A mobile device application to reduce medication errors and time to drug delivery during simulated paediatric cardiopulmonary resuscitation: a multicentre, randomised, controlled, crossover trial

Johan N Siebert, Frédéric Ehrler, Christophe Combescure, Christian Lovis, Kevin Haddad, Florence Hugon, Fanny Luterbacher, Laurence Lacroix, Alain Gervaix, Sergio Manzano for the PedAMINES Trial Group*

Summary

Background Vasoactive drug preparation for continuous infusion in children is both complex and time consuming and places the paediatric population at higher risk than adults for medication errors. We developed a mobile device application (app) as a step-by-step guide for the preparation to delivery of drugs requiring continuous infusion. The app has been previously tested during simulation-based resuscitations in a previous single-centre trial. In this trial, our aim was to assess this app in various hospital settings.

Methods We did a prospective, multicentre, randomised, controlled, crossover trial to compare this app with an internationally used drug-infusion-rates table for the preparation of continuous drug infusion during standardised, simulation-based, paediatric post-cardiac arrest scenarios using a high-fidelity manikin. The scenarios were split into two study periods to assess the two preparation methods consecutively, separated by a washout distraction manoeuvre. Nurses in six paediatric emergency centres in Switzerland were randomly assigned (1:1) to start the scenario with either the app or the infusion-rates table and then complete the scenario using the other preparation method. The primary endpoint was the proportion of participants committing a medication error, which was defined as a deviation from the correct weight dose of more than 10%, miscalculation of the infusion rate, misprogramming of the infusion pump, or the inability to calculate drug dosage without calculation and guidance help from the study team. The medication error proportions observed with both preparation methods were compared by pooling both study periods, with paired data analysed using the unconditional exact McNemar test for dependent groups with a two-sided α level of 0·05. We did sensitivity analyses to investigate the carryover effect. This trial is registered with ClinicalTrials.gov, number NCT03021122.

Findings From March 1 to Dec 31, 2017, we randomly assigned 128 nurses to start the scenario using the app (n=64) or the infusion-rates table (n=64). Among the 128 drug preparations associated with each of the two methods, 96 (75%, 95% CI 67–82) delivered using the infusion-rates table were associated with medication errors compared with nine (7%, 3–13) delivered using the mobile app. Medication errors were reduced by 68% (95% CI 59–76%; p<0·0001) with the app compared with the table, as was the mean time to drug preparation (difference 148·2 s [95% CI 124·2–172·1], a 45% reduction; p<0·0001) and mean time to drug delivery (168·5 s [146·1–190·8], a 40% reduction; p<0·0001). Hospital size and nurses' experience did not modify the intervention effect. We detected no carryover effect.

Interpretation Critically ill children are particularly vulnerable to medication errors. A mobile app designed to help paediatric drug preparation during resuscitation with the aim to significantly reduce the occurrence of medication errors, drug preparation time, and delivery time could have the potential to change paediatric clinical practice in the area of emergency medicine.

Funding Swiss National Science Foundation.

Geneva Children's Hospital, Department of Paediatric Emergency Medicine
(J N Siebert MD, K Haddad RN, F Hugon RN, F Luterbacher MD, L Lacroix MD, Prof A Gervaix MD, S Manzano MD) **and Division of Medical Information Sciences, Department of Radiology and Medical Informatics**
(F Ehrler PhD, Prof C Lovis MD), **Geneva University Hospitals, Geneva, Switzerland; Division of Clinical Epidemiology, Department of Health and Community Medicine, University of Geneva and Geneva University Hospitals, Geneva, Switzerland**
(C Combescure PhD); **and Faculty of Medicine, University of Geneva, Geneva, Switzerland**
(Prof C Lovis, Prof A Gervaix, S Manzano)

Correspondence to:
Dr Johan N Siebert, Geneva Children's Hospital, Department of Paediatric Emergency Medicine, Geneva University Hospitals, 1211 Geneva 14, Switzerland
johan.siebert@hcuge.ch

See **Online** for appendix

Introduction

Fast, accurate, and safe preparation and administration of continuous infusion is both complex and time consuming in paediatric critical situations, such as septic shock, cardiogenic shock, and return of spontaneous circulation (ROSC) following cardiopulmonary resuscitation from cardiac arrest.[1,2] Most drugs given intravenously to children are provided in vials originally prepared for the adult population, which leads to the need for a specific individual, weight-based drug dose calculation and preparation for each child that varies widely across age groups. This error-prone process and the lower dosing-error tolerance of children place them at a high risk for life-threatening medication errors.[3] Medication errors have been reported in up to 41% of cases during simulated paediatric resuscitations, 65% of which were incorrect

Research in context

Evidence before this study
Medication errors are among the most common medical errors. Most drugs given intravenously to children are provided in vials prepared for the adult population, which leads to the need for a specific individual, weight-based drug dose calculation and preparation. This error-prone process places children at a high risk for life-threatening medication errors, particularly in critical situations where the preparation and administration of continuous infusions are both complex and time consuming. Efforts have been undertaken to develop cognitive tools such as tables, calculators, colour-coded resuscitation tapes, or prefilled syringes to reduce medication errors. However, these tools were intended for drugs requiring a direct intravenous bolus route and not continuous infusion. Although increasingly used in some countries, there is mixed evidence that smart infusion pumps prevent medication errors and adverse drug events. The evaluation of new methods to reduce medication errors and time to deliver vasoactive drugs as continuous infusions during paediatric resuscitation is of paramount importance but research in this area is scarce. We searched PubMed for all available studies referring to continuous infusion of vasoactive drugs during cardiopulmonary resuscitation. The search extended arbitrarily from Jan 1, 1990, until Dec 11, 2018, with no language restriction. The following medical search terms were explored and connected by Boolean operators: "resuscitation" "cardiopulmonary resuscitation", "CPR", "drug", "medication errors", "risk", "effect", "infusion", "time", and "delay". The search was restricted to paediatric ages (from birth to age 18 years). We searched for all clinical trials, reviews, case reports and meta-analyses. 39 articles whose titles or abstracts included the search terms were reviewed. All identified articles were then submitted to our inclusion criteria for eligibility: articles had to describe time to preparation or delivery of vasoactive drugs for continuous infusion during cardiopulmonary resuscitation in children, or related medication errors. We only identified our previous single-centre trial as meeting these criteria.

Added value of this study
We developed a mobile device application—the paediatric accurate medication in emergency situations (PedAMINES) app—as a step-by-step guide for preparation to delivery of drugs requiring continuous infusion. The key finding is that medication errors with current tools were frequent and that time to preparation and delivery of vasoactive drugs for continuous infusion was dramatically reduced with the use of the app. We add new evidence of the benefit of a mobile app to improve the management of paediatric life-threatening situations by quickly delivering expertise in vasoactive drug administration, compared with an internationally used drug-infusion-rates table.

Implications of all the available evidence
We consider that this app has the potential to change critical care clinical practice when vasoactive continuous infusions have to be prepared and to improve quality of care in the paediatric vulnerable population. Its development also contributes to the goals of the WHO 3rd Global Patient Safety Challenge, which has the aim to reduce severe, avoidable medication-associated harm by 50% in all countries over the next 5 years.

medication dosage, making it the most common error.[4] In neonatal and intensive care units, as many as 70% of handwritten continuous infusion orders can contain medication errors.[5] Occurrence of medication errors further increases in critical care environments requiring the administration of several drugs where each can have its own concentration, dose, and volume.[3]

Early post-ROSC myocardial dysfunction and arterial hypotension are common and associated with increased neurological disability and mortality following successful resuscitation from cardiac arrest.[6] The 2015 American Heart Association guidelines recommend that providers consider immediate correction of hypotension by starting intravenous fluids and vasoactive drugs in the post-arrest phase.[7] The proper preparation and delivery of commonly administered vasopressors[8] in a very short period of time could favourably affect paediatric resuscitation outcomes.

In a previous single-centre, randomised controlled trial, medication errors, time to drug preparation, and time to drug delivery after ROSC were reduced by using a mobile device application—the paediatric accurate medication in emergency situations (PedAMINES) app[9]—designed to help paediatric drug preparation

(appendix). The aim of the present multicentre study was to compare this app with an internationally used drug-infusion-rates table method[10] (see appendix for further details) for the preparation of continuous drug infusion during standardised, simulation-based, paediatric post-cardiac arrest scenarios. We hypothesised that use of the app might extend and scale up our previous single-centre observations by similarly reducing occurrence of medication errors and time to drug preparation and delivery when used in various hospital settings, including those where nurses and doctors are less exposed to paediatric resuscitation.

Methods

Study design and participants
We did a prospective, multicentre, randomised, controlled, crossover trial at three tertiary and three regional paediatric emergency departments in Switzerland with a total of approximately 150 000 visits per year. The trial protocol has been published previously.[11] The trial was approved by the Geneva institutional ethics committee and conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study was

carried out in accordance with the Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online TeleHealth guidelines[12] and the Reporting Guidelines for Health Care Simulation Research.[13] Although the intervention could not be masked, all investigators remained unaware of the outcomes until all data were unlocked for analysis at the end of the trial. All certified paediatric nurses working at the six departments were eligible for inclusion in the study. Requirements for participant inclusion were to have followed a standardised 5-min introductory course on the use of the mobile device app and written informed consent. They were excluded if they had previously used a numerical device aimed at helping with vasoactive drug preparation. All participants were assumed to have equivalent experience and competence with the infusion-rates table because of their similar training background.

Randomisation and masking

Nurses were randomised using a stratified, single, constant 1:1 allocation ratio determined with web-based software. Written informed consent was obtained from each participant after full information disclosure prior to participation in the study. Blinding to the vasoactive drugs and doses intended for use was maintained during recruitment to minimise preparation bias. Allocation concealment was ensured with the allocation software and was not released until the nurses started the scenario. Study team members were revealed to the participants just before the scenario started. All scenarios were video-recorded for later analysis. Post-scenario video review was done without blinding by two reviewers (JNS and FL) who reviewed footage independently and were blinded to each other's reviews. The data analyst (CC) was not blinded to treatment allocation.

The PedAMINES app

The app was developed at Geneva University Hospitals (Geneva, Switzerland) following a user-centred and evidence-based approach with emergency department caregivers, software developers, and ergonomists. On the basis of paediatric resuscitation observations and focus groups, the team worked closely together to identify the key functionalities and processes to be implemented.[14]

The app lists all the available resuscitation drugs with doses automatically adapted to the weight or age of the patient based on information entered when starting the app. At the time of the study, 15 drugs for continuous infusion and 19 drugs for direct intravenous injection were listed in the app and were at the participating nurse's disposal. With one touch, any of the listed drugs can be selected and shown with a detailed preparation according to a standardised and simplified pathway. In the case of a continuous infusion, this pathway is composed of three steps: (1) drug selection, (2) dilution of the initial drug concentration, and (3) conversion of the prescribed dose rate in μg/kg per min into an infusion pump rate in mL/h.

For each drug, the exact amount to prepare is clearly displayed and thus avoids the necessity for calculations (see appendix for an example screenshot). This is based on the app's ability to automatically calculate the optimal weight-based final infusion-pump rate and describe the preparation sequence required to achieve it, independently of the user's competency in this domain. When using the app, the user can interact with it to start, pause, stop, increase, or decrease the perfusion rate at any time Multiple drugs can be prepared and run in parallel. All actions done by the user are sequentially saved locally on the device in historic files to preserve information that can be retrieved at any time for debriefing or medicolegal purposes. Historic files can also be erased or safely exported and saved in institutional electronic health records. We experienced no technical issues with the app during the study.

Procedures

On the day of participation after random allocation, each participating nurse received a standardised 5-min training session on how to use PedAMINES. The participants were then asked to perform a 15-min highly realistic cardiopulmonary resuscitation scenario on a high-fidelity manikin (SimJunior; Laerdal Medical, Stavanger, Norway), including post ROSC. The procedure was standardised across all sites using the same manikin. The scenario was conducted in situ in paediatric shock rooms to increase realism and was filmed with three video cameras (GoPro; San Matteo, CA, USA), worn by the participating nurse and placed within the room.

The untimed portion of the simulation involved a re-suscitation team comprising two study team members—a doctor (JNS) and a nurse (KH)—and the participating nurse. The untimed portion of the simulation started by turning on the three video cameras, with the participant and the doctor waiting outside the shock room. Both were invited to enter the shock room by the nurse investigator. When entering the room, a clinical statement to recognise the life-threatening condition of the patient, including his weight and age, was given by the nurse investigator as follows: "Here is Junior, a 16 kg, 3-year-old boy who drowned 8 min ago in a pool and was brought to the emergency department by his parents. He is unconscious, pale, and not breathing." At this moment, the doctor asked the participant to take a central pulse. Because of the invariable absence of a pulse, the participant was asked to assist the doctor in doing a 2-min full course massage and ventilation (15:2 ratio) manoeuvre, with the massage carried out by the participant, to increase the participant's stress level. During this time, the doctor asked the nurse investigator to place a 3-derivation electrocardiogram, an upper-arm blood pressure monitor, and a digital pulse oximeter on the manikin. Monitoring alarms were activated to increase the realism. The doctor then asked the nurse investigator to place a peripheral vascular access on the

manikin's right hand. At this time, an asystole rhythm was recognised and verbalised by the doctor. On the basis of the American Heart Association paediatric cardiac arrest algorithm for asystole,[7] a bolus of 0·01 mg/kg epinephrine (0·1 mL/kg of 0·1 mg/mL concentration) was ordered by the doctor and administered by the nurse investigator. ROSC ensued with arterial hypotension. The doctor said, "He now has a return of spontaneous circulation with a pulse but with low blood pressure. It's hypotensive shock! This patient needs a vasoactive drug, right now!" The participant was then asked to prepare and inject a 5 μg/kg per min continuous infusion of dopamine, using a syringe pump already in place, for a 16 kg boy, either with the help of the app or with the Shann infusion-rates table[10] depending on their randomised allocation, and the timed scenario began.

During the timed scenario, both the doctor and the nurse investigator maintained a stressful resuscitation atmosphere by frequently reporting vital sounds aloud and asking the participant to promptly provide the drugs. The nurse investigator was asked to administer a 20 mL/kg sodium chloride 0·9% intravenous bolus. The nurse investigator then had to evaluate and repeat the primary assessment (ABCDE approach) according to the Pediatric Advanced Life Support recommendations.[15] The participant was then asked to do a washout distraction manoeuvre consisting of aspirating secretions in the throat when the manikin emitted a retching sound. After this task had been completed, the crossover occurred. The doctor said, "OK, airways are now clear. But despite the volume expansion with sodium chloride and dopamine infusion, the patient is still in hypotensive shock! He needs a second vasoactive drug, right now!" The participant was asked to prepare and inject a 0·1 μg/kg per min continuous infusion of norepinephrine by crossing over the procedure—ie, by using the app if previously they had used the infusion-rates table or vice versa. To render the task uniform between both groups, the final volume of norepinephrine required a decimal point-dependent calculation with both the infusion-rates table and mobile device app preparation methods. During this time, both the doctor and the nurse investigator maintained a stressful resuscitation atmosphere as described above. When the drug was ready to be injected, the participant was asked to deliver it to the patient using a second syringe pump already in place. The beginning of the injection corresponded to the end of the scenario. The GoPro cameras were turned off 1 min later. Before leaving the shock room, the participant was asked to recall and describe precisely how they had prepared both drugs and was asked to complete a questionnaire about the scenario immediately afterwards.

The delivery of both drugs required programming the same pump in a similar manner among all participants. The time elapsed after drug preparation until its delivery—ie, time needed to set up the pump—was assessed for all participants to ensure uniformity. The measured deviation between the amount of drug delivered and the actual prescribed dose were measured by the amount of drug in the syringe and video recorded. To ensure that participants had heard and understood the prescription orders correctly, they had to confirm the orders verbally and written transcriptions were checked and video recorded.

Outcomes

The primary outcome was the proportion of medication dosages containing errors that occurred during the sequence from drug preparation to drug injection. We defined an emergency medication dose administration error as a deviation from the correct weight dose of more than 10%.[16] These errors were measured both as the percentage deviation from the amount of delivered drug compared with the correct weight dose as prescribed by the doctor and the absolute deviations from that dose. Miscalculation of the infusion rate, misprogramming of the infusion pump, and the inability to calculate drug dosage without calculation and guidance help from the nurse investigator were also considered medication errors. The accumulation of some or all of these errors was defined as a cumulative error.

Secondary outcomes were the elapsed time in seconds between the oral prescription by the doctor and time to drug preparation completion by the participant, the elapsed time in seconds between the oral prescription by the doctor and time to drug delivery by the participant, analysis of the type of medication errors (ie, error in transcription of the doctor's order into the medication dose, wrong choice of drug, wrong vial's initial concentration), and perceived stress and satisfaction scores after completion of the scenario, as measured in the questionnaire using ten-point Likert scales (appendix).

Other secondary outcomes were measured in this trial and they will be analysed and discussed in a separate article. These outcomes were (1) the participants' stress level assessed by measuring continuously their heart rate using a smartwatch during the resuscitation scenario and (2) the acceptability and usability testing of the app assessed using a 52-item questionnaire based on the unified theory of acceptance and use of technology model.[17]

Statistical analysis

Power calculations were based on the detection of a minimum difference of 30% in the proportion of nurses committing a medication error, which we considered to be a sufficient difference to modify the practice (appendix). Assuming that 15% of nurses would commit a medication error with the app and 45% without the app, eight participants per group had to be recruited in each participating centre to provide the trial with 90% power at a two-sided α level of 0·05. To prevent a potential loss of power due to mis-specification of assumptions, ten participants were recruited per group and per centre, giving a total sample size of

120 participants. Further information regarding the sample size calculation has been published previously.[11]

The proportion of medication errors committed was reported for each method and by study period, with the exact Clopper-Pearson 95% CI. For the primary analysis, the medication error proportions observed with both preparation methods were compared by pooling both study periods. Paired data were then analysed using the unconditional exact McNemar test for dependent groups with a two-sided α level of 0·05. Potentially, the efficacy of the app could be different depending on the first method used in the crossover design—ie, a carryover effect. To investigate this effect, we did sensitivity analyses in which we compared the mean difference in the proportion of medication errors between both preparation methods by study period (independent observations) using Fisher's exact test and by randomised group (paired observation) using the unconditional exact McNemar test, with a two-sided α level of 0·05. All such differences were reported with exact 95% CIs. The carryover effect was tested in a logistic, multivariable generalised estimating equation (GEE) model with an exchangeable working correlation matrix as follows: the study period and the preparation method were introduced as independent variables and an intercept term was introduced to model a modification of the preparation method's effect between the first and second study periods. The null hypothesis that the interaction term was null was tested to detect a carryover effect. Errors were also measured as the percentage of deviation from the amount of delivered drug compared with the original dose prescribed by the doctor.

The secondary outcomes (time to drug preparation and time to drug delivery) were reported for each method and by study period. Mean time to drug prepration observed with both preparation methods was compared by pooling both study periods. Data were then analysed using a t test for paired data with a two-sided α level of 0·05. Mean time to drug preparation was also compared between both preparation methods by study period (independent observations) and by randomised group (paired observation) using a two-sided exact test for independent or dependent groups, respectively, with a two-sided α level of 0·05. All differences in time to drug preparation were reported with exact 95% CIs. The carryover effect was tested in a linear, multivariable GEE model with an exchangeable working correlation matrix in a similar way as for the primary outcome. The same analyses were done for time to drug delivery.

For primary and secondary outcomes, the efficacy of the app was tested by individual hospital to avoid confounding. In addition, analyses were conducted to test differences between tertiary and regional hospitals or nurses' experience with both preparation methods. First, the association between the outcomes and these factors was tested for each preparation method using χ² tests for the error proportions, a t test for independent groups, and an ANOVA test for time to drug preparation and time to drug delivery. Second, an effect size modification of the app due to these factors was also tested using logistic GEE models for the analysis of the error proportions and t tests for independent groups, as well as ANOVA tests for analyses of time to drug preparation and delivery. Finally, means and SDs were determined for perceived stress and satisfaction scores of individuals from the Likert-scale questionnaire for each preparation method and compared using a t test for paired data.

All videos were reviewed by the first reviewer (JNS). To assess the reproducibility of the video review procedure, a second reviewer (FL) independently duplicated the review in a randomly selected 10% of all videos. Details regarding the statistical analysis of the inter-rater reliability scores are available in the appendix.

In the case of missing data, a complete case analysis was done. No multiple imputation was planned. All statistical tests were two-sided with a type one error risk of 0·05. We used GraphPad Prism version 7 for graph figures, Stata/IC version 14 for descriptive analyses, R version 2.15.2 for GEE models and statistical tests, and StatXact version 11.1.0 for exact statistical tests and exact 95% CIs. This trial is registered with ClinicalTrials.gov, number NCT03021122.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.
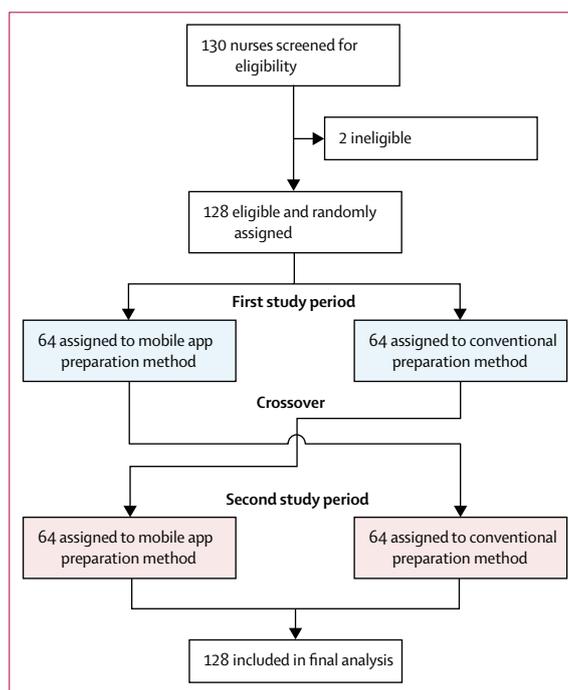

Figure 1: **Trial profile**

	Infusion-rates table first (n=64)	Mobile app first (n=64)
Age, years	37·4 (10·4)	37·1 (9·1)
Gender		
Female	60 (94%)	61 (95%)
Male	4 (6%)	3 (5%)
Years since nurse certification	13·3 (9·4)	13·9 (9·0)
Years since paediatric emergency department certification	5·9 (6·3)	6·5 (7·0)
Own and use a tablet or smartphone at home	63 (98%)	60 (94%)
Number of resuscitations having required vasoactive drugs preparation for continuous infusion in the past 2 years		
In both tertiary and regional hospitals	1·9 (4·2)	2·6 (6·9)
In tertiary hospitals	3·0 (5·8)	3·9 (9·6)
In regional hospitals	1·0 (1·3)	1·5 (2·7)
Number of simulated cardiopulmonary resuscitation scenarios in the past 2 years		
In both tertiary and regional hospitals	2·8 (3·0)	2·7 (3·3)
In tertiary hospitals	4·0 (3·0)	3·8 (4·5)
In regional hospitals	1·8 (1·2)	1·8 (1·1)
Last preparation of vasoactive drug infusion		
Never done	29 (45%)	28 (44%)
>24 months	21 (33%)	15 (23%)
<24 months and ≥12 months	5 (8%)	7 (11%)
<12 months and ≥6 months	4 (6%)	9 (14%)
<6 months	5 (8%)	5 (8%)

Data are n (%) or mean (SD). Randomisation groups as presented as those who used the infusion-rates table method during period 1 and the mobile app during period 2 (infusion-rates table first) and those who used the mobile app during period 1 and the infusion-rates table during period 2 (mobile app first).

Table 1: Baseline characteristics

	Global errors		Time to drug preparation, s	Time to drug delivery, s
	Number*	Proportion (95% CI)		
Periods 1 and 2				
Infusion-rates table	96/128	75% (67–82)	329·6 (143·1)	421·2 (146·5)
Mobile app	9/128	7% (3–13)	181·4 (54·7)	252·8 (62·1)
Period 1				
Infusion-rates table	49/64	77% (64–86)	327·5 (154·0)	433·0 (152·4)
Mobile app	6/64	9% (4–19)	158·2 (49·8)	232·8 (61·3)
Period 2				
Infusion-rates table	47/64	73% (60–85)	331·7 (132·7)	409·5 (140·6)
Mobile app	3/64	5% (1–13)	204·7 (49·5)	272·7 (56·6)

Data are n/N or mean (SD) unless otherwise stated. To verify that the longer time spent to prepare the drugs with the infusion-rates table was not influenced by a type of drug that would have required more complex calculations than the others, tasks were assessed for uniformity. Tasks were uniform using the infusion-rates table regardless of the drugs used (median time to drug preparation 286 s for dopamine vs 311 s for norepinephrine, p=0·68; median time to drug delivery 382·5 s for dopamine vs 393·5 s for norepinephrine, p=0·49). *Number of errors over number of preparation opportunities.

Table 2: Outcomes descriptive analysis by method and study period

Results

From March 1 to Dec 31, 2017, 130 nurses were assessed for eligibility, of whom 128 were randomly assigned to either the mobile app preparation method first (n=64) or the infusion-rates table preparation method first (n=64), without any dropouts or missing data (figure 1). Baseline characteristics seemed balanced in the two groups (table 1). We observed good to excellent inter-rater agreement for video reviewing (appendix).

Because data did not support a carryover effect in the proportion of participants committing a medication error (appendix), both study periods were pooled. Of the 256 drug doses delivered, 96 (75%) of 128 delivered using the infusion-rates table method were associated with medication errors compared with nine (7%) of 128 delivered using the mobile app (table 2). Medication errors were therefore reduced by 68% (95% CI 59–76; p<0·0001) using the mobile app (table 3). Among the 96 errors committed with the infusion-rates table, 18 (19%) were overdoses ranging from 19% to 60 000% (median 1099% [IQR 217–4615]) of the normal prescribed dose and

53 (55%) were underdoses ranging from 10% to 99·96% (median 90% [69–97]; appendix). 68 (71%) of the errors were due to an inappropriate amount of drug drawn from the vial whereas three (3%) were due to inappropriate dilution with sodium chloride. Three (3%) of the remaining errors were due to the indiscriminate use of the whole dopamine vial, four (4%) were related to wrong pump infusion rates, and 18 (19%) were preparations having required strong support from the nurse investigator. 72 (75%) of 96 incorrect infusions were cumulative errors. Among these, nurses unable to prepare the drugs without support accounted for 58 (81%) of the errors and 16 (22%) contained wrong infusion rates. We observed no errors in the communication of the drug doses (ie, no errors in the prescription given by the doctor nor these prescriptions being misheard by the participants).

Among the nine errors committed when using the app, three (33%) were overdoses ranging from 19% to 33% (median 33% [IQR not possible]) of the normal prescribed dose and six (67%) were underdoses ranging from 17% to 90% (median 41% [29–64]; appendix). Five (56%) of the errors were due to an inappropriate amount of drug drawn from the vial and four (44%) were due to inappropriate dilution with sodium chloride. One participant correctly chose dopamine but followed the wrong drug preparation instruction on the app (dobutamine instead of dopamine). Another participant used norepinephrine at 0·1 mg/mL initial concentration instead of 1 mg/mL, despite correct instructions on the app. No preparation required help from the nurse investigator. A benefit from using the mobile app was observed in all centres but with some

	Errors		Mean time to drug preparation		Mean time to drug delivery	
	Difference (95% CI)	p value*	Difference (95% CI)	p value†	Difference (95% CI)	p value†
Period‡						
Period 1	67% (53–79)	p<0·0001	169·4 (129·1–209·6)	p<0·0001	200·1 (159·3–241·0)	p<0·0001
Period 2	69% (55–80)	p<0·0001	127·0 (91·8–162·2)	p<0·0001	136·8 (99·1–174·5)	p<0·0001
Randomisation group§						
Infusion-rates table first	72% (59–82)	p<0·0001	122·8 (85·2–164·5)	p<0·0001	160·3 (125·9–194·7)	p<0·0001
Mobile app first	64% (49–76)	p<0·0001	173·5 (144·2–202·8)	p<0·0001	176·6 (147·1–206·1)	p<0·0001
All groups and periods	68% (59–76)	p<0·0001	148·2 (124·2–172·1)	p<0·0001	168·5 (146·1–190·8)	p<0·0001

Differences are between participants using the infusion-rates table and participants using the mobile app. For mean time to drug preparation or delivery, the difference was calculated as the values for participants using the infusion-rates table minus the values for those using the mobile app. Randomisation groups as presented as those who used the infusion-rates table method during period 1 and the mobile app during period 2 (infusion-rates table first) and those who used the mobile app during period 1 and the infusion-rates table during period 2 (mobile app first). *p values calculated using Fisher's exact test for analyses by period and the exact unconditional McNemar test for analyses by randomisation group and all groups and periods. †p values calculated using t tests for comparison of means with independent groups, except for the analysis by randomisation groups and by all groups and periods, which were calculated using a t test for comparison of means with paired data. ‡Difference in proportion of participants committing medication errors within the specified period, in different randomisation groups. §Difference in proportion of participants committing medication errors within the specified randomisation group, in different periods.

Table 3: Outcome differences

heterogeneity in the effect size (appendix). The hospital size (tertiary *vs* regional) and nurses' years of experience did not modify the intervention effect (appendix).

Mean time to drug preparation and time to drug delivery was shorter with the app than with the infusion-rates table in both study periods (table 2; appendix). Overall, time to drug preparation decreased by 45% with the app and time to drug delivery decreased by 40% (tables 2, 3). The shorter time to drug delivery with the mobile app was similar in both study arms, regardless of whether participants started the scenario with the app or the table (table 3). Shorter time to drug preparation and time to drug delivery were observed overall when using the app but with some heterogeneity (appendix) and without any difference between tertiary and regional hospitals (appendix). Nurses' years of experience did not modify the intervention effect (appendix). Finally, the variability of individual recorded times was lower with the app than with the table (table 2; figure 2).

The questionnaire was completed by all participants. Participants rated the overall perceived stress before the scenario as 4·8 (SD 1·9) on the 10-point Likert scale. After scenario completion, they reported higher stress using the infusion-rates table than the app (8·6 [SD 1·6] *vs* 4·9 [2·0]; p<0·0001). The app obtained a mean overall satisfaction score of 9·4 (1·0) out of 10.

Discussion

Early haemodynamic alterations after ROSC or shock states can require vasoactive support as continuous drug infusions. However, despite conversion methods intended to simplify their preparation in children,[18] such infusions remain difficult to use and prone to medication errors. In this multicentre, randomised, controlled, crossover trial, we report lower medication error rates with the mobile app PedAMINES than with an internationally used infusion-rates table for the preparation of continuous drug infusions
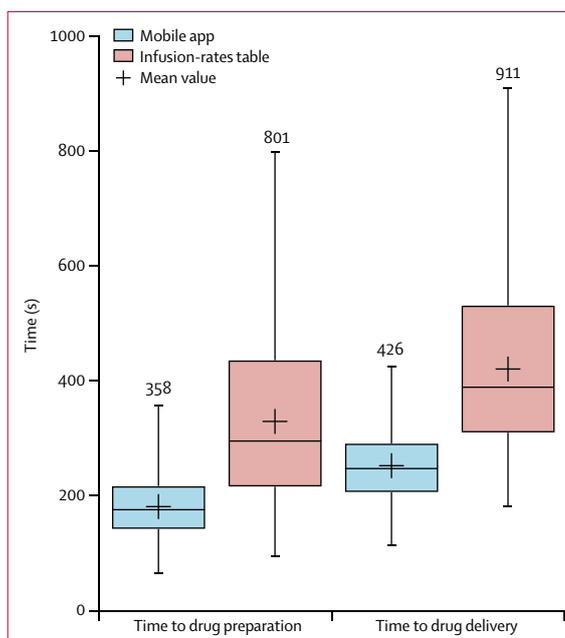
Figure 2: Boxplots of time to drug preparation and time to drug delivery for participants when using the mobile app compared with when using the infusion-rates table

Solid horizontal lines denote median and IQR; the endpoints of the whiskers indicate the range. The long upper whiskers show that participants were more varied among the most positive quartile groups. Upper range values are given for clarity. The difference between groups was significant for both time to drug preparation and time to drug delivery using the t test for paired data (p<0·0001).

among paediatric emergency department nurses with little experience in preparing vasoactive infusions. This result was observed in both tertiary and regional hospitals, irrespective of nurses' years of experience. Inter-individual variance was also reduced with the app, suggesting a worthwhile benefit of its use by nurses with different experience levels.

Paediatric emergency departments present a unique clinical practice environment that is especially at risk for the occurrence of medication errors, particularly when procedures such as continuous infusions preparation in critical situations are complex and uncommon. To date, there is a paucity of studies providing insight into the magnitude of errors made in continuous infusions during emergency medical situations in critical care settings, and especially in paediatric emergency departments. This lack of data might not reflect the true reality of this phenomenon. The 75% occurrence of medication errors we observed using the infusion-rates table is consistent with these studies. 70–73% errors have been observed in handwritten continuous infusions in neonatal and paediatric intensive care units where nurses are more exposed to critically ill children requiring vasoactive continuous infusions.[5,19] Numerous interventions involving information technologies have been developed to improve the security of the medication process.[20] However, apart from computerised physician order entry systems and so-called smart intravenous pumps, few robust data are available to measure their real impact on patient safety.[21] Smart pumps are available and extensively used in the USA, but they are expensive and do not have features that help to prepare a syringe for a specific weight-based infusion rate for a drug supplied in a specific concentration. Furthermore, no conclusive evidence shows that smart pumps prevent medication errors and adverse drug events.[22,23] Some authors have advocated to replace tasks inducing cognitive load during paediatric resuscitation as much as possible by automated actions to optimise patient care and diminish medication errors.[24] Multiple dose calculators are available on the web or as smartphone apps but most are not evidence based. These programmes most often calculate the infusion rate for a specific drug concentration, whereas the PedAMINES app handles the conversion of specific drug concentrations in mL/h into an infusion rate in µg/kg per min. They also do not provide information on how to prepare the drug solution, whereas PedAMINES does. This is an important consideration for paediatric patients. Although emergency medication given to adults being resuscitated are often in prefilled ready-to-inject syringes containing a single dose adapted for most patients, drugs given to paediatric patients are typically provided in vials not adapted for this population. The correct dose must first be calculated before being drawn. Errors with infusions frequently result from mistakes during preparation due to wrong drug-volume calculations, imprecision of volume measurements, or incorrect mixing during dilution.[25] At this stage, even small errors can have a large detrimental impact on the amount of drug delivered.[5,26] We suggest that a mobile device app designed to help paediatric drug preparation might circumvent some of these flaws.

Although the components contributing to survival from resuscitation are complex and numerous, survival relies in part on time to drug preparation.[27] In a study[28] with adults in cardiac arrest, the chance of ROSC was decreased by 4% for every 1-min delay in delivery of a vasopressor bolus dose. The immediate post-arrest period is also a time in which patients are at substantial risk of re-arrest. Although optimal management of post-ROSC has not been established, maintaining sufficient cardiac perfusion by vasopressor support during and immediately after cardiac arrest is recommended as part of a bundle of care to improve haemodynamic status, avoid or minimise any hypotension-related ischaemia to vital organs, and attempt to improve long-term survival and neurological outcomes.[6,7,29,30] In our study, use of the app reduced time to drug preparation and time to drug delivery by 45% and 40%, respectively. The ability to reduce the delay from the moment the drug is prescribed might contribute to improving haemodynamic support.

Our study has some limitations. First, it was done during a resuscitation simulation-based scenario rather than tested in real-life situations. However, high-fidelity simulation is an essential method to teach resuscitation skills and technologies that cannot be practised during real cardiopulmonary resuscitation because the diversity among patients and their diseases makes such studies hard to standardise in critical situations.[31] Moreover, standardising the scenario and the environment helped to avoid effect modifiers by limiting the influence of undesired variables on the outcomes. Second, the 5-min app training was dispensed just before the scenario. In real life, the interval between training and actual use would probably be months. However, training with the app months before the study would have unblinded participants to its purpose and could have created a preparation bias. Finally, our findings might not be generalisable to providers with extensive experience in preparing vasoactive infusions, such as neonatal and paediatric intensive care unit nurses.

In conclusion, this randomised trial showed fewer medication errors and shorter times to drug preparation and delivery for continuous drug infusions when using a mobile app designed to help paediatric drug preparation compared with an infusion-rates table. A next step would be to determine in real-life studies whether the reduced occurrence of medication errors and time saved owing to the use of this app translates into similar results in clinical practice. The results generated from this simulation-based study might be of great importance and might be sufficient to change and improve future paediatric emergency and critical care practice.

Contributors
JNS was the chief investigator, conceived the study, led the design, collected the data, contributed to the statistical outcome analyses, prepared the figures and tables, and drafted the paper. FE conceived the study, contributed to the design, and was responsible for the development of the project software PedAMINES. CC contributed to the design and carried out the trial analyses. CL contributed to the development of the project software. KH was a study investigator, coordinated the study in each trial centre, and was in charge of the

References
1   Moyen E, Camire E, Stelfox HT. Clinical review: medication errors in critical care. *Crit Care* 2008; **12:** 208.
2   Polischuk E, Vetterly CG, Crowley KL, et al. Implementation of a standardized process for ordering and dispensing of high-alert emergency medication infusions. *J Pediatr Pharmacol Ther* 2012; **17:** 166–72.
3   Kaufmann J, Laschat M, Wappler F. Medication errors in pediatric emergencies: a systematic analysis. *Dtsch Arztebl Int* 2012; **109:** 609–16.
4   Porter E, Barcega B, Kim TY. Analysis of medication errors in simulated pediatric resuscitation by residents. *West J Emerg Med* 2014; **15:** 486–90.
5   Lehmann CU, Kim GR, Gujral R, Veltri MA, Clark JS, Miller MR. Decreasing errors in pediatric continuous intravenous infusions. *Pediatr Crit Care Med* 2006; **7:** 225–30.
6   Topjian AA, Telford R, Holubkov R, et al. Association of early postresuscitation hypotension with survival to discharge after targeted temperature management for pediatric out-of-hospital cardiac arrest: secondary analysis of a randomized clinical trial. *JAMA Pediatr* 2018; **172:** 143–53.
7   de Caen AR, Berg MD, Chameides L, et al. Part 12: pediatric advanced life support: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2015; **132** (suppl 2)**:** S526–42.
8   American Heart Association. Web-based integrated guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 12: Pediatric advanced life support. 2015. https://eccguidelines.heart.org/wp-content/themes/eccstaging/dompdf-master/pdffiles/part-12-pediatric-advanced-life-support.pdf (accessed Dec 10, 2018).
9   Siebert JN, Ehrler F, Combescure C, et al. A mobile device app to reduce time to drug delivery and medication errors during simulated pediatric cardiopulmonary resuscitation: a randomized controlled trial. *J Med Internet Res* 2017; **19:** e31.
10 Shann F. Drug doses, 17th edn. Melbourne: RCH Intensive Care Unit, The Royal Children's Hospital, 2017.
11 Siebert JN, Ehrler F, Lovis C, et al. A mobile device app to reduce medication errors and time to drug delivery during pediatric cardiopulmonary resuscitation: study protocol of a multicenter randomized controlled crossover trial. *J Med Internet Res Protoc* 2017; **6:** e167.
12 Eysenbach G. CONSORT-EHEALTH: improving and standardizing evaluation reports of web-based and mobile health interventions. *J Med Internet Res* 2011; **13:** e126.
13 Cheng A, Kessler D, Mackinnon R, et al. Reporting guidelines for health care simulation research: extensions to the CONSORT and STROBE statements. *Simul Healthc* 2016; **11:** 238–48.
14 Hagberg H, Siebert J, Gervaix A, et al. Improving drugs administration safety in pediatric resuscitation using mobile technology. *Stud Health Technol Inform* 2016; **225:** 656–57.
15 American Heart Association. Pediatric advanced life support (PALS) provider manual, 1st edn. Dallas, TX: American Heart Association, 2016.
16 Marcin JP, Dharmar M, Cho M, et al. Medication errors among acutely ill and injured children treated in rural emergency departments. *Ann Emerg Med* 2007; **50:** 361–67.
17 Venkatesh V, Morris MG, Davis GB, Davis FD. User acceptance of information technology: toward a unified view. *MIS Q* 2003; **27:** 425–78.
18 Sherry E, Burton GW, Wilkins DG. Infusion nomograms. *Anaesthesia* 1993; **48:** 396–401.
19 Vaidya V, Sowan AK, Mills ME, Soeken K, Gaffoor M, Hilmas E. Evaluating the safety and efficiency of a CPOE system for continuous medication infusions in a pediatric ICU. *AMIA Annu Symp Proc* 2006; **2006:** 1128.
20 Bonnabry P. Information technologies for the prevention of medication errors. *CHIMIA* 2005; **59:** 359–61.
21 Acheampong F, Anto BP, Koffuor GA. Medication safety strategies in hospitals-a systematic review. *Int J Risk Saf Med* 2014; **26:** 117–31.
22 Franklin BD. 'Smart' intravenous pumps: how smart are they? *BMJ Qual Saf* 2017; **26:** 93–94.
23 Schnock KO, Dykes PC, Albert J, et al. The frequency of intravenous medication administration errors related to smart infusion pumps: a multihospital observational study. *BMJ Qual Saf* 2017; **26:** 131–40.
24 Luten R, Wears RL, Broselow J, Croskerry P, Joseph MM, Frush K. Managing the unique size-related issues of pediatric resuscitation: reducing cognitive load with resuscitation aids. *Acad Emerg Med* 2002; **9:** 840–47.
25 Adapa RM, Mani V, Murray LJ, et al. Errors during the preparation of drug infusions: a randomized controlled trial. *Br J Anaesth* 2012; **109:** 729–34.
26 Parshuram CS, To T, Seto W, Trope A, Koren G, Laupacis A. Systematic evaluation of errors occurring during the preparation of intravenous medication. *CMAJ* 2008; **178:** 42–48.
27 Andersen LW, Berg KM, Saindon BZ, et al. Time to epinephrine and survival after pediatric in-hospital cardiac arrest. *JAMA* 2015; **314:** 802–10.
28 Hubble MW, Johnson C, Blackwelder J, et al. Probability of return of spontaneous circulation as a function of timing of vasopressor administration in out-of-hospital cardiac arrest. *Prehosp Emerg Care* 2015; **19:** 457–63.
29 Lopez-Herce J, del Castillo J, Matamoros M, et al. Post return of spontaneous circulation factors associated with mortality in pediatric in-hospital cardiac arrest: a prospective multicenter multinational observational study. *Crit Care* 2014; **18:** 607.
30 Neumar RW, Nolan JP, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. *Circulation* 2008; **118:** 2452–83.
31 Cheng A, Auerbach M, Hunt EA, et al. Designing and conducting simulation-based research. *Pediatrics* 2014; **133:** 1091–101.