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ORIGINAL PAPER

The Effect of Computerized Physician Order Entry and Decision Support System on Medication Errors in the Neonatal Ward: Experiences from an Iranian Teaching Hospital

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Abstract Medication dosing errors are frequent in neonatal wards. In an Iranian neonatal ward, a 7.5 months study was designed in three periods to compare the effect of Computerized Physician Order Entry (CPOE) *without* and *with* decision support functionalities in reducing non-intercepted medication dosing errors in antibiotics and anticonvulsants. Before intervention (Period 1), error rate was 53%, which did not significantly change after the implementation of CPOE *without* decision support (Period 2). However, errors were significantly reduced to 34% after that the decision support was added to the CPOE (Period 3; $P<0.001$). Dose errors were more often intercepted than frequency errors. Over-dose was the most frequent type of medication errors and curtailed-interval was the least. Transcription errors did not reduce after the CPOE implementation. Physicians ignored alerts when they could not understand why they appeared. A suggestion is to add explanations about these reasons to increase physicians' compliance with the system's recommendations.

Keywords Medical order entry systems · Decision support systems, clinical · Medication errors · Infant, newborn · Patient safety · Iran

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Background

Medication errors can prolong hospital stay and increase costs and mortality [1]. Children are at higher risk from medication errors because of weight-based dosing, lower tolerance to a dosing error, and limitations in communicating with health providers to explain the adverse event [2]. The problem becomes even more significant in neonatal wards where the patients are more susceptible to medication errors because of their unique issues [3, 4]. Potential Adverse Drug Events (ADE) occur three times more often in newborns than in adults. Most of the medication errors happen at the prescribing stage, and the most common type is dose error [5]. Antibiotics are among the most frequently

involved drug groups [5, 6]. Severe adverse events have been reported due to dose miscalculation of the prescribed anticonvulsants [7].

Many studies in adults and paediatrics have reported that computerized physician order entry (CPOE) has the ability to reduce different types of medication errors [8–12]. However, there are studies that have identified the negative effects of CPOE in facilitating certain types of medication errors or increasing mortality rate [13–17]. These results are not necessarily contradictory but they are difficult to compare because of different design and implementation methods [18].

Despite its importance, few studies have evaluated the effect of CPOE on prescription *dosing* errors in a neonatal ward or Neonatal Intensive Care Unit (NICU). Gard et al. [19] reported elimination of the self-reported dose calculation errors of antibiotics in a NICU following the implementation of a computer-generated antimicrobial dose calculator. Cordero et al. [20] found that gentamicin dose calculation error among very low birth-weight neonates was eradicated after the implementation of CPOE. These studies show that CPOE has been effective at reducing dose medication errors in neonatal patients.

Despite the benefits, implementation of CPOE is challenging for different reasons, including physicians' resistance [21] and high costs [22]. Physicians' compliance with the system's recommendations is low and a majority of the warnings are ignored [23]. Despite the great effort on the national level, only about 23% of the children hospitals and less than 15% of the general hospitals in the USA, the leading country in CPOE, have implemented CPOE [24, 25]. The success rate is even less in many European countries that have implemented CPOE [24]. Implementation of these systems in middle- or low-income countries is more challenging because of financial as well as human resource constraints [26]. In 2007 a CPOE project was started in the Islamic Republic of Iran. Iran is a low-middle-income country in the Middle East, with almost 70 million inhabitants [27].

In the cooperation strategic plan, Iran has promised the World Health Organization to extend the use of health information technology and evidence-based decision-making in the health sector [28]. Previous studies on medication errors and ADEs in Iran have revealed that preventable medication errors frequently happen. In one study that was conducted in a tertiary-care teaching hospital in Tehran, nearly 60% of the adverse events were preventable. The most probable causes were inappropriate doses, intervals, and choice of the prescribed drugs [29]. In another study, medication-related problems in Iran were responsible for 11.5% of admissions and were mostly preventable. Dose-related problems were among the most frequent causes [30]. The results of these studies demonstrate that the Iranian healthcare system may benefit from the implementation of CPOE with dose decision support functionalities, especially in those clinical settings that are heavily dependent on accurate dose calculation like the neonatal ward. However, the effects should be investigated.

The aim of this study was to investigate the effect of *physician order entry* and *decision support system* on reducing medication dosing errors of antibiotics and anticonvulsants in an Iranian neonatal ward.

Methods

Setting

Hamadan is a province in North West of Iran, with almost 1,700,000 inhabitants. Besat is a 400-bed tertiary-care referral teaching hospital in the capital city of Hamadan, providing different clinical services. Besat's neonatal ward is a 17-bed clinical ward that includes two NICU beds.

Inclusion criteria and study population

Neonates, who received antibiotics for infectious diseases or anticonvulsants for seizure, were included in the study. For the included patients, all administered antibiotics and anticonvulsants were included. A prescribed medication that was continued during a day and had led to administration was defined as a *medication-day*. Therefore, even if the prescribed medication was repeated in several renewed orders on the same day, it was considered as one medication-day. When the dose and frequency of the prescribed medication was correct in all orders of the same day, it was considered as one correct medication-day otherwise it was counted as one erroneous medication-day.

System description

Clinical information system

Sayan-HIS (Sayan Rayan Co. Ltd., Hamadan, Iran) is a commercial patient-centred hospital information system (HIS) that is used in all 15 university-affiliated hospitals in Hamadan. The clinical information system of Sayan-HIS includes functionalities for order entry. When the physician's order is entered into the computer, the prescription system delivers the requested order for medications, lab tests, and imaging to their relevant target hospital sections at the appropriate time. The user interface of the prescription system remained intact during the study period.

The system constrains the selection of drugs and their possible pharmaceutical forms (vial, ampoule, tablet, etc.) through drop-down lists and pre-constructed orders. A

minimum and maximum dose reminder is also available. This alert is to some extent useful for adults but not for neonates whose dose may vary up to tenfold for the same drug because of the weight-based dose calculation.

Clinical Decision Support System

Before CPOE implementation, a knowledge-base was created by using the local guidelines of best practice based on the paediatric reference books that were approved by the National Board of Paediatrics in Iran [31, 32]. The knowledge-base was completed for all routine antibiotics and anticonvulsants, based on the patient's clinical diagnosis, age, weight, gestational age, and glomerular filtration rate (GFR). Three neonatal sub-specialists reviewed the knowledge-base and approved its compliance with the original guidelines. A computer function was developed to calculate GFR for neonates based on the patient's creatinine clearance, body surface area (BSA), age, and gestational age. A paediatric nephrologist tested the functionality of the GFR calculator, reviewed its compliance with the references [33, 34], and approved it. All prescribers were informed that they had to comply with the mentioned guidelines while setting the dose and frequency of medications.

At the time of order entry, a rule based CDSS examined the dose and frequency of each prescribed medication, based on the mentioned references (Fig. 1). It requested the prescription system to provide detailed information required for retrieving relevant dose and frequency ranges from the knowledge-base. According to the calculated GFR, the renal function evaluator component determined whether the dose should be adjusted, and to what extent. Based on all above information, the clinical inference unit calculated the patient specific appropriate dose and frequency, and compared the results with the prescribed dose and frequency. If the prescribed dose or frequency was not within the normal range, the DSS informed the prescriber about the appropriate dose and/or frequency by demonstrating a warning message that asked for correction. The prescriber was however, allowed to ignore it. If the prescriber accepted the correction, the order was updated based on the DSS recommendation. Prescriber's response to the warning, was recorded in an error registration table. Detailed information on decision flow is shown in Fig. 2.

The design of the CDSS was based on a previous study where the physicians believed that, since these advanced technologies are not affordable everywhere in Iran, interns and residents should be able to set appropriate doses without computer support, but could receive feedback if the error was going to harm the patient [26].

Definition of medication errors

In this study we investigated prescription and transcription errors, but not the administration errors. Among different prescription parameters, dose and frequency were selected because they are the most common source of prescription errors in the neonatal setting [5, 6].

Over- or under-dosages and curtailed or prolonged intervals were considered as medication errors. Those medication errors that were prevented before they reached patients were categorized as intercepted and those that reached patients were categorized as non-intercepted medication errors.

A prescription error was defined as a medication that was prescribed with an erroneous dose or frequency by the physician. Prescription errors occur at the time of selecting the reference dose, calculating the patient-specific dose, and registering dose in the order book. A transcription error was defined as a medication that was registered with an erroneous dose in the paper-based nursing report while the prescribed order was correct. The other types of dose transcription errors such as delayed or omitted doses were not included in this study.

Study periods and their characteristics

This study was designed to cover three consecutive 2.5-month intervals consisting of Period 1—Before intervention; Period 2—Physician order entry; and Period 3—Physician order entry and CDSS providing dose and frequency warnings. This study was conducted between May 2007 and December 2007 (Table 1).

Period 1—Before intervention

In the neonatal ward, residents were responsible for calculating the appropriate dose and frequency of the prescribed medications and registering them in the paper-based order sheets. In Period 1, nurses transcribed prescription orders to the computer and physicians did not interact with the computer system (Fig. 3). They also transcribed prescribed medications to the paper-based nursing Cardex that was used for drug preparation. After the administration, the delivered dose and administration time was registered in the paper-based administration chart.

During this period, two of the authors (A.K. and A.A.) conducted group and private training sessions for the residents to teach them how to use the prescription system. Residents could also obtain access to a demo version of the system for further training.

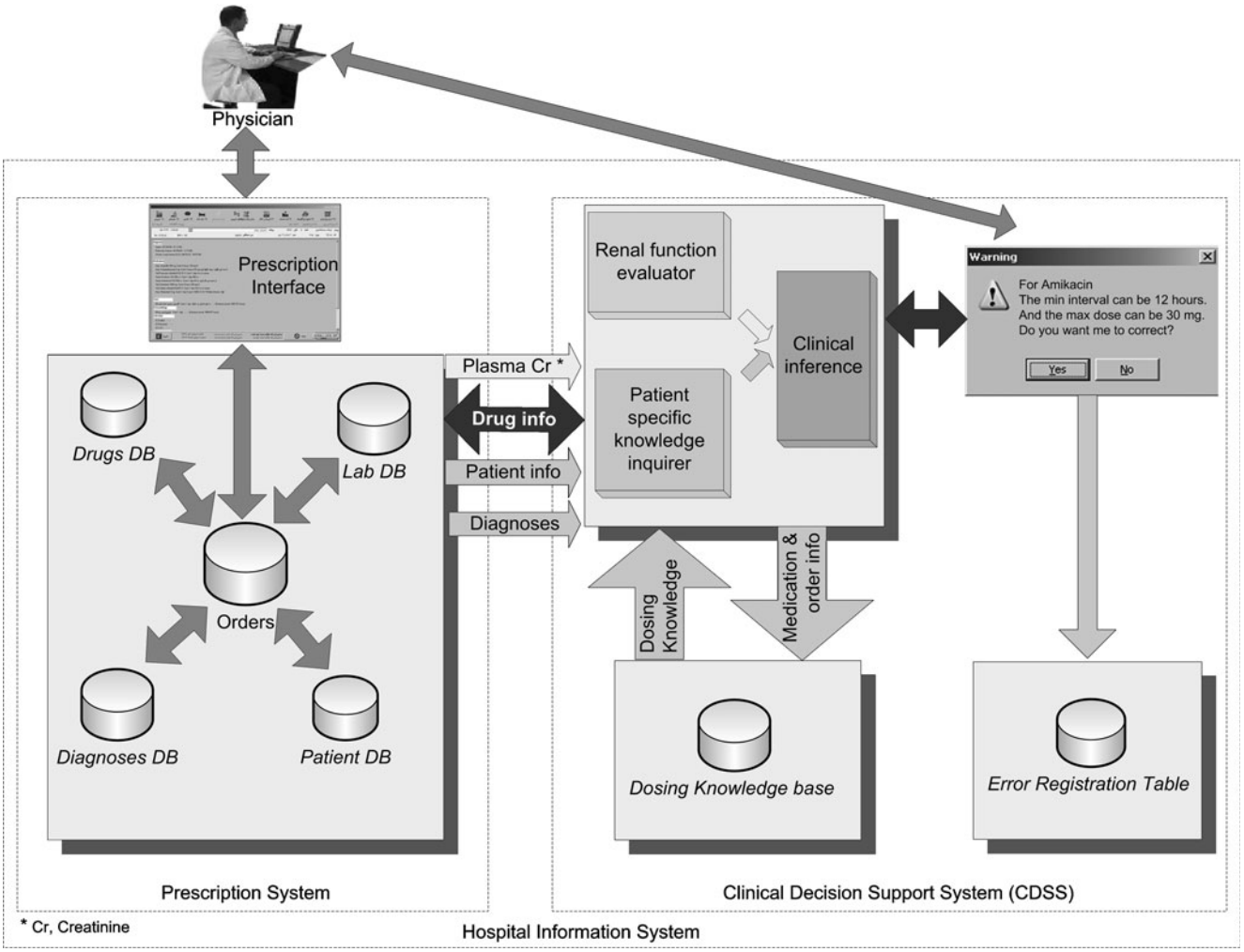

Fig. 1 Schematic view of the CDSS architecture, and its interactions with the prescription system

Period 2—Physician order entry

In Period 2, physician order entry was introduced as a separate period to evaluate the role of physicians' data entry without the assistance of the computer-generated warnings in reducing or increasing dose and/or frequency medication errors. At the beginning of this period, paediatric residents took responsibility for entering prescription orders into the computer (Table 1). However, when a resident had completed the electronic registration of an order, a nurse checked and electronically countersigned the order to verify it (Fig. 3). In this period, transcription of paper-based orders to the computer was eliminated but transcription to the cardex and paper-based nursing reports were continued (Asterisks in Fig. 3).

To evaluate the non-intercepted medication errors in Period 1 and 2, patients' order books were reviewed to complete missing information on weight, height, gestational age, and the clinical diagnosis in the HIS, and medication errors were assessed retrospectively (Table 1).

Period 3—Physician order entry and CDSS providing warnings

In Period 3, residents continued to enter prescriptions into the computer (Table 1). In addition, warning messages became functional and informed physicians following a dose or frequency medication error (Fig. 3). If the prescriber ignored a warning, the next warning would appear when one of the decision criteria (diagnosis, age, weight, GFR, etc.) was changed in the renewed order or a new erroneous dose and/or frequency was set for that medication.

In this period, when a resident complained about a warning that was perceived by him /her as being inappropriate, A.K. asked him/her to explain how did he/she calculate the dose and frequency for that medication and

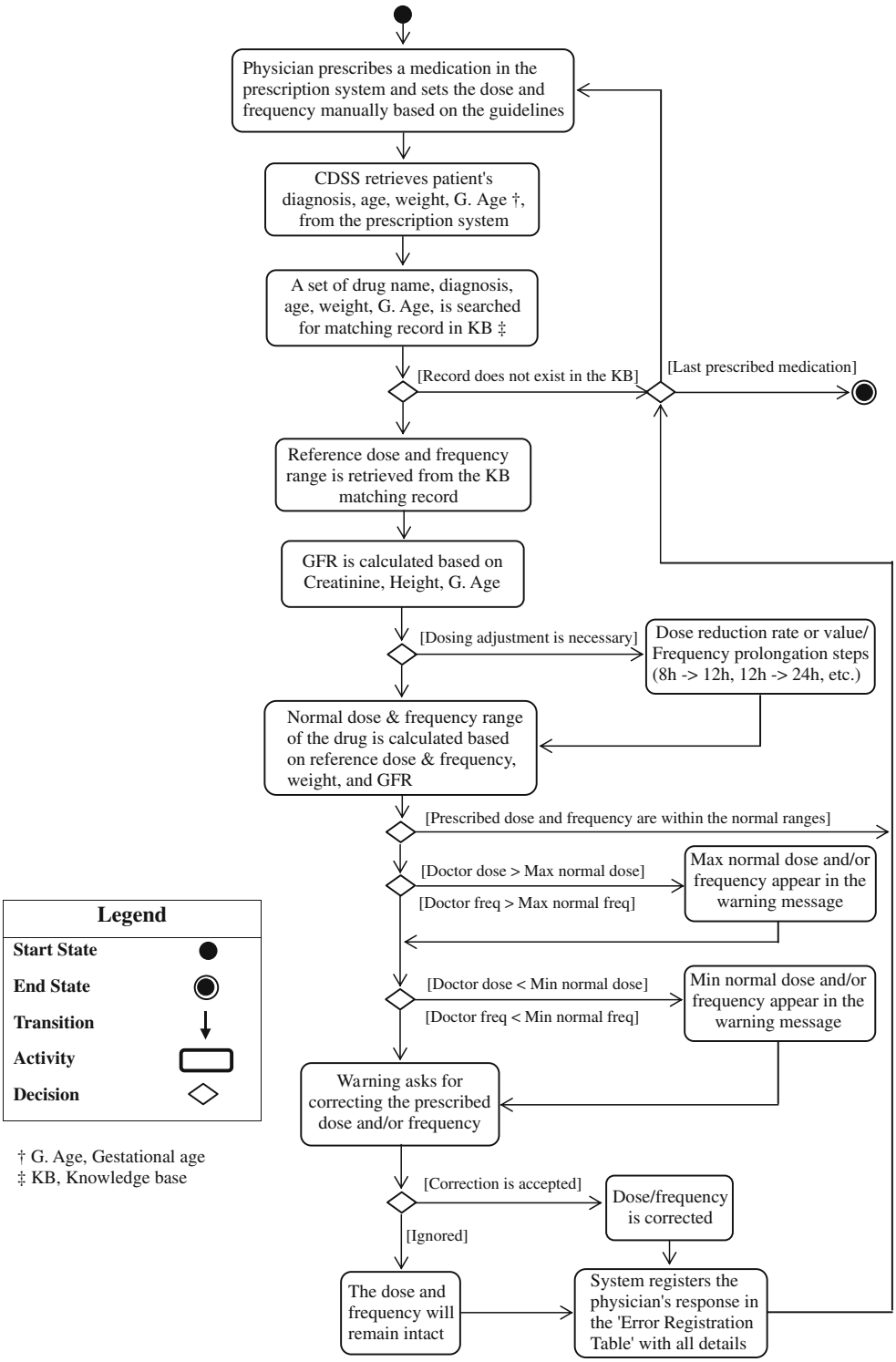

Fig. 2 Dosing decision support system workflow (activity diagram)

took notes. Then he reviewed the system's calculation method and compared the two approaches far from the resident. The aim was to explore the reasons for the ignored warnings and the possible causes of medication errors without influencing the prescriber. At the end of Period 3 the results of these investigations were categorized into main causes of errors (presented in the result section).

Statistics

A two-tailed Chi-square test was performed to find statistically significant differences in the proportion of medication errors between Period 1 and 2, and Period 2 and 3 [35]. We also employed Chi-square for trend (Mantel extension) to investigate whether there was a linear incremental or

Table 1 CPOE implementation periods at the neonatal ward of the Besat hospital

	Period 1 May–Jul 2007	Period 2 Jul–Oct 2007	Period 3 Oct–Dec 2007
Intervention	No intervention	POE	POE + CDSS
CDSS functionality	N/A	N/A	Warnings
Order entry	Nurses	Physicians	Physicians
Documentation	HWP	E-Prints	E-Prints
Transcription to	Computer + Cardex + PBNR	Cardex + PBNR	Cardex + PBNR
Review process	EO + EMAC + PBO + PBNR	EO + EMAC + PBNR	EO + EMAC + PBNR + ERT

POE physician order entry, *CDSS* clinical decision support system, *HWP* hand-written prescription, *E-Prints* electronic prints (of prescriptions), *PBNR* paper-based nursing report, *PBO* paper-based orders, *EO* electronic orders, *EMAC* electronic medication administration chart, *ERT* error registration table, *N/A* not available

decreasing trend in the proportion of the non-intercepted medication errors from Period 1 to Period 3 [36]. The change in error rate between the study periods was calculated as $r = |\text{Initial period error rate} - \text{Final period error rate}|$.

Medication-day (a prescribed medication that is continued during a day and has led to administration) was used as the unit of analysis. Medication-days account for both the number of concurrent medications used for one patient and the duration that a medication is continued. The risk of harm/benefit per each medication-day can be considered as one standard unit. Therefore, in this error calculation method, the number of concurrent patients, medications, and the length of stay cannot adversely affect medication errors.

Ethical considerations

The National Ethical Committee at the Ministry of Health and Medical Education in Iran issued ethical permission for this study in 2005. Residents and nurses were informed of their rights to withdraw at any time. All physicians and nurses volunteered to take part in the study.

Results

Baseline characteristics

During the study period, 248 patients met the inclusion criteria and were included in this study (Table 2). There were no significant difference in sex, and gestational age in the three periods. The average age on admission was about 3 to 6 days. The median length of hospital stay of the included patients was about 7 days and their prescribed medications were continued between 5 and 6 days.

In Period 2, 69 orders belonging to eight patients who met the inclusion criteria, but the orders were entered by the nurses, were excluded from the study. The reason was that the aim of this period was to investigate the effect of *physicians*' order entry.

Non-intercepted medication errors

Most of the non-intercepted medication errors occurred during the *prescription* stage (Table 3). The rate of *transcription errors* was not significantly different in the three periods.

Before intervention (Period 1), the rate of non-intercepted medication errors was about 53% (Table 3). Introducing CPOE *without* the CDSS functionality in Period 2 *did not* significantly decrease or increase non-intercepted medication errors. However, after the introduction of the dose and frequency CDSS in Period 3, the rate of non-intercepted medication errors was reduced to 34% (19% reduction compared to Period 1; $P<0.001$; Table 3).

Dose and frequency errors

Dividing non-intercepted medication errors into dose and frequency errors showed a 3% non-significant reduction in dose errors between Period 1 and 2, while there was no significant difference between frequency errors of these two periods. Both dose and frequency errors had significant reduction between Period 2 and 3 (Table 4). However, dose errors were more often intercepted than frequency errors (19% reduction for dose errors and 5% for frequency errors compared to Period 1).

Sub-types of dose and frequency errors

After dividing dose errors into over-dose and under-dose, and frequency errors into prolonged and curtailed intervals, apart from the curtailed interval, all other error types showed a highly significant linear reduction from Period 1 to Period 3 ($P<0.001$; Fig. 4). Over-dose was the most

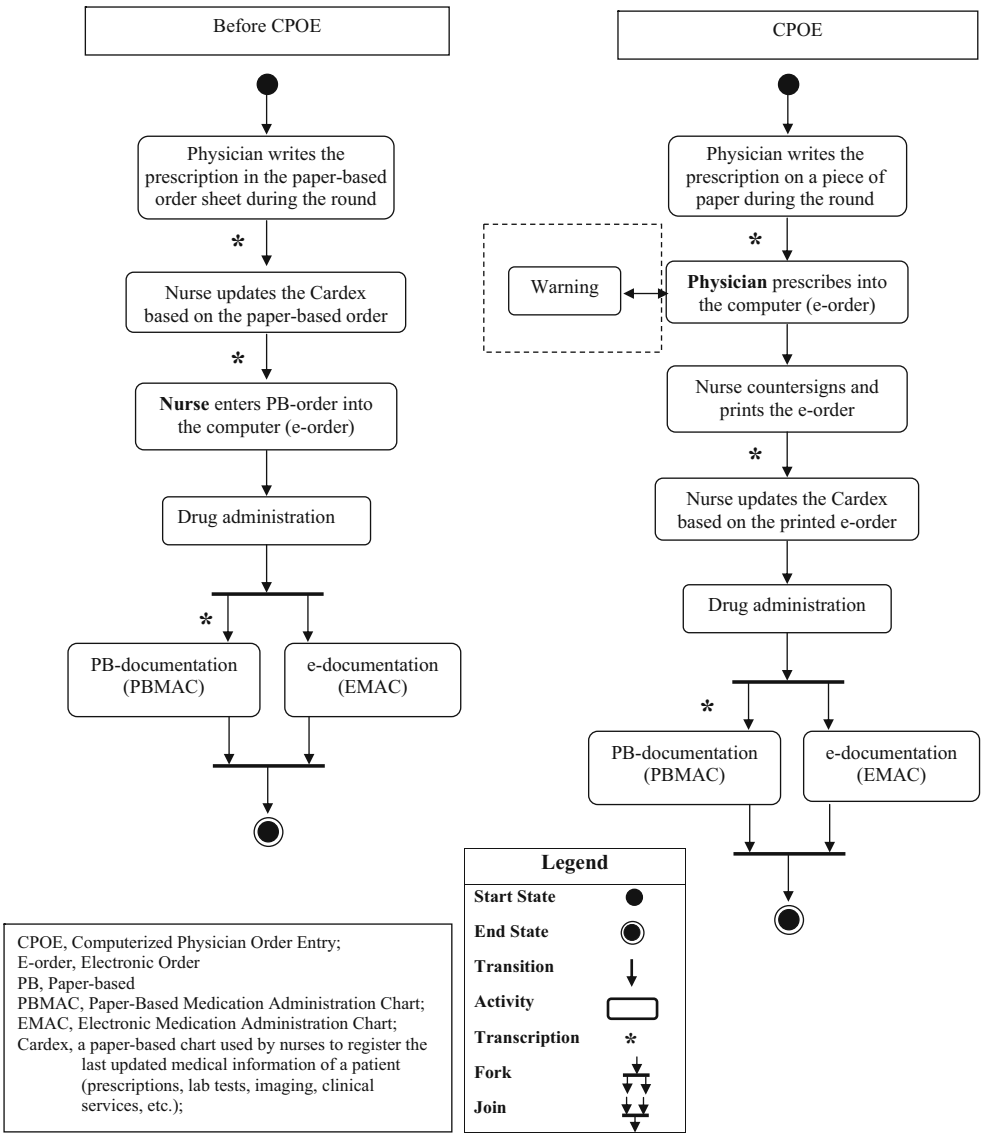

Fig. 3 Medication prescription and administration workflow before and after CPOE in the neonatal ward of the Besat hospital. Note that the warnings *only* appeared in the period 3

frequent, and curtailed-interval the least frequent error type in Period 1 and Period 2. After the introduction of CDSS functionality, over-dose dropped by 40% in Period 3 (11% reduction from Period 1 to Period 3). However, curtailed interval was not significantly reduced. Under-dose dropped by 60% (8% reduction) and prolonged interval by 24% (5% reduction).

While only 21% (20/96) of the patients in Period 1 and 18% (15/83) in Period 2 were error-free, the rate was increased to 35% in Period 3 (28/79; P=0.02).

In Period 3, Physicians complied with 53 warnings while ignored 108 (33% compliance rate).

Main causes of errors

Based on the personal discussions with prescribers to find specific reasons for the errors and ignored warnings, five main causes were identified: medication-diagnosis mismatch, dose adjustment difficulties, ignoring the new age-group, selecting a "neighbouring cell", and miscalculations.

Medication-diagnosis mismatch

Sometimes antibiotics were prescribed with an inappropriate diagnosis. For example, meningitis dose was prescribed for a less severe infectious disease.

Dose adjustment difficulties

Residents seemed to have problems in correctly interpreting the GFR and detecting renal impairment. The situation became more complicated when the prescriber had to

Table 2 Distribution and characteristics of the included patients, orders, and medications in the three periods

	Period 1	Period 2	Period 3
Patients[a]	96	83	79
Male/female	47/49	43/40	42/37
Median age on admission (days)	5	3	6
Median gestational age (weeks)	38	38	38
Orders	1,248	1,080	878
Medications in the orders	2,728	2,350	2,059
Patient-days[b]	735	686	576
Medication days[c]	1,688	1,489	1,331
Median length of hospital stay (days)	6.8	6.8	6.6
Mean of medication repeats (days)[d]	5.5	5.8	5.3

[a] Two included patients in period 2 and 8 in period 3 have been admitted in the previous period but have stayed at the ward in the next period

[b] The number of days that included patients received antibiotics or anticonvulsants

[c] The number of days that included medications were continued for the included patients

[d] The average number of days that an included medication of an included patient was repeated

recalculate the dosage based on every new plasma creatinine result.

Ignoring the new age group

Based on the mentioned dose table [31], the frequency and/or dose should have changed for most of the antibiotics when the age of the hospitalized patient changed from the seventh to the eighth day of life. Interviews and personal discussions revealed that prescribers had rarely applied the necessary change.

Selecting a "neighbouring cell"

In order to select the appropriate dose and frequency in the guideline table [31], residents had to find the appropriate age and weight group for the selected medication based on the diagnosis. Sometimes they calculated the dose and frequency based on a wrong "neighbouring cell", probably because of visual mistakes, or by choosing the inappropriate diagnosis, age or weight group.

Miscalculations

Miscalculations occurred frequently. During the shifts, three residents were responsible for all paediatric patients in the paediatric intensive care unit, the neonatal ward, the two general paediatric wards, and the emergency ward of the hospital. They were busy, under tension and stress, and could easily make mistakes while calculating dose and frequency.

Discussion

Period 1

In this study, the error rate in Period 1 was much higher than in many similar studies in western countries [10, 37]. There are a number of possible reasons that may explain this circumstance. For example, unlike many western hospitals, in Iran nurses prepare the ready-to-administer doses without any supervision or involvement of hospital pharmacists which increases the risk of medication errors [26, 38, 39].

The absence of a clinical pharmacist during the clinical rounds to detect the potential adverse events and to remind the prescribers of their medical faults at the time of prescription is another problem in this setting. The result of two studies in the US and UK demonstrates a 66% to 80% reduction of medication errors following the active involvement of a senior clinical pharmacist in the clinical rounds [40, 41].

Table 3 Distribution of non-intercepted medication errors in the three periods

Error type	Period 1, n=1,688	Period 2, n=1,489	Period 3, n=1,331	P value, period 1 and 2	P value, period 2 and 3	P value for trend
Prescription	876 (52%)[a]	749 (50%)	442 (33%)	0.4	<0.001	<0.001
Transcription	15 (1%)	16 (1%)	15 (1%)	0.6	0.9	0.5
Medication errors[b]	891 (53%)	765 (51%)	457 (34%)	0.4	<0.001	<0.001

[a] Numbers in parentheses represent the percentages of crude numbers divided by n (n is the number of medication days in Table 2)

[b] A medication that contains both dose and frequency errors is considered as one medication-day error. Medication errors are the sum of prescription and transcription errors

Table 4 Distribution of non-intercepted dose and frequency errors in the three periods

Error type	Period 1, n=1,688	Period 2, n=1,489	Period 3, n=1,331	P value, period 1 and 2	P value, period 2 and 3	P value for trend
Dose errors[a]	690 (41%)[b]	559 (38%)	297 (22%)	0.06	<0.001	<0.001
Frequency errors	423 (25%)	377 (25%)	261 (20%)	0.9	<0.001	<0.001

[a] A medication error may contain both dose and frequency errors. Therefore, the sum of dose and frequency errors is higher than the total medication errors.

[b] Numbers in parentheses represent the percentages of crude numbers divided by n (medication-days)

In the neonatal ward and NICU, calculation of dose is complicated and depends on several criteria [42, 43]. In our study the high workload, tension, and stress of the residents during their shifts resulted in a number of dose calculation errors. Previous studies have shown that dose calculation errors occur frequently among paediatric residents [44, 45].

Another explanation of the high error rate is the methods to detect medication errors [12]. Studies like Simpson et al. [41] which are based on the critical or spontaneous reports can detect only a fraction of medication errors [46]. Chart reviews, especially when they are coupled with voluntary reports like the study conducted by Kaushal et al. [5], can detect a higher proportion of prescription errors. Direct observation is appropriate for detecting administration errors [46], though it is prone to biases like Hawthorne effect [47]. The studies like Cordero et al. [20] that have reviewed handwritten and electronic medical records have detected a higher rate of medication errors. In sum, methods are diverse and the results are difficult to compare. In our investigation the researchers have reviewed both the hand written and electronic medical records of orders and nursing charts in all periods.

Period 2

The introduction of CPOE without CDSS functionalities did not significantly reduce dose and frequency *prescription* as well as *transcription* errors, which is inline with the study conducted by Shulman et al. [48]. In that study, following the implementation of a CPOE without DSS, the rate of dose errors did not decrease and remained constant. In their study, quick prescription and selection of drug dosages from drop-down menus by prescribers was mentioned as one of the factors contributing to medication errors. However, that study was performed in a general intensive care unit.

In our study, one probable reason that CPOE did not reduce medication errors was that, in absence of a dosing DSS, if we compare CPOE workflow with before CPOE workflow (Fig. 3), we observe that CPOE has no specific advantage to the before CPOE period in terms of preventing medication errors. Dose calculation in the neonatal setting is complicated and prone to miscalculations [44, 45]. The amount of active substance in ampoules and vials is usually appropriate for a single injection in adults. Therefore, by using pre-constructed order sets with default dose and frequency values and drop-down menus in a computerized prescription system, it is probably possible to reduce dosing errors in adults. However, in the neonatal setting sometimes the appropriate dosage is less than one-tenth of the pharmaceutical product. Therefore, in such a context, the system should help the prescriber for individual patients, and default values and drop-down menus are not useful.

It can even be argued that since nurses were experienced in typing, order entry by residents who had no previous experience in data entry, and were under a high tension and stress, should increase calculation as well as typing errors, as the other studies addressed previously [15, 16, 48]. However, we had several training sessions for residents before switching to physician order entry, and nurses verified prescriptions and informed the residents in the case of obvious typing mistakes. Therefore, physician order entry in period 2 did not significantly worsen the error rate of Period 1. Group and individual training sessions based on the user level and physician–nurse collaboration are mentioned as essential elements in successful implementation of CPOE [49–53].

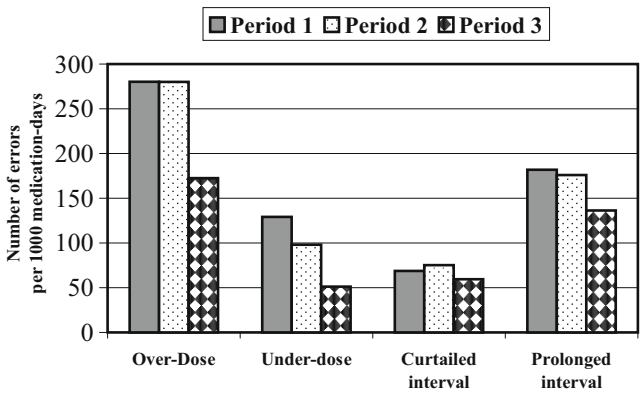

Fig. 4 Distribution of sub-types of dose and frequency errors in the three study periods

One of the major advantages of a CPOE without DSS is to prevent transcription errors by reducing frequent transcriptions and paperwork between care providers. This has been demonstrated in previous studies in the US and Europe [48, 54]. However, in Iran the laws do not allow withdrawal of paper-based orders. Therefore, even CPOE cannot reduce transcriptions in this context [55]. Comparison of the prescription workflow between CPOE and before CPOE period reveals that transcription activities (asterisks in Fig. 3) were not reduced after the introduction of CPOE. Indeed, reduction of transcription errors requires simplification of the prescription workflow and reduction of paperwork. However, *transcription* errors had a small share in the total number of errors in all three periods and *prescription* errors contributed to most of the errors. Kaushal et al. [5] have also mentioned that most of the medication errors in the neonatal setting occur in the prescribing stage.

Period 3

In our study, as in a number of previous studies, the combination of physician order entry and a decision support system in Period 3 resulted in a significant reduction of medication errors [8, 9, 19, 20, 56]. The reduction pattern shows that the rate of prescription errors was reduced but the rate of transcription errors remained constant. This strengthens the hypothesis that the rate of transcription errors is mostly related to the complexity of the prescription workflow and the number of transcription activities, not to the DSS. Since the number of transcription activities was not different in the three periods, the rate of transcription errors remained constant over time. It seems that DSS is not useful in reducing transcription errors, but is significantly useful in reducing prescription errors. Since most of the errors in the neonatal patients happen in the prescription stage [5], this reduction highlights the value of introducing CDSS in those neonatal wards that wish to improve their quality of care but cannot increase the number of care providers because of economic or other constraints.

Another pattern that could be observed is that in this period, the dose errors were more often intercepted than the frequency errors. One possible explanation is that miscalculations are always dose errors and it is easier to detect them by a warning in comparison with other causes of errors.

Despite the significant reduction, medication errors were not eliminated as they were in the study by Cordero et al. [20] and Gard et al. [19]. Different reasons may account for such a difference. Gard et al. used incident reports which can underestimate the real number of errors. However, Cordero et al. used a rigorous method, but they only assessed one antibiotic (gentamicin). They also had a clinical pharmacist who was actively involved in the intervention. In addition, in their system, the initial dosages were suggested by the system and not by the warnings. Therefore, they had prevented the errors from the beginning.

The other reason is the role of ignored warnings. van der Sijs et al. [23] have presented a list of previous studies which demonstrate that between 22% and 90% of the *dose* alerts were overridden. This may be due to several reasons including alert fatigue, physician's resistance, and inappropriate warnings. In addition, the complexity of appropriate dose calculation among neonates [44, 45] increases the risk of overridden warnings. In our study, when physicians could not understand the reason of the alert, especially in the complicated situations like renal insufficiency, they would perceive the warning as being inappropriate and ignored them. A warning without any explanation is probably effective when an obvious mathematical calculation occurs. However, for the other causes of errors, the method of calculation and the reason that the warning was appeared should be demonstrated to increase physician's compliance.

When a warning only suggests a number as a correct dose, and does not provide the rationale behind the calculation method and the reason that the warning is appeared, it will be difficult for the prescriber to guess how this number is calculated and why this warning is appeared. One suggestion is to add an explanation to the warnings based on the investigated causes of errors. For example, the explanation can inform the prescriber that the patient's renal function is impaired and dose should be reduced by a certain percentage or frequency should be prolonged. Then the prescriber will understand why the suggested dose or frequency does not match with the original guideline. Otherwise, the prescriber will ignore the warning, assuming that the DSS has suggested a dose or frequency that is incorrect.

The frequency of alerts is another important problem. In period 3, the alerts were only shown when a new dose was set or one of the dose decision criteria was changed. Therefore, if the resident ignored a correct alert, the warning was not shown in the following orders and they would remain erroneous. This could both increase medication errors and reduce the rate of error free patients. A possible remedy is to design the system to provide alerts more frequently, although this may increase users' frustration and increase the risk of non-reviewed ignored warnings, as stated by other studies [57].

Limitations

This study was performed in a neonatal setting, and therefore, the results are not generalizable to adults. We selected the same patient group over time because we could not divide patients or prescribers into two groups and set a control group

in the neonatal ward. CPOE implementation is a systemic change that affects prescription flow in the ward.

We also could not form a control group from the other wards of the hospital since the guidelines and measurement methods for medication errors were different between the neonatal and other wards.

Since medication errors in this study showed a linearly decreasing trend from Period 1 to 3, and we did not have a control group, it is possible that the errors were reduced not only because of the warnings, but also due to the better performance of prescribers. This can occur because the residents were under a continuous training program. They participated in different seminars and clinical rounds, and accordingly their knowledge could improve over time. Nevertheless, previous studies have reported that dose calculation skill among paediatric residents is not related to their experience, grade, level of training, or commitment to recheck their calculated doses [44, 45].

It is also possible that prescribers improved their performance in Period 3 because they knew that their errors would be investigated, which might led to the Hawthorne effect [47]. However, physicians knew from the beginning of the study that their errors would be investigated, and this general awareness was not limited to Period 3. In addition, the additive design of the interventions in our study reduces the impact of the Hawthorne effect on the obtained results. However, the Hawthorne effect should always be taken into consideration in the so-called before and after intervention study designs.

The decision support system could assess only those medications that were included in its knowledge-base, rather than all medications that were prescribed and administered in the neonatal ward. However, the calculation method is generalizable to many other drugs that are prescribed with the same dosing criteria in this ward. Exceptions could be serums and IV electrolytes like sodium and potassium chloride that are prescribed based on different criteria.

Conclusions

In the neonatal ward physician order entry *without* the decision support functionality does not reduce non-intercepted dose and frequency medication errors of antibiotics and anticonvulsants. However, when paired with a dose decision support system, it is capable of reducing these errors. The system is not effective in reducing transcription errors in this context. It seems that the reduction of transcription errors requires simplification of the prescription workflow and restriction of the paperwork. However, most of the errors occurred at the prescribing stage where CDSS is quite effective. This effectiveness, to some extent might compensate the lack of clinical pharmacists and other mechanisms required to recheck the accuracy of the prescribed dosages in those hospitals that they have serious human resource constraints.

When physicians do not understand the reasons of the alerts, they may ignore them. Therefore, we suggest adding explanations to the warnings which can describe to the prescriber, how the system has calculated the appropriate dose, and what is the reason that the warning is appeared. Such an attempt may increase physicians' compliance with the system's recommendations and further reduce medication errors.

Infrequent warnings increase the risk of repeated medication errors. Using frequent warnings that appear in every erroneous order may reduce this risk though it may reduce physicians' compliance.

Therefore, further studies are required to investigate the compliance of physicians with the frequent warnings and explanations and the effect of such a design on dosing medication errors.

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Authors' contribution

All authors contributed to the final approval of the submitted manuscript.

Alireza Kazemi contributed to conception and design of the study, performed observations, conducted the analysis with co-authors, and drafted the manuscript.

Johan Ellenius was involved in conception of the study, analysis, and revising the manuscript.

Faramarz Pourasghar was involved in data collection and revising the manuscript.

Shahram Tofighi was involved in conception of the study, and revising the manuscript.

Aref Salehi was involved in design of the study and revising the manuscript.

Ali Amanati was involved in data collection and revising the manuscript.

Uno Fors contributed to development of the study, analysis, and revising the manuscript.