정 개선을 위한 정맥주사 정보 시스템의 평가

Evaluation of an intravenous preparation information system for improving the reconstitution and dilution process

2017년 2월

서울대학교 대학원

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지도교수 신 완 균

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ABSTRACT

Evaluation of an intravenous preparation information system for improving the reconstitution and dilution process

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Background: There are very few studies reporting the impact of providing intravenous (IV) preparation information on quality use of antimicrobials, particularly regarding their reconstitution and dilution. Therefore, to improve these processes in IV antimicrobial administration, an IV preparation information system (IPIS) was implemented in a hospital.

Objective: We aimed to evaluate the effect of improving reconstitution and dilution by implementing an IPIS in the electronic medical record (EMR) system.

Methods: Prescriptions and activity records of nurses for injectable antimicrobials requiring reconstitution and dilution for IV preparation from January 2008 to December 2013 were retrieved from EMR, and assessed the accuracy of reconstitution or dilution solutions based on the instructions provided by the package insert. We defined proper

reconstitution and dilution as occurring when the reconstitution and dilution solutions prescribed were consistent with the nurses' acting records. The types of intervention in the IPIS were as follows: a pop-up alert for proper reconstitution and passive guidance for proper dilution. We calculated the monthly proper reconstitution rate (PRR) and proper dilution rate (PDR) and evaluated the changes in these rates and trends using interrupted time series analyses.

Results: Prior to the initiation of the reconstitution alert and dilution information, the PRR and PDR were 12.7% and 46.1%, respectively. The reconstitution alert of the IPIS rapidly increased the PRR by 41% ($p < 0.001$), after which the PRR decreased by 0.9% ($p = 0.013$) per month after several months. However, there was no significant change in the rate or trend of the PDR during the study period.

Conclusions: This study demonstrated that the provision of reconstitution alerts by the IPIS contributed to improving the reconstitution process of IV antimicrobial injection administration. However, the sustainability of the impact was not evident. Furthermore, solutions to ensure the continuous effectiveness of alert systems are warranted and should be actively sought.

Keywords: Electronic medical record, Intravenous preparation information system, Interrupted time series analysis, Proper reconstitution rate, Proper dilution rate

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Proper reconstitution and dilution, which ensures the correct concentration and stability of intravenous (IV) drugs, is essential to optimizing the efficacy and safety of administered medications. However, the process of IV preparation of some medications for administration to patients is complex and error-prone [1-4]. Previous studies reported that IV preparation errors occurred in 20% from Germany [1] and 26% from two European countries [2]. In addition, reported dilution error was as high as 49% in Germany hospital wards [3].

In Korea, pharmacy departments of general hospitals do not dispense all IV drugs in the form of ready-to-use IV bags except for cytotoxic drugs and total parenteral nutrition mixtures. Instead, they have adopted a floor stock system for fluid distribution due to the shortage of pharmacists. Therefore, most injectable medications are distributed to wards in their original vials or ampules. While injectable drugs provided in solution form can be administrated to patients without reconstitution or dilution, injectable drugs provided in powder form should be either simply reconstituted or also diluted following reconstitution with fluids stocked in wards, prior to administering them to patients. Reconstitution is the process of changing a medication from powder form to an injectable, solution form, and dilution is the process of reducing the concentration of the reconstituted solution to a lower concentration that could be directly infused into patients. Errors resulting from the process of reconstitution or dilution can create stability problems such as inadequate dissolution and inactivation or precipitation of chemicals that might cause harm to patients, such as thrombus formulation and even death, in some cases [3, 5]. The provision of insufficient information to medical teams or lack of

knowledge of medication characteristics is a well-known source of medication errors [6-8].

Two previous studies reported that antimicrobials were the medications most prevalently associated with IV administration errors [9,10]. Many strategies have been implemented to promote quality use of antimicrobials [11]. In nurses' IV preparation processes, reconstitution and dilution errors were not negligible [12, 13]. Proper reconstitution and dilution, which ensures the correct concentration and stability could be one of such strategies and is critical to the efficacy and safety of treatment with injectable antimicrobial agents. Therefore, based on the decision of the Drug Committee of Seoul National University Hospital, an IV preparation information system (IPIS) for injectable antimicrobial prescriptions was implemented in the electronic medical record (EMR) system to promote the clear description of medication orders and reduce IV medication preparation errors in our tertiary teaching hospital.

There are numerous previous studies on the effects of clinical decision support systems or medication information provision [14-19]. However, the impacts of error prevention programs involving IV reconstitution and dilution, as well as the continuation of the intervention effect have not been investigated. Therefore, we aimed to evaluate the effect of improving reconstitution and dilution by implementing an IPIS in the EMR system.

METHODS

Setting and design

This study was conducted at a 1,500-bed tertiary care teaching hospital of the Seoul National University Hospital (SNUH). SNUH initiated the computerized physician order entry (CPOE) system requiring daily medication orders by physicians in 1999 and implemented a comprehensive EMR system in 2004. Since the EMR system was initiated, the doctors and nurses employed in SNUH have been educated on using the EMR system and the new functions for clinical decision support. To prevent IV preparation errors, the Drug Committee of the SNUH made the decision, to implement a directive requiring doctors to prescribe reconstitution and dilution solutions for injectable antimicrobial orders, to record the medical orders clearly, and to provide IV preparation information to doctors and nurses.

Based on this decision, pharmacists built a database of proper reconstitution and dilution solution instructions for injectable antimicrobial drugs, and an IPIS was implemented in the EMR system of the SNUH comprising reconstitution alerts and dilution information. However, the reconstitution alert and dilution information of the IPIS commenced sequentially in June 2010 and April 2011. Records of prescribed IV antimicrobials provided in powder form for adult patients from January 2008 to December 2013 were retrieved from the electronic records and reviewed by two pharmacists. They also reviewed the nurse's administration records. A retrospective interrupted time series design was applied in assessing whether the IPIS improved the reconstitution and dilution processes of IV antimicrobial administration.

Ethics statement

This study was approved by the Institutional Review Board of the Seoul National University Hospital (SNUH, H-1311-083-536, Republic of Korea). Because the study posed no more than minimal risk to the participants and involved no medical procedure, the review board agreed that written informed consent was not required. Patient records was anonymized and de-identified prior to analysis.

Implementation of the intravenous preparation information system

In June 2010, a pop-up information system for reconstitution solutions available at the point of injectable antimicrobial order entry was implemented in the EMR. For example, any medical doctor who prescribed amphotericin B injection would find pop-up-alert information conveying the pertinent message "Amphotericin-B is a powdered injection that requires reconstitution prior to administration. Would you like to prescribe 'water for injection, 20 mL' for reconstitution?" (Fig. 1).

The physicians in SNUH could accept or ignore the alert message. If the alert message was accepted, the suggested reconstitution solution was prescribed automatically. Otherwise, the doctors did not order the reconstitution solution, and nurses reconstituted the IV antimicrobial with a solution stocked in the floor according to IV preparation manual in the ward.

From April 2011, e-formulary containing dilution information that could be viewed easily in the EMR system by nurses, as well as doctors, was provided. Physicians and nurses in the SNUH could access some information regarding the prescribed drug in the e-formulary in the EMR by right-clicking the mouse on the prescription medical record. In addition, if they clicked the menu bar button and 'formulary' button in the EMR, they could see the e-formulary and search for the drug information (Fig. 2).

Dilution information is displayed as "Administer intravenously after reconstituting with water for injection and further diluting in 5% dextrose solution." (Fig. 2). The information for reconstitution was provided by a pop-up alert, while the dilution information was of a passive guidance type in this IPIS.

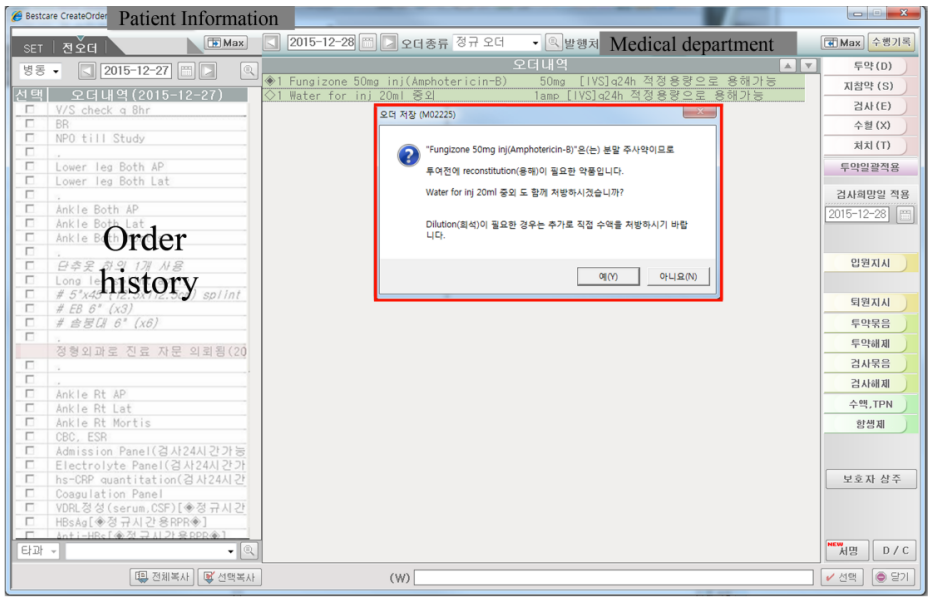

Fig. 1 – Example of the screen capture, which contains the reconstitution alert

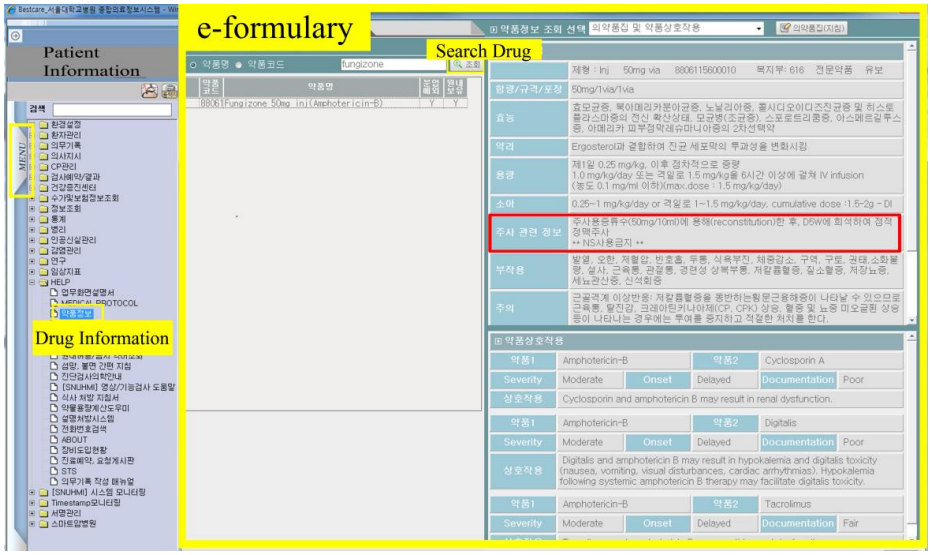

Fig. 2 – Example of the screen capture, which contains the e-formulary

Definition of parameters determined

In this study, we included injectable antimicrobials that required reconstitution and dilution before administration (Table 1).

We classified these agents into two groups according to the required reconstitution solution. The P1 group involved the powdered form of the antimicrobials, which was reconstituted in saline solution to the final dilution. For example, if a physician selects 'ceftazidime' from the P1 group and 'normal saline 100ml' for dilution purposes, it would be possible to reconstitute ceftazidime with 10 ml solution from 100 mL of normal saline and then dilute the reconstituted solution with same saline. However, the P2 groups consisted of antimicrobials requiring only water for reconstitution into the injected form; therefore, it was necessary to prescribe separate solutions for reconstitution and dilution. In case of 'amphotericin B' of the P2 group, the antimicrobial must be diluted with saline only after being reconstituted with water for injection.

We classified the physicians into surgery and non-surgery groups. In addition, we defined the period before the provision of reconstitution alerts as the baseline period (January 2008–May 2010). The period between the commencement of reconstitution alerts and initiation of dilution information was defined as the IPIS reconstitution set (IPIS_R) period (June 2010–March 2011). The IPIS reconstitution and dilution set (IPIS_RD) period was the time between the commencement dilution information provision and the last month of the study period (April 2011–December 2013).

Due to the daily-order system, physicians should prescribe the same antimicrobial used for more than one day during the required period repeatedly. Thus, we classified the initial and repeated prescriptions as the first and second

or subsequent prescriptions, respectively, while a given patient was in the hospital.

Table 1 – Summary of reconstitution and dilution information on packaging label of injectable antimicrobials.

The injectable antimicrobials were selected from the Seoul National University Hospital (SNUH) formulary[a].

Group	Antimicrobials	Reconstitution solution[b]	Dilution solution[c]	Contraindicated solutions
P1[d]	Ampicillin	NS	D5W, NS	
	Ampicillin/sulbactam	NS, WFI	D5W, NS, HS	
	Ceftazidime	NS	D5W, NS, D10W, DS, HS	
	Cefepime	NS, WFI	D5W, NS, D10W, DS, HS	
	Cefmetazole	NS, WFI	D5W, NS, D10W, DS, HS	
	Caspofungin	NS, WFI	NS, NSH, HS	D5W
	Cefotetan	NS, WFI	D5W, NS, D10W, DS, NSH, HS	
	Ceftezole	NS, WFI	D5W, NS	
	Ceftizoxime	NS, WFI	D5W, NS, D10W, DS, NSH, HS	
	Cefazolin	NS, WFI	D5W, NS	
	Ertapenem	NS, WFI	NS	D5W, D10W
	Flomoxef	NS, WFI	D5W, NS	
	Imipenem, cilastatin	NS	NS	HS
	Meropenem	NS	D5W, NS	
	Penicillin G	NS	D5W, NS	

P2[e]	Amphotericin B	WFI	D5W	NS
	Amphotericin B liposomal	WFI	D5W, D10W	NS
	Azithromycin	WFI	D5W, NS, DS, NSH, NAK	
	Colistimethate	WFI	D5W, NS, DS, NSH, HS	
	Cefuroxime	WFI	D5W, NS, D10W, DS, HS	
	Ceftriaxone	WFI	D5W, NS, D10W, DS, NSH, HES	HS
	Cefotaxime	WFI	D5W, NS	
	Cefoxitin	WFI	D5W, NS, D10W, DS	
	Erythromycin	WFI	NS, HS	D5W
	Piperacillin	WFI	D5W, NS	
	Vancomycin	WFI	D5W, NS	
	Voriconazole	WFI	D5W, NS, DS, NSH	

[a]Seoul National University Hospital Formulary 2008 Edition

NS, normal saline (0.9% NaCl solution); WFI, water for injection; D5W, 5% dextrose solution; HS, Hartmann's solution (Linger's solution); D10W, 10% dextrose solution; DS, 5% dextrose and 0.9% NaCl solution; NSH, 0.45% NaCl solution; NAK, NaCl, KCl in dextrose solution; HES, hydroxyethyl starch in normal saline.

[b]Injectable solution for use in the process of changing from the powdered form of the injected drug to the solution form

[c]Injectable solution for use in the process of changing from the reconstituted injected drug to low-concentration injected drug

[d]Antimicrobials requiring saline solution for reconstitution

[e]Antimicrobials requiring only water for injection for reconstitution

Proper reconstitution and dilution of intravenous antimicrobials

Prescriptions and nurses' activity records for injectable antimicrobials that required reconstitution and dilution for IV preparation were assessed for correctness based on the contents of packaging labels authorized by the Korean Ministry of Food and Drug Safety. The injectable antimicrobial prescription was regarded as properly reconstituted if the solution was used in agreement with what was specified on the packaging label, was prescribed at the same time with the antimicrobial, and if the activity record of the nurses adhered to the prescription. Furthermore, a dilution was determined as proper if the dilution solution was prescribed in accordance with the packaging label specifications for diluting the injectable antimicrobial drug. We calculated the monthly proper reconstitution rate (PRR) and proper dilution rate (PDR) as the percentage of proper prescription divided by total IV antimicrobial prescriptions.

Data analysis

First, we used descriptive statistics to summarize the PRR and PDR of each period (baseline, IPIS_R, and IPIS_RD). Because the provision of reconstitution alerts and dilution information occurred in the middle of the month, the data for that month were censored in the statistical analysis. A chi-squared test was used to compare the PRR and PDR of each subgroup (P1 versus [vs.] P2, non-surgery vs. surgery, and initial vs. repeated) in each period. Furthermore, we used a segmented regression model to evaluate the changes in level and trends of PRR and PDR caused by providing either reconstitution alerts or dilution information. The following equation was used for the segmented regression model:

$$Y_t = \beta_0 + \beta_1 * Time\_baseline + \beta_2 * reconstitution\_alert + \beta_3 * Time\_IPIS\_R + \beta_4 * dilution\_information + \beta_5 * Time\_IPIS\_RD + \varepsilon$$

where, Y_t is PRR or PDR per month and $Time\_baseline$ indicates the number of months as a continuous variable from the start of the study period (1–72). The $reconstitution\_alert$ is the dummy variable (0 and 1) representing the number of months before and after the reconstitution alert (January 2008–May 2010 and July 2010–December 2013, respectively). $Time\_IPIS\_R$ is a continuous variable indicating the number of months after alerting reconstitution and is at 0 before alerting reconstitution. $Dilution\_information$ is a dummy variable that is at 0 and 1 for the months before and after the provision of dilution information, respectively (January

2008–March 2011 and May 2011–December 2013, respectively). $Time\_IPIS\_RD$ is a continuous variable indicating the number of months after the provision of dilution information and is at 0 before the provision of dilution information. The coefficient B_0 estimates the base level of the proper rate at the point of study commencement, B_1 estimates the trend of proper rate in baseline period, B_2 estimates the change in proper rate right after the provision of reconstitution alerts, B_3 estimates the trend of proper rate during IPIS_R period, B_4 estimates the change in proper rate right after providing dilution information, B_5 estimates the trend of proper rate in IPIS_RD period, and ε estimates the random error.

We used the Durbin–Watson test to examine the presence of autocorrelation among the monthly PRRs and PDRs. When statistically significant autocorrelation was detected, we used a stepwise autoregression to select the order of the autoregressive error model. In the final models, the Durbin–Watson statistic was close to the preferred value of 2, indicating that no serious autocorrelation remained. The Q statistics test and Lagrange Multiplier test were used to test for heteroskedasticity and the statistics were not significant in final models. In addition, the PRRs were analyzed in detail based on the antimicrobial group, medical department, and initial or repeated prescription.

We estimated the absolute differences of PRRs with reconstitution alerts and PRRs without reconstitution alerts at the midpoint of the IPIS_R period, as well as the absolute difference of PRRs with dilution information and PRRs without dilution information at the midpoint of the IPIS_RD period, using a segmented

regression model. The midpoints of the IPIS_R and IPIS_RD periods were November 2010 and August 2012, respectively. The 95% confidence intervals of the absolute differences were calculated according to the method of Zhang et al. [20]. The analyses were performed using the statistical package for the social sciences (SPSS) version 22.0 (IBM Corp., Armonk, NY, USA) and statistical analysis software (SAS) version 9.4 (SAS Institute, Cary, NC, USA), and p-values ≤ 0.05 were considered statistically significant.

RESULTS

A total of 887,303 cases of injectable antimicrobial prescriptions were analyzed from January 2008 to December 2013. At the baseline, IPIS_R, and IPIS_RD periods, the PRRs were 12.7, 54.5, and 37.7%, respectively (Table 2).

All of the prescriptions identified as being prepared with improper reconstitutions were due to absence of the reconstitution solution. Therefore, 87.3, 45.5, and 62.3% of reconstitutions during the baseline, IPIS_R, and IPIS_RD periods were disregarded by physicians. The proportions of prescriptions with an incorrect dilution solution were 28.6, 24.7, and 18.4%, and those of prescriptions without dilution solution were 25.3, 28.3, and 29.1% at the baseline, IPIS_R, and IPIS_RD periods, respectively. There was no serious autocorrelation among the monthly PRRs and PDRs, as the Durbin–Watson statistic was close to the preferred value of 2.

The subgroup analysis for each period revealed significant differences between each subgroup (P1 vs. P2, non-surgery vs. surgery, and initial vs. repeated, Table 2). At the baseline period, the PRRs were higher for the P1, non-surgery, and repeated prescription groups than they were for the P2, surgery department, and initial prescription groups, respectively. During the IPIS_R and IPIS_RD periods, the PRRs were higher in the P1 and non-surgery groups than they were in the P2 and surgery department groups, respectively. However, the PRRs of the initial prescription were higher than those of repeated prescription were. The PDRs at the baseline, IPIS_R, and IPIS_RD periods were higher in the P2, non-surgery, and repeated groups than they were in the P1, surgery department, and initial prescription groups, respectively. The overall monthly PRR increased immediately after the alerting reconstitution

and decreased after several months while the overall monthly PDR appeared not to change (Fig. 3).

Table 2 – Number of reviewed medical records, proper reconstitution rate (PRR), and proper dilution rate (PDR) in each period of this study.

Period		Overall	Antimicrobial group		Medical department		Initial or Repeated	
			P1 group[a]	P2 group[b]	Non-surgery	Surgery	Initial[c]	Repeated[d]
Baseline[1]	Medical records (n)	352,100	188,701	163,399	158,975	193,125	83,909	268,191
	PRR (%)	12.7	23.2	0.6	21.2	5.7	8.1	14.1
	p-value		**<0.001**		**<0.001**		**<0.001**	
	PDR (%)	46.1	43.2	49.5	60.9	34.0	39.1	48.3
	p-value		**<0.001**		**<0.001**		**<0.001**	
IPIS_R[2]	Jun 2010							
	Medical records (n)	12,631	6,748	5,883	5,503	7,128	3,212	9,419
	Jul 2010–Mar 2011							
	Medical records (n)	117,507	62,738	54,769	52,747	64,760	31,303	86,204
	PRR (%)	54.5	60.6	49.8	58.1	51.6	64.4	50.9
	p-value		**<0.001**		**<0.001**		**<0.001**	
	PDR (%)	47.0	43.7	50.9	66.3	31.3	38.9	49.9
	p-value		**<0.001**		**<0.001**		**<0.001**	

IPIS_RD[3]	Apr 2011								
	Medical	records (n)	13,409	7,191	6,218	6,195	7,214	3,630	9,779
	May 2011–Dec 2013								
	Medical	records (n)	391,656	210,878	180,778	167,418	224,238	113,542	278,114
	PRR (%)		37.7	47.9	26.7	40.6	36.3	49.4	33.6
	p-value			**<0.001**		**<0.001**		**<0.001**	
	PDR (%)		52.5	43.9	62.4	76.7	33.6	41.3	57.0
	p-value			**<0.001**		**<0.001**		**<0.001**	

n, Numbers

Bold texts indicate p-values less than 0.05.

[a]Antimicrobials requiring saline solution for reconstitution.

[b]Antimicrobials requiring only water for injection for reconstitution.

[c]Intravenous (IV) antimicrobials prescribed for the first time while a patient was in the hospital.

[d]Second and subsequent IV antimicrobial prescriptions following the first prescription.

[1]Baseline period, January 2008–May 2010.

[2]IPIS_R period, June 2010–March 2011, data from June 2010 was censored.

[3]IPIS_RD period, April 2011–December 2013, data from April 2011 was censored.

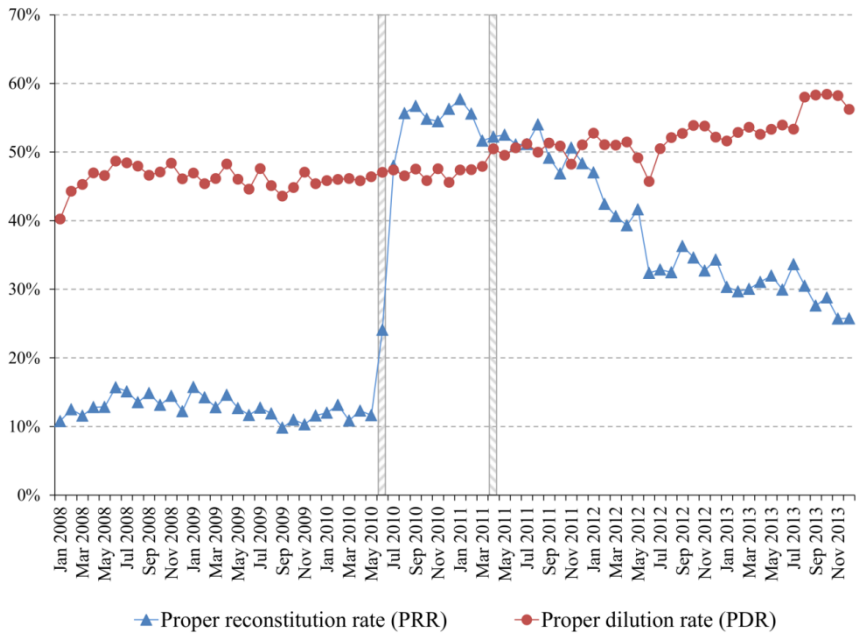

Fig. 3 – Overall monthly rates of proper reconstitution and dilution, 2008–2013. Intervention points were in June 2010 (reconstitution alert) and April 2011 (dilution information) in this study.

Interrupted time series analysis

Interrupted time series analysis showed an increasing change (41.0%, $p < 0.001$) in the overall PRR immediately after the reconstitution alert and a decreasing trend (-0.9%, $p = 0.013$) in the overall PRR during IPIS_RD period (Fig. 3, Table 3).

During the baseline period, the PRR of surgery department group decreased by 0.15% ($p = 0.011$), while no trend was observed in the overall PRR. Immediately after the provision of reconstitution alerts, the PRRs increased rapidly in the P1, P2, non-surgery department, surgery department, initial prescription, repeated prescription groups by 36.1, 45.7, 32.9, 45.3, 54.9, and 35.0%, respectively ($p < 0.001$ each). During the IPIS_R period, the overall PRR showed no significant trend. The subgroup analysis showed a monthly increasing trend of 0.74% ($p = 0.035$) only in the surgery department.

Immediately after the provision of the dilution information, there was no significant change in the overall PRR but the PRRs declined by 6.8% ($p = 0.024$) in the P2 group and 4.7% ($p = 0.03$) in the surgery department.

During the IPIS_RD period, the overall PRR decreased by 0.9% per month ($p = 0.013$). There were monthly declining PPR trends in the P2, non-surgery department, surgery department, initial prescription, and repeated prescription groups of 1.5, 1.2, 1.4, 1.4, and 1.1%, respectively ($p = 0.002$, 0.046, 0.001, 0.001, and 0.03, respectively, Table 3). Table 4 shows estimates of the PRR from the segmented regression analyses, January 2008–December 2013.

We estimated that the PRR following the commencement of reconstitution alerts was higher by 41.2% (37.1–45.4%) than it was before reconstitution

alerts at the midpoint of the IPIS_R period (Table 4). At the midpoint of the IPIS_RD period, the PRR following the provision of dilution information was estimated to be lower by 17.4% (2.6–32.1%) than it was before the provision of dilution information. The overall PDR showed no significant change during the study period (Table 5).

Each antimicrobial group showed a trend similar to that of the overall antimicrobial group result. The non-surgery department showed increasing monthly trends of 0.11 and 0.9% ($p = 0.03$ and 0.013, respectively) during the baseline and IPIS_R periods, respectively. The PDRs for both the initial and repeated prescriptions were similar to that of overall prescriptions.

Table 3 – Segmented regression analysis of proper reconstitution rate (PRR) from 2008–2013.

Variable	Proper reconstitution rate	Antimicrobial group		Department		Initial or Repeated	
		P1 group[a]	P2 group[b]	Non-surgery	Surgery	Initial[c]	Repeated[d]
β_0[1]	12.7	24.7	0.7	19.6	7.9	9.0	14.4
p-value	**<0.001**	**<0.001**	0.72	**<0.001**	**<0.001**	**<0.001**	**<0.001**
β_1[2]	0.00	-0.11	-0.01	0.12	-0.15	-0.05	-0.02
p-value	0.984	0.248	0.963	0.381	**0.011**	0.435	0.851
β_2[3]	41.0	36.1	45.7	32.9	45.3	54.9	35.0
p-value	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
β_3[4]	0.06	0.27	0.47	0.02	0.74	0.41	0.24
p-value	0.875	0.591	0.331	0.970	**0.035**	0.270	0.636
β_4[5]	-2.3	0.4	-6.8	-1.0	-4.7	-0.1	-3.2
p-value	0.342	0.892	**0.024**	0.789	**0.030**	0.973	0.287
β_5[6]	-0.9	-0.9	-1.5	-1.2	-1.4	-1.4	-1.1
p-value	**0.013**	0.077	**0.002**	**0.046**	**<0.001**	**0.001**	**0.030**

Bold texts indicate p-values less than 0.05.

[a]Antimicrobials requiring saline solution for reconstitution.

[b]Antimicrobials requiring only water for injection for reconstitution.

[c]Intravenous (IV) antimicrobial prescription prescribed for the first time while a patient was in the hospital.

[d]Second and subsequent IV antimicrobial prescriptions following first prescription.

[1]Base level of proper rate at the point of study commencement.

[2]Trend of proper rate at baseline period.

[3]Change of proper rate immediately after provision of reconstitution alert.

[4]Trend of proper rate during IPIS_reconstitution set (IPIS_R) period

[5]Change of proper rate immediately after provision of dilution information.

[6]Trend of proper rate during IPIS_reconstitution and dilution set (IPIS_RD) period

Table 4 – Comparison of estimations with and without provision of intravenous preparation information system (IPIS) for each period.

	Estimated absolute difference at midpoint of IPIS_R period (95% CI)*		Estimated absolute difference at midpoint of IPIS_RD period (95% CI)†	
Proper reconstitution rate	41.2	(37.1 to 45.4)	-17.4	(-32.1 to -2.6)
Antimicrobial group				
P1 group[a]	37.4	(32.6 to 42.2)	-13.7	(-33.7 to 6.3)
P2 group[b]	48.1	(42.8 to 53.4)	-31.1	(-49.7 to -12.5)
Medical department				
Non-surgery	33.1	(26.1 to 40.0)	-19.8	(-42.2 to -2.6)
Surgery	49.0	(46.0 to 52.0)	-27.4	(-41.4 to -13.3)
Initial or Repeated				
Initial[c]	56.9	(53.4 to 60.5)	-35.3	(-57.4 to -13.3)
Repeated[d]	36.1	(30.7 to 41.5)	-31.7	(-60.5 to -2.9)

[a]Antimicrobials requiring saline solution for reconstitution.

[b]Antimicrobials requiring only water for injection for reconstitution.

[c]Intravenous (IV) antimicrobials prescribed for the first time while a patient was in the hospital.

[d]Second and subsequent IV antimicrobial prescriptions following first prescription.

*Absolute difference in estimated proper reconstitution rate (PRR) with and without reconstitution alerts at month 35 (November 2010).

†Absolute difference in estimated proper reconstitution rate (PRR) with and without dilution information at month 56 (August 2012)

Table 5 – Segmented regression analysis of proper dilution rate (PDR) from 2008–2013.

Variable	Proper dilution rate	Antimicrobial group		Department		Initial or Repeated	
		P1 group[a]	P2 group[b]	Non-surgery	Surgery	Initial[c]	Repeated[d]
β_0[1]	46.2	42.0	49.8	59.4	35.1	39.3	48.3
p-value	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
β_1[2]	0.00	0.06	-0.02	0.11	-0.07	-0.01	0.00
p-value	0.923	0.495	0.474	**0.030**	0.151	0.852	0.934
β_2[3]	0.3	0.5	0.1	-0.8	-1.0	1.3	-0.3
p-value	0.869	0.858	0.951	0.713	0.610	0.382	0.867
β_3[4]	0.2	-0.2	0.4	0.9	-0.1	-0.2	0.4
p-value	0.538	0.602	0.123	**0.013**	0.762	0.276	0.158
β_4[5]	0.40	-0.01	2.46	-2.51	1.08	0.69	-0.09
p-value	0.830	0.996	0.134	0.242	0.579	0.645	0.963
β_5[6]	0.05	0.23	0.01	-0.49	0.31	0.41	-0.16
p-value	0.872	0.588	0.967	0.158	0.312	0.068	0.603

Bold texts indicate p-values less than 0.05.

[a]Antimicrobials requiring saline solution for reconstitution.

[b]Antimicrobials requiring only water for injection for reconstitution.

[c]Intravenous (IV) antimicrobial prescription prescribed for the first time while a patient was in the hospital.

[d]Second and subsequent IV antimicrobial prescriptions following first prescription.

[1]Base level of proper rate at the point of study commencement.

[2]Trend of proper rate at baseline period.

[3]Change of proper rate immediately after provision of reconstitution alert.

[4]Trend of proper rate during IPIS_reconstitution set (IPIS_R) period

[5]Change of proper rate immediately after provision of dilution information.

[6]Trend of proper rate during IPIS_reconstitution and dilution set (IPIS_RD) period.

DISCUSSION

To the best of our knowledge, this is the first report evaluating the effects of incorporating an injectable antimicrobials preparation information system on an EMR. The verification of appropriate solution for IV admixture and preparation of IV drugs by centralized IV admixture services in pharmacy departments ensure the safety and stability of IV drugs and contribute to the quality use of IV antimicrobials [21, 22]. However, for a hospital that is unable to adopt the centralized preparation of IV drugs because of a lack of pharmacists, information systems such as the IPIS used in this study could be a strategy for improving IV preparations [12, 13, 22-25]. We found that implementing the IPIS in the setting of our study encouraged medical doctors to specify the reconstitution solution clearly, and the PRR increased over several months.

Potential intravenous preparation error

The observed low PRRs and PDRs during the overall study period might be interpreted to mean that significant IV preparation errors potentially occurred. The proportions of prescriptions with an incorrect dilution solution, which were 28.6, 24.7, and 18.4% at the baseline, IPIS_R, and IPIS_RD periods, respectively, could be regarded as IV preparation errors that reached patients. Because 87.3, 45.5, and 62.3% of reconstitutions were disregarded by physicians in the baseline, IPIS_R, and IPIS_RD periods, the reconstitution choice of IV antimicrobials must have been made by nurses. In cases where IV antimicrobial prescriptions were administered without orders for reconstitution and dilution, nurses had to select the reconstitution and dilution solution. In such cases, double-checking of the selected reconstitution and dilution solution was not feasible, and the risk of errors in IV preparation process would increase. Even though patients could have received IV antimicrobials correctly reconstituted and diluted based on the nurses' choices in the ward, we could not confirm that proper reconstitution and dilution occurred. The dilution errors might be higher than 28.6, 24.7, and 18.4% in baseline, IPIS_R, and IPIS_RD periods, respectively, and those error rates might be similar or even higher than IV preparation errors reported in other studies (20, 26, and 49%, respectively) [1-3]. Because of the design of this retrospective study, we could not determine whether nurses selected the correct reconstitution and dilution solutions without a physician's order.

The findings by McDowell et al. showed that removing the reconstitution step by pre-preparation, such as with ready-to-use solution, reduced the overall IV error rate from 73% to 17%, which implied that the reconstitution step is

error-prone [4]. Although the IPIS system was implemented to reduce potential errors from reconstitution and dilution process, the overall PRR and PDR during the IPIS_RD period were 37.7 and 52.5%, respectively. The low PRRs and PDRs found in this study resulted largely from omitting reconstitution or dilution solution prescriptions by physicians' low level of concern regarding the reconstitution and dilution, the nurses may have selected the solutions themselves prior to IV administration to patients. Therefore, not clarifying the reconstitution or dilution solutions required in medication orders might result in some, if not all, IV preparation error [26].

There were large differences in the PRRs between P1 and P2 groups (23.1% and 0.6% at the baseline period). Furthermore, the PRRs of the P2 group increased rapidly immediately after the reconstitution alert, decreased rapidly following the dilution information provision, and remained lower than those of the P1 group. The complexity and need for prescribing another solution might have led to this large difference in PRRs. We confirmed that when the injection-preparation procedure is more complex, potential intravenous errors might increase [4, 13].

Impact of implementing the intravenous preparation information system

In this study, the overall PRR during the baseline period showed no trend and after implementing the reconstitution alert in the IPIS, the overall PRR increased rapidly. In every subgroup, there was a similar effect on the overall PRR immediately after reconstitution alert provision.

Our data suggest that using the CPOE system would positively influence the process of medication [15]. However, there are previous reports that the CPOE system could actually enhance medication error [21, 27, 28]. In this study, the reconstitution alert and dilution information of the IPIS were provided sequentially. In this regard, we considered the possibility of dilution errors resulting from doctor's initial confusion, owing to the unfamiliar reconstitution alerts in this study. Therefore, we performed the analysis over three periods (i.e., baseline, IPIS_R, and IPIS_RD periods). However, we found that there was no change or trend in the overall PDR following the provision of reconstitution alerts by incorporating IPIS in the EMR. Rather, there was an increasing trend in the PDR of the non-surgery group during the IPIS_R period. From that point, we speculated that the reconstitution alert of the IPIS improved the PRR, as suggested by the lack of evidence of a decrease in the PDR of injectable antimicrobial prescriptions in the EMR.

The provision of clear IV preparation information is essential for the correct preparation of IV medications by doctors and nurses [12, 25, 29, 30]. The guidelines for reconstitution and dilution can be distributed to the wards to prevent IV preparation error [12]. However, in this study, we found that the provision of dilution information through the e-formulary did not improve the PDR. There was no alert system to ensure proper dilution, and only passive

information was provided. Although problems in understanding the directions or disagreement among users might arise, we suggest that the lack of improvement in the PDR indicates that the doctors did not refer to the dilution information. To improve the dissemination of IV preparation information to the medical team, a more efficient system may be required [31].

Adherence to alerts or information

Two previous studies suggested the need for further investigation of the methods of supplying information to medical teams [32, 33]. This present study revealed that the alert type of reconstitution information was more effective than passive guidance type of dilution information was. These finding confirmed the results of a previous study showing that active alerts provided at the time of prescription were more effective than passive alerts were [34]. This prompted us to reconsider the type of information that should be provided to the medical team to implement the best strategy for improving IV microbial prescription quality in the EMR.

There are situations where doctors tend to override alerts in the clinical decision support system [35-38]. Repetitive alerts tend to be ignored to a higher degree [36]. In this study, the adherence of doctors to repetitive alerts of intra- and inter-patient prescription requirements appeared low. The PRR of repeated prescriptions, which was higher than that of initial prescriptions during the baseline period, became lower during the IPIS_R and IPIS_RD periods. Based on this observation, the findings that doctors might adhere less to daily repetitive alerts than they do to the initial alerts for patients was consistent to previous study [36].

In this study, a transient increase in the PRR was observed immediately after the reconstitution alert of the IPIS was initiated and then decreased. This suggests that the adherence of doctors to repetitive inter-patient alerts was low. As PDR did not change in all periods, we suggest that the decreased PRR would be resulted from the low adherence of physicians to repetitive alerts several months after being provided the reconstitution alert, rather than from being

provided dilution information. However, we cannot explain the exact reason why the PRR seemed to stabilize after May 2012, unless this phenomenon reflects an equilibrium between overriding and complying with the reconstitution alert. From the perspective of ensuring safe and qualitative medication prescription, it would be important for physicians not to ignore alerts or information provided at the prescription stage [39]. In the surgery group, the trend of PRRs in the IPIS_R period and the level of PRRs immediately after providing dilution information significantly changed, in contrast to the findings with the non-surgery group. We suggest that the physicians of the surgery department reacted to the alert more positively and rapidly and then ignored the alert in EMR [40-42]. However, more studies to determine the reasons underlying these differences are required.

In this study, we could not identify the reasons accounting for the low adherence of physicians through surveillance. However, we speculated that the doctors might have assumed that reconstitution solutions for IV preparation have a low impact on the clinical outcomes of the patients and, therefore, ignored the repeated alerts in the EMR [36, 40-44].

After implementing the new system, it is critical for users or providers to monitor the impact of the system and if necessary, improve the alert contents [43, 45-47]. This study confirmed that system optimization would be required and can be achieved by monitoring the impact of alerts or information provision in medical institutions. Adopting an electronic medication administration record (eMAR) system embedded with IPIS could be an alternative approach. Furthermore, seeking and implementing strategies to ensure the continuous positive effect of alert systems is warranted.

Study limitation

The current study has several limitations. First, we studied the impacts of an IV preparation information system (IPIS), which was implemented as a homegrown system only in a single hospital. Therefore, our findings need to be confirmed in multiple hospital settings, to enable generalization, and more studies of IPISs are needed. In most countries where IV preparation errors were reported, ready-to-use IV bags, eMARs, and smart pumps with bar codes are not in common use yet [12, 13, 22-25, 48-54]. However, these systems will likely be implemented in the future. Until then, an IPIS implemented in a prescribing system could help reduce IV administration errors. The results of this study can still serve as a reference for the development and implementation of an IPIS because there are no similar previous reports on this system.

Second, rather than observing the IV medication processes [1-3, 12, 13], this study analyzed proper reconstitution and dilution by reviewing medical records of doctor's prescription and nurse's activity record and did not monitor the actual reconstitutions and dilutions of injectable antimicrobials administered to patients. When nurses administered the IV antimicrobials provided in powder form, which were prescribed without reconstitution and dilution orders, they likely prepared them with solution of choice, without double-checking. Therefore, the low PRR and PDR cannot be directly interpreted to reflect a confirmed high rate of administration error, but rather can be interpreted as being associated with an increased risk administration error. Because the nurses' activity records did not contain any information regarding un-prescribed reconstitution or dilution solutions, we could find no discrepancy between the nurses' records and the physicians' prescriptions regarding reconstitution and

dilution. In addition, it is possible that the nurses' may have kept incomplete records regarding improper reconstitution and dilution procedures occurring during this study [55, 56]. Furthermore, we could not evaluate the clinical conditions and outcome for patients and could only assess potential errors. However, reconstituting antimicrobials with an improper solution would result in discarding the mixed solution, leading to monetary loss. In addition, under an extreme scenario, crystals from a wrong mixing solution may result in thrombus formulation if infused directly into patients. Thus, efforts to improve the quality of IV preparations should be continued.

Third, although we used a database spanning 6 years, the duration of the IPIS_R period after providing the reconstitution alert and before providing the dilution information could be considered insufficient. A general recommendation is 12 data points before and after the intervention for conducting segmented regression analysis [57]. To assess the impact of both interventions including alerting reconstitution and providing drug information, we divided the periods before and after the individual intervention. Further studies involving the determination of the outcome using shorter time intervals may be necessary to confirm our present results.

Fourth, although we observed a declining trend in the PRR using the interrupted time series analysis, we could not predict what the last PRR and PDR would be in the end or the cause of the declining of PRR.

CONCLUSION

This study demonstrated the existence of substantial errors in the IV preparation process and, therefore, we concluded that the reconstitution alert using the IPIS in the EMR system was effective in improving the PRR of IV antimicrobials. However, after several months the effect was observed to decline monthly. In contrast, providing passive information on dilution using the IPIS had no apparent impact and did not facilitate the achievement of a proper dilution rate. Therefore, we suggest that IPIS in the EMR system requires monitoring and additional strategies should be sought to ensure the continuous positive impact of the alerting system with an improvement in IV antimicrobial drug reconstitution.

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국 문 초 록

배경 : 정맥주사 준비 중에서, 특히 재구성과 희석의 정보를 제공함으로 인한 정맥주사 항균제의 질적 사용을 보고한 연구는 거의 없었다. 한 병원에서, 정맥주사 항균제 투여의 재구성과 희석 과정을 개선하기 위해 정맥주사준비 정보 시스템(IPIS)이 적용되었다.

목적 : 전자의무기록 시스템 내에서 정맥주사 정보 제공 시스템의 적용으로 인한 재구성과 희석의 개선에 효과를 평가하고자 하였다.

방법 : 2008년 1월부터 2013년 12월까지의 전자의무기록에서 재구성과 희석 후에 정맥주사 투여를 해야 하는 항균제의 처방과 그에 대한 간호사 수행기록을 수집하여, 주사용 항균제의 재구성과 희석의 허가 정보를 기준으로 평가했다. 재구성과 희석 용액의 처방이 되었고 간호사의 수행기록과 일치된 경우를 적절한 재구성과 희석으로 정했다. IPIS 에서의 중재의 형태로는 재구성은 팝업 경고, 희석은 수동적인 안내였다. 월별로 적절한 재구성률과 적절한 희석률을 계산했고, 단절적 시계열 분석을 통해서 이 비율들의 변화와 경향을 평가했다.

결과 : 재구성 경고와 희석 정보 제공 이전의 적절한 재구성률과 희석률은 12.7 과 46.1% 였다. 정맥주사준비 정보 시스템의 재구성 경고로 인해 적절한 재구성률은 41% ($p < 0.001$) 상승했고, 수개월 후에 매월 0.9%씩 ($p = 0.013$) 감소했다. 그런데, 연구기간 동안 적절한 희석률에는 유의한 변화도 없었고 추이 변화도 없었다.

결론 : IPIS 의 재구성에 대한 경고로 인해 정맥주사 항균제 투여의 재구성 과정이 개선되었다. 그런데, 그 효과는 지속되지

않았다. 이 연구에서는 경고성 정보 제공 효과를 확인할 수 있었고, 지속적인 유지 방법을 적극적으로 모색해야 할 것이다.

주요어 : 재구성, 희석, 정맥주사 준비, 전자의무기록, 정맥주사준비 정보 시스템(IPIS), 단절적 시계열 분석, 적절한 재구성률(PRR), 적절한 희석률(PDR)

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