Effectiveness of pharmaceutical care in an intensive care unit from China

A pre- and post-intervention study

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ABSTRACT

الأهداف: وصف مدى تطور وتطبيق خدمات الرعاية الصيدلية بين المرضى، بالإضافة إلى تقييم فعالية تدخل الصيادلة السريريين.

الطريقة: أُجريت هذه الدراسة في مركز واحد وعلى مرحلتين (قبل وبعد مرحلة التدخل)، وحدة العناية المركزة، مستشفى تابع للجامعة، الصين. لقد تلقى المرضى في مرحلة ما بعد التدخل (مارس 2011م إلى يونيو 2011م) رعاية صيدلية من قبل صيدلي سريري، فيما تلقى المرضى في مرحلة ما قبل التدخل (ديسمبر 2010م إلى مارس 2011م) رعاية طبية روتينية. وعلى ضوء ذلك قمنا بعمل مقارنة بين مرحلة ما بعد التدخل ومرحلة ما قبل التدخل من أجل تقييم نتائج التدخل الصيدلي.

النتائج: لقد قام الصيدلي السريري بعمل 232 تدخل صيدلي لحوالي 416 مريض أُدخل إلى وحدة العناية المركزة وذلك خلال 3 أشهر. لقد تم قبول 202 مريض (87.1%) من قبل الطبيب أو الممرض، في حين كان تعديل الجرعة (العدد: 83، 35.8%) هو أكثر أنواع التدخل الصيدلي السريري انتشاراً. لقد نقصت نسبة الأخطاء في صرف الأدوية لكل مريض في المجموعة التي تلقت تدخلاً صيدلياً من 1.68 إلى 0.46 (p<0.001). وقد تحسنت الأخطاء في صرف الأدوية والمتعلقة بكل من: مقدار الجرعة الغير صحيحة أو الفواصل الزمنية بين الجرعات بشكل واضح (نقصت من 0.87إلى 0.14) (p<0.001). كما قلت تكلفة صرف الأدوية لكل مريض في اليوم من 347.43 إلى 307.36 دولار أمريكي (p=0.095). بالمقابل فإن طول فترة البقاء في وحدة العناية المركزة لم تتغير بصورة واضحة من الناحية الإحصائية (6.14 مقابل 5.93 يوم)(p=0.14).

خاتمة: أظهرت الدراسة بأن تدخل الصيدلي السريري قد أدى إلى تقليل واضح من الناحية الإحصائية في نسبة الأخطاء الطبية، كما يمكن أن يكون له تأثير على حفظ المبالغ المصروفة على الأدوية، بالمقابل لم يكن له تأثير واضح على تقليل مدة البقاء في وحدة الرعاية المركزية.

Objectives: To describe the development and implementation of pharmaceutical care services in an in-patient setting, and to examine the effectiveness of pharmacist interventions.

Methods: A single-center, 2-phase (pre-/post-intervention phase) design was performed in an intensive care unit (ICU) of a university-affiliated hospital. Patients in the post-intervention phase (March 2011 to June 2011) received pharmaceutical care from a clinical pharmacist, while patients in the pre-intervention phase (December 2010 to March 2011) received routine medical care. The pre- and post-intervention phases were then compared to evaluate the outcomes of pharmacist interventions.

Results: During the 3-month study period, the clinical pharmacist made 232 interventions for 416 admitted patients; of these, 202 (87.1%) were accepted by physicians or nurses, and dosage adjustment (n=83, [35.8%]) was the type of intervention implemented most often. In the group that received the participation of pharmacists, medication errors per patient decreased from 1.68 to 0.46 (p<0.001); medication errors, of incorrect dose or dosing interval, were markedly improved (decreased from 0.87 to 0.14; p<0.001), the drug cost per patient-day decreased from $347.43 to $307.36 ($p$=0.095), and the length of ICU stay did not change significantly (6.14 days versus 5.93 days; p=0.14).

Conclusion: The presence of the pharmacist in the ICU resulted in significant reduction of medication errors and had potential drug-cost-saving effects, but did not have an influence on decreasing the length of ICU stay.

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There are reports indicating that thousands of patients die each year because of medication errors.[1] Critically ill patients in the intensive care units (ICU) most often receive multiple medications and undergo surgical procedures, which place them at higher risk of being subjected to medication errors and the associated adverse drug events that follow.[2] It is for this reason that, 62.2% of ICU in the United States are equipped with clinical pharmacy services such as correction/clarification of orders, providing consultation on drug information, drug interactions, alternative therapies, and therapeutic drug monitoring.[3,4] The influence of clinical pharmacists in the ICU has been shown to result in reduction in adverse events,[5] improved dosing of medications[6,7] and cost savings,[8] lower mortality rates during ICU stay, decreased duration of ICU stay,[9] and so on. Although, clinical pharmacy services in the ICU have brought about significant benefits in patients with critical illnesses, the institution of this service has seen less progress in China until recently. The full-time clinical pharmacy services in China were actually started at 2005 after a series of documentations about clinical pharmacists issued by the Ministry of Health of China, in order to meet the rapid development of hospital pharmacy and to improve pharmaceutical care services in China. Although clinical pharmacists in some hospitals have carried out many works to standardize daily work routines of clinical pharmacists, to make a standard operation flowchart of medication orders, and a standard operation flow chart of clinical pharmacist student training,[10] the reports of analyses of pharmacist interventions, and measurement of pharmaceutical care outcomes in the ICU of China are still not available until now. The differences between China and Europe/USA in the implementation of pharmacy interventions could potentially be attributed to the differences in cultures, laws, politics, and healthcare systems.

This study aimed to introduce and evaluate full-time clinical pharmacy services in the ICU-based health services delivery of the healthcare system in China. The following questions would be discussed in this article: (1) which type of interventions did the pharmacist carry out? (2) Are clinical pharmacy services in the ICU well accepted by physicians and nurses? (3) What additional value did a pharmacist bring through full-time services in the ICU?

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Methods. This study was carried out in the 33-bed general ICU of a university-affiliated hospital. A total of 94 medical personnel are employed in the unit; among these are 10 full-time physicians, 73 registered nurses, 4 respiratory therapists, and one full-time clinical pharmacist.

A single-center, 2-phase (pre-/post-intervention phase) design was performed for this study. The pre-intervention phase, without pharmacist involvement in this period, served as the baseline group, and was conducted from December 2010 to March 2011 (91 days, with 409 patients) to know baseline information of patient characteristics and medication errors in ICU before pharmacist intervention. In the post-intervention phase, which served as the interventional group, a full-time experienced pharmacist served in the ICU during this period; this phase was carried out between March and June 2011 (91 days, with 416 patients) to analyze the type of pharmacist interventions and to measure the influence on pharmaceutical care outcomes through the presence of a full-time pharmacist service in the ICU. All patients admitted to the ICU in the 2 phases were enrolled into the study. **Figure 1** presents a flowchart of the study design. Research Review committee approval was obtained for initiation of the present study.

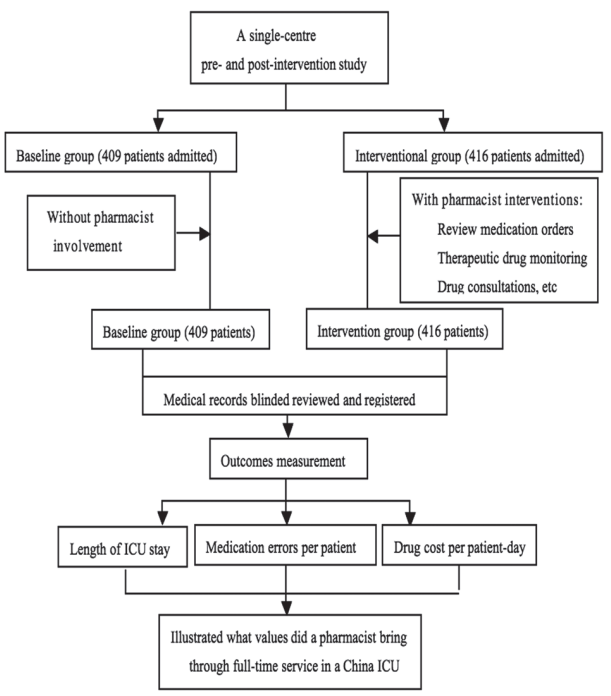

Figure 1 - Flowchart of patients admitted to the intensive care unit (ICU) in a single-center, 2-phase (pre-/post-intervention phase) design.

Pharmacist interventions. Pharmacy services were provided for 8 hours a day, 5 days a week. Pharmacist participated in daily clinical rounds in the morning, carried out pharmaceutical ward-rounds in the afternoon, and routinely attended case discussion and clinical professional meetings at the specified time. The clinical pharmacy services provided include review of medication orders, consultations with physicians or nurses, therapeutic drug monitoring in critically ill patients, conducting of lectures for rational usage of drugs, detection and reporting of adverse drug reactions (ADR), and participation in consultations and treatment in cases of emergencies with regard to drug safety. During the pharmacy services in the ICU, interventions provided by the pharmacist were recorded in detail. For this purpose, the pharmacist had to complete a registration form for each intervention after reviewing medication orders, counseling physicians, or carrying out other activities rendering pharmacy services. The registration form filled by the pharmacist includes details of patients' baseline demographic characteristics (gender, age, and diagnosis), type of interventions, specific recommendations, who initiated the pharmaceutical activities, and whether or not these were accepted by the physicians. All interventions thus recorded were then evaluated in terms of the type of interventions, the acceptance rate, and who initiated the pharmaceutical activities.

Outcome measurement and definitions. At the end of the study, a comparison of pre- and post-intervention phases was made to evaluate the outcomes of pharmacist interventions; the variables compared included medication errors per monitored patient, length of ICU stay, and drug cost per patient-day. Medication errors are usually defined as any preventable event occurring during drug ordering, transcribing, dispensing, administering, or monitoring.[11] In this study, medication errors were focused on the errors in ordering process, errors in other processes were not evaluated. Medication errors were expressed as the total absolute number of errors and the incidence of medication errors per monitored patient (average errors per patient). Drug cost per patient-day was calculated as the total drug cost in ICU divided by the length of ICU stay (total drug cost in ICU/length of ICU stay).

Data collection. A blinded coordinating investigator (a pharmacist student) recorded the patients' data in 2 phases, including details of patients' baseline characteristics [gender, age, diagnosis, renal function, and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores,[12]], length of ICU stay, and total drug cost during ICU stay. All costs in Chinese Yuan currency were converted to US dollars (exchange rate, 6.3 Yuan = US$1).

Further, after being discharged from the hospital, all of the patient medical records from both phases were reviewed by an ICU specialist and a pharmacist, both of whom were blinded to the patients' allocation status. Any order issues detected were discussed by the ICU specialist and the pharmacist, and if a consensus was reached, then those issues were scored as medication errors. If no consensus was reached, the medication orders issued would be scored as "rational". International and national pharmacotherapy guidelines and local evidence-based pharmacotherapy protocols were followed for evaluation of medication errors. Examples of medication errors are shown in **Figure 2**.

Statistical analysis. All data collected were entered into statistical analysis software (SPSS© Version 19.0) for statistical analyses. Comparisons between pre- and post-intervention phases with regard to patient characteristics, APACHE II scores, medication errors, were made by using student's t-test for continuous variables, non-parametric test Mann-Whitney test for values, which were not normal distribution, and chi-square test for categorical data. A *p*-value of less than 0.05 was considered statistically significant.

Results. Demographic characteristics of patients admitted during the baseline and intervention periods are shown in **Table 1**. Variables compared included age, gender, patients with renal insufficiency, patients receiving renal replacement therapy, and APACHE II

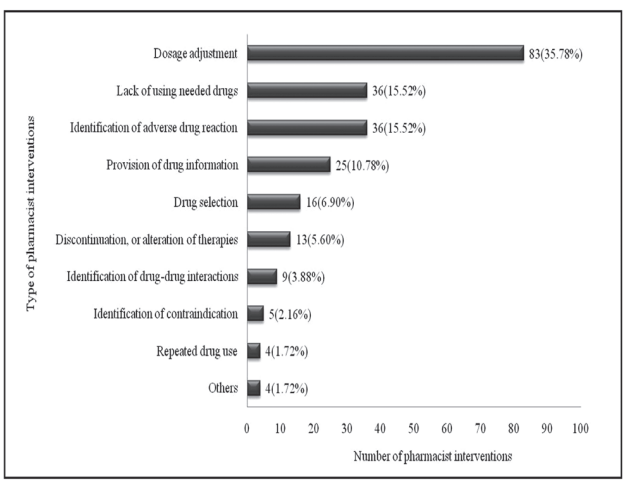

Figure 2 - Type and number of interventions recommended by clinical pharmacist during the intervention period.

score; no significant differences (p<0.05) were found for all of these variables.

The full-time pharmacist in the ICU carried out 232 interventions among 416 admitted patients during the 3-month intervention period (0.56 intervention per patient). **Figure 2** illustrated that the most frequent type of intervention was the dosage adjustment (n=83, [35.8%]), followed by identification of adverse drug reaction, lack of using needed drugs, and provision of drug information; other interventions, such as drug selection, discontinuation, or alteration of therapy, identification of drug-drug interactions, and so on, constituted less than 10% of interventions.

Among the 232 interventions, 145 (62.5%) were proactive (such as instigated) by a pharmacist, whereas the other 81 (37.5%) interventions were initiated by medical/nursing staff when the pharmacist was on the ward or contacted by email/phone (**Figure 3**).

Figure 4 summarizes the acceptance rate of pharmacist interventions, 190 interventions (81.9%) were accepted without any changes and 12 (5.2%) were accepted with changes, resulting in an acceptance rate of approximately 87.1%. The influence of pharmacist interventions on medication errors, length of ICU stay, and drug cost per patient-day is shown in **Table 2**. The incidence of medication errors (medication errors per patient) decreased significantly after pharmacist interventions (p<0.001), whereas the average length of ICU stay did not show a significant difference in pre-intervention phase and post-intervention phase (p=0.14). With a pharmacist's participation, the drug cost per patient-day decreased, but this difference was not statistically significant (p=0.095).

The improvement of medication errors after pharmacist interventions was further analyzed in **Table 3**. Data in **Table 3** indicate that the pharmacist had the most role in correcting wrong dose or dosing interval in the incidence of medication errors reduced from 0.87 [95%CI, 0.68 - 1.06] to 0.14 [95%CI, 0.091

Table 1 - Demographic characteristics of patients admitted during the baseline and intervention periods included in this study in an intensive care unit of a university affiliated hospital.

Characteristics	Pre-intervention (N=409)	Post-intervention (N=416)	Statistics analysis used	*P*-value
Age (years) (mean±SD)	63.24±17.55	61.31±17.10	t-test,	0.17
Gender			Chi-square test	0.19
Male	246	261		
Female	163	155		
Patients with renal insufficiency (%)*	99 (24.2)	105 (25.2)	Chi-square test	0.33
Patients receiving renal replacement therapy (%)	64 (15.6)	67 (16.1)	Chi-square test	0.36
APACHE II score (mean±SD)	15.34±9.24	13.95±7.55	t-test	0.11

*Patients with renal insufficiency were defined as patients were older than 18 years and had an estimated creatinine clearance (CrCl) less than or equal to 50 mL/min upon admission or during the ICU stay

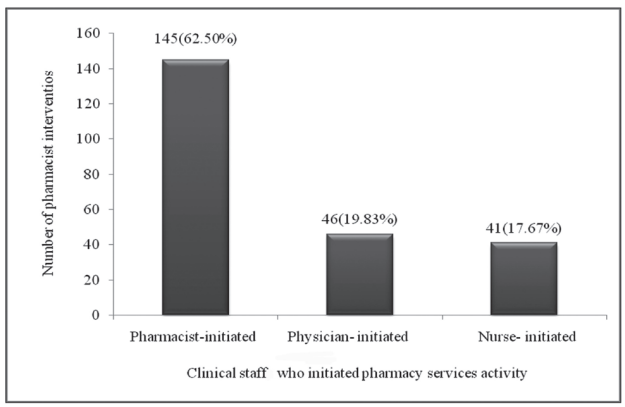

Figure 3 - Source of pharmacist interventions during the intervention period.

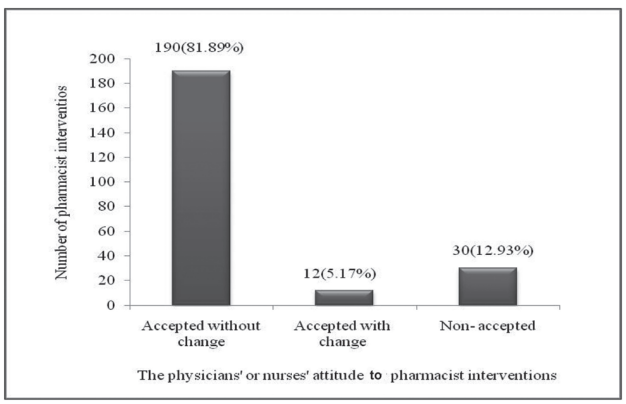

Figure 4 - The acceptance rate of pharmacist interventions during the intervention period.

Table 2 - The effect of pharmacist interventions on medication errors, length of intensive care unit (ICU) stay, and drug cost per patient-day.

Study phase	N	Number of errors	Average errors* per patient (95% CI)	Length of ICU stay (days) (95% CI)	Drug cost per patient-day ($) (95% CI)
Pre-intervention	409	687	1.68 (1.40 - 1.97)	5.93 (5.52 - 6.70)	347.43 (304.18 - 390.02)
Post-intervention	416	191	0.46 (0.30 - 0.62)	6.14 (5.16 - 6.70)	307.36 (262.40 - 352.31)
P-value			<0.001	0.14	0.095
Statistics analysis			Mann-Whitney test	Mann-Whitney test	Mann-Whitney test

*Average errors per patient calculated from the number of medication errors (number of errors) divided by the number of patients (number of patients).

Table 3 - Medication errors during the study period included in this study in an intensive care unit of a university affiliated hospital.

Type of errors	Pre-intervention (N=409)		Post-intervention (N=416)		*P*-value
	Number of errors n (%)	Average errors per patient (95% CI)	Number of errors n (%)	Average errors per patient (95% CI)	
Wrong dose or dosing interval	351 (51.1)	0.87 (0.68 - 1.06)	58 (30.4)	0.14 (0.091 - 0.19)	0.001
Unnecessary drug use	65 (9.5)	0.16 (0.11 - 0.21)	23 (12.0)	0.055 (0.041 - 0.069)	0.001
Lack of using needed drugs	58 (8.4)	0.14 (0.089 - 0.19)	12 (6.3)	0.029 (0.021 - 0.037)	0.001
Inappropriate drug selection	44 (6.4)	0.11 (0.083 - 0.14)	17 (8.9)	0.041 (0.033 - 0.049)	0.001
Repeated drug use	39 (5.7)	0.095 (0.078 - 0.11)	8 (4.2)	0.019 (0.013 - 0.025)	0.001
Drug-drug interaction	34 (5.0)	0.083 (0.068 - 0.098)	7 (3.7)	0.017 (0.014 - 0.020)	0.001
Wrong duration of therapy	30 (4.4)	0.073 (0.061 - 0.085)	10 (5.2)	0.024 (0.018 - 0.030)	0.0015
Others	66 (9.6)	0.16 (0.11 - 0.21)	56 (29.3)	0.13 (0.086 - 0.17)	0.25
Total	**687 (100)**		**191 (100)**		

* Conducted using the Mann-Whitney test

- 0.19] (p<0.001), the following items also improved significantly: unnecessary drug use (0.16 versus 0.055, p<0.001), lack of using needed drugs (0.14 versus 0.029 p<0.001), inappropriate drug selection (0.11 versus 0.041, p<0.001), repeated drug use (0.095 versus 0.019, p<0.001), drug-drug interaction (0.083 versus 0.017, p<0.001). Other items evaluated, such as unwarranted discontinuation or alteration of therapies, contraindications, and so on, did not show a significant difference (0.16 versus 0.13, p=0.25).

Discussion. As the organization and structuring of the China's Healthcare System healthcare system is different from developed countries such as the USA or United Kingdom, and the participation of pharmacists in ICU teams in China has been established only in recent years, reports on analysis of pharmacist interventions and measurement of pharmaceutical care outcomes in China ICU are scarce until now. This is the first study to investigate the effectiveness of pharmaceutical care in an ICU in China, and can prove beneficial to a better understanding of the value of pharmacy services in the China's healthcare system. Due to the high-risk status of patients in the ICU and need for interventions in a complex environment,[13] critically ill patients are at risk of undergoing twice as many medications errors as patients outside the ICU,[14] and nearly all patients may suffer a potentially life-threatening error during their stay.[15] Several methods have been introduced to prevent medication errors, and one of these important interventions is the involvement of a pharmacist.[16] By committing a part- or full- time clinical pharmacist to the ICU patient care team, the number of medication errors can be reduced by as much as 3 to 5 fold,[17,18] In this study, the medication errors were reduced by 3.66 times through the interventions of a full-time pharmacist. Notably, it has been reported that clinical pharmacists did not apparently influence the rate of medication errors in the general medical and surgical units because of the low baseline error rates and part-

time participation.[18] Taking the findings of the present study into consideration, we report that full-time participation by a pharmacist and the relatively higher baseline error rates in the ICU contribute to a reduction of medication errors by 3.66 times through pharmacist interventions.

It should be noted that dosage adjustment was the most frequent type of pharmacist interventions in the study. Critically ill patients tend to have renal or liver insufficiency during their ICU stay.[19] In the ICU department in the present study, 25% of the patients, on average, suffered from renal insufficiency, and approximately 16% received renal replacement therapy (**Table 1**). These patients are at higher risk for dosage or dosing-interval errors, accounting for 351 (51.1%) of all errors in the baseline period (**Table 3**). Pharmacological knowledge is an independent predictor of medication errors by healthcare providers.[20] Although physicians are skilled in diagnosing diseases, their knowledge of pharmacokinetics may be deficient, particularly among clinically inexperienced physicians. Therefore, dosage adjustment was most required in these patients when drugs that are primarily cleared by the renal (mostly antibiotics) system were prescribed. In this study, pharmacist interventions had resulted in a reduction of 6.21 times in dosage or dosing-interval errors.

An unexpected observation during the study was that the current pharmacy services did not have an influence on decreasing the length of ICU stay (p=0.78). It has been reported that pharmacist participation in the general medicine setting could apparently shorten length of hospital stay,[5,21,22] whereas pharmacist intervention in patients requiring medical progressive care had little effect on length of stay.[23] These results indicate that the condition of the patients, from critical illness to general illness, must be considered when interpreting findings with regard to length of stay. Patients in the ICU are always critically ill and, in the complex environment, a large number of factors such as severity of illness, multiple care providers, extremes of age, sedation, and so on are eventually associated with the length of their ICU stay. For all of these reasons, it can be easily understood that the effect of pharmacist participation on the length of ICU stay was negligible.

Further, the economic effect of pharmacist interventions was evaluated in the study. A number of studies have demonstrated the clinical and economic benefits of pharmacist interventions in hospitals;[24-26] however, these results were mostly reported for North American or European countries, and the economic impact of pharmacist interventions in China have been scarcely reported. This study showed that a cost savings of $40.07 per patient-day is possible with pharmacist participation, although the difference was not statistically significant. Cost savings with regard to drug use in this study may be attributed to change of dosage, discontinuation of therapy, and switching from a more expensive to a less expensive drug. It should be noted that there are some methodological limitations in this study; these include: the absence of a control group without pharmacist interventions, focusing on drug cost-saving only, exclusion of cost of pharmacist employment, and so forth. Therefore, a more detailed study will be required. However, the results of this study illustrated the potential drug cost-saving value of pharmacist intervention in an ICU in China.

As stated previously, China has started implementing full-time clinical pharmacy services only in recent years; therefore, the authors primarily focused on the acceptance of this change by the clinical staff. Not surprisingly, the presence of the pharmacist in the ICU was well accepted by physicians and nurses, evidenced by the fact that 87.1% of the interventions were accepted. These findings can be attributed to the following reasons: firstly, nurses are expected to be more receptive of this change because of the reduction in their work responsibility;[7] secondly, the benefits of pharmacist participation, such as ensuring the safety of medication usage and providing drug information, were well recognized by the physicians; and finally, the most important reason for acceptance could be the series of guidelines with regard to clinical pharmacists that were issued by the Ministry of Health in China in recent years, which ensured that the hospital management authorities were inclined to the development and implementation of clinical pharmacy services in the hospital setting in China.

Study limitations. Several limitations associated with this study should be recognized. The first is that the study was only conducted in a general adult ICU. Due to the situations in other ICUs (such as surgical ICU and neonatal ICU) are significantly different, our findings cannot be generalized to all types of units or hospitals. The second limitation is that the pharmacist was only present for 40 hours a week; however, errors are more common during evenings or weekends when the ICU staff experience greater fatigue or lack of concentration, and data from evenings or weekends (when pharmacists were absent) were collected as well, and may eventually affect the results that were obtained. The third is the methodological limitations of pre- and post-intervention study, since other factors rather than the interventions (heath policies, pharmacotherapy guidelines) may change over the period, however

the continuous design of pre- and post-intervention phase can lessen such influences in a limited extent. Lastly, based on the results obtained in this study, there is a requirement for further research into those errors occurring most frequently or in specific types of patients.

In conclusions, this study shows that the presence of the pharmacist in the ICU was well accepted by physicians and nurses in China. Dosage adjustment appeared to be the most frequent type of intervention of the pharmacist interventions provided. Although the pharmacist interventions had little effect on decreasing length of ICU stay, possibly due to the complexity and severity of illness of patients in ICU, it resulted in a significant reduction of medication errors in the ICU and potential drug cost-saving for the patients. These results would be beneficial to convince policymakers to maintain their investment in the development and implementation of clinical pharmacy services in the ICU in the China's healthcare system.

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