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Article (Accepted Version)

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Conflicts of interest: None

SUMMARY

What is known?

- Intraventricular haemorrhages (IVH) caused by rapid changes in blood pressure in neonates lead to adverse effects such as poor long-term neurodevelopment and increased mortality.
- Inotropes, commonly dopamine, are used in neonatal intensive care units (NICU) to treat hypotension by increasing peripheral vascular resistance.
- Majority of studies that observed dopamine instability have utilised protocols with high temperature (>50 °C).

What this study adds?

- Laboratory studies on dopamine instability under simulated NICU settings show rapid degradation within the first hour of the infusion, followed by gradual degradation over 24 hours.
- This coincides with a rapid fluctuation in mean arterial pressure (MAP) observed following infusion changeover of dopamine.
- Changing our standard operating procedure (SOP) so that dopamine infusions were administered 30 minutes after preparation and for a duration of 12 hours removed rapid fluctuations observed in the MAP during infusion changeover.

ABSTRACT

OBJECTIVE To evaluate whether changing dopamine infusions every 12 hours and preparing these infusions 30 minutes before administration reduces blood pressure fluctuations in pre-term and term neonates.

DESIGN This was a retrospective study using data from live patients on the neonatal unit and prospective study exploring stability of infusions in a laboratory based neonatal ward simulation.

SETTING Single centre study in a tertiary neonatal surgical unit in a university teaching hospital.

PATIENTS Neonates who received more than one subsequent dopamine infusion and had invasive arterial blood pressure monitoring, during their admission in the neonatal unit, were included.

INTERVENTIONS As part of the Quality Improvement project the SOP was changed, and dopamine infusions were prepared by nursing staff and left to rest for 30 minutes before administering to the neonate. Additionally, infusions were replaced every 12 hours.

MAIN OUTCOME MEASURES The percentage change in mean arterial pressure (MAP) and the percentage loss in the drug concentration during infusion during changeover.

RESULTS Our findings indicate that up to 15 % of the initial dopamine concentration is lost after 24 hours. This results in a sharp variation in the dopamine concentration during infusion changeover that correlates with observed rapid fluctuations in MAP.

In changing the SOP, no signficant difference in the concentration of dopamine and MAP were observed over 12-hours.

CONCLUSIONS Delaying administration of dopamine infusions by 30 minutes after preparation combined with changing infusions 12 hourly has reduced MAP fluctuations. Therefore, the risks associated with MAP fluctuations, including intraventricular haemorrhages, are reduced.

Introduction

Neonatal hypotension is a common condition with one third to a half of neonates being hypotensive within 24 hours of admission to neonatal intensive care units (NICUs) [1]. This hypotension can be transient or persisting depending on its cause [2-4]. Neonatal hypotension is initially treated with volume support followed by inotrope therapy (dopamine or dobutamine) if blood pressure (BP) has not improved. The main goal of initiating inotrope therapy in a hypotensive neonate is to increase cardiac output and raise BP thereby maintaining adequate organ and tissue perfusion [5 6]. Although inotrope therapy is widely used in neonatal hypotension, its efficacy in this patient population is often debated [7-10]. At present, there is a lack of neonatal specific formulations and doses are prepared from adult vials. There are also observations of the fluctuations in BP following inotropic infusion changeover [11-14]. It has been proposed that these fluctuations in BP can lead to poor organ perfusion, intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), retinopathy of prematurity and mortality [15]. Additionally, IVH have been associated with poor neurological, motor and cognitive outcomes at both 1 and 2-3 years of age

[16]. It is currently unclear whether the fluctuations arise as a result of therapy or hypotension [2 4 7 17] but given the risks associated, it is crucial to minimise the fluctuations where possible.

The infusion changeover technique [14 18], knowledge and training of the nursing staff, [19] and the stability of dopamine itself have been investigated as possible reasons for these BP fluctuations following infusion changeover. Little alteration in the frequency of rapid fluctuations in BP were observed when changeover technique and training of nursing staff were investigated as a cause. Stability studies have questioned dopamine's stability when exposed to light, plastic, infusion vehicles and other drugs [20-27]. Many of the stability studies conducted on dopamine were undertaken at room temperature and concluded dopamine to be stable. Stability was assumed at all temperatures, which led to dopamine being used in neonatal clinical practice. The doses used in these stability studies were often unrepresentative of clinical dosing regimens, therefore their conclusions cannot be applied to the neonatal population. The lack of data representative of the neonatal environment led to the study which assessed the role of light and infusion vehicles on dopamine's stability at 35 °C, where a loss in stability was observed [20].

In this retrospective and prospective study, we evaluated how the MAP varied during infusion changeover following implementation of a new standard operating procedure (SOP) for delivery of dopamine as part of the unit´s quality improvement project. This SOP was based on analysis of the changes in dopamine concentration during infusion in neonatal simulated ward conditions.

Methods

Patient and public information

The parent's forum group at the NICU were informed regarding the project proposed and consulted for their thoughts on the outcomes of our findings.

Evaluation of dopamine concentration in laboratory based neonatal simulated ward conditions.

In the old SOP, infusions were administered for a maximum of 24 hours. Based on the changes in dopamine stability observed, a new SOP was established to minimise changes in dopamine concentration, where infusions were prepared in syringes at room temperature, rested horizontally on a sterile field for 30 minutes (except the first dose) prior to infusion for a maximum of 12 hours. The dopamine dose used to correct haemodynamic imbalance in neonates is initially 3 micrograms/kilogram/minute with a maximum dose of 20 micrograms/kilogram/minute[28]. Therefore, the dosing regimens prepared were 0.6 mg/ml for neonatal weights of 1 kg (median weight seen in the NICU), 0.24 mg/ml for 400 g and 3 mg/ml for 5 kg (range of weights observed in the NICU). All doses were prepared by diluting vials of 200mg/5ml dopamine hydrochloride (Martindale Pharmaceuticals, Essex, UK) in 50 ml syringes in either 0.45% NaCl, 0.9 % NaCl, 10 % glucose or 5 % glucose (Baxter Healthcare Ltd, Norfolk, UK). Infusions were placed into an incubator (Thermo Fisher Scientific) set at 35 °C. Concentrations were analysed 30 minutes, 1 hour and 2 hours after the start of the infusion and 30 minutes and 1 hour before the end of the infusion for either SOP using high performance liquid chromatography (method in Supplementary information).

Patient group and selection criteria

Our tertiary neonatal unit uses BadgerNet® for daily online recording of all babies within neonatal services. Neonates of all gestations, weights and sexes that received more than one subsequent dopamine infusion during their admission into the unit and had their BP monitored invasively were selected in this retrospective and prospective study. Using BadgerNet, 13 neonates meet the selection criteria who were on the old SOP and 17 neonates met the criteria for the new SOP (additional details on the patient group in Supplementary information). In the neonatal unit, for the new SOP, following dilution of the dopamine by the nursing staff from the adult vial into the 50 ml syringe, the prepared dopamine was kept horizontally on a sterile field without being shaken, to avoid contamination. This was kept for 30 minutes before commencing administration.

Data collection and statistical analysis

MetaVision® (a clinical information system for intensive care) captures all clinical observations on each neonate eligible to the study. Data on the birth weight, rate of the dopamine infusion in micrograms/kilogram/minute, total infusion duration, other infusions running at the same time including other inotropes, mean arterial pressure (MAP) 30 minutes and 1 hour pre-infusion initiation and 30 minutes, 1 hour and 2 hours post-infusion initiation was collected. The neonates under the old and new SOP were then compared. In order to measure dopamine concentration, the peak area from chromatography responses were obtained from identical sampling points

as the MAP. Data was analysed using either a one-way or two-way ANOVA with post hoc Tukey tests, where significance was considered when $P<0.05$.

Results

Initially, the changes in dopamine concentration were measured through a laboratory setting simulated neonatal ward. Figure 1A&B shows changes when utilising the old SOP in various commonly used diluent vehicles and neonate weights. There was a significant change in the concentration of dopamine observed with time ($p<0.05$, two-way ANOVA) and a significant change in how this dopamine concentration altered in different diluent vehicles ($p<0.05$, n=10 Figure 1A). At both -1 hour and -0.5 hour before changeover, the dopamine concentration was more stable in 0.45 % NaCl when compared to 10% and 5% glucose ($p<0.05$, n=10, Sidak test). When comparing the effect of dopamine stability on doses utilised for varying weights of neonates, there was a signficant increase in percentage of dopamine lost with increased weight of the neonate ($p<0.05$, n=10, Figure 2C). However, with neonatal weights ≤ 0.4 kg, there is no difference in the dopamine concentration during infusion changeover.

Due to the rapid loss in stability in the first 30 minutes followed by gradual loss in stability over 24 hours, the new SOP protocol was established to counteract these changes. No signficant difference in the percentage of dopamine concentration lost from initial concentration was observed in the varying diluent vehicles (Figure 1C, n=10) or weight of the neonate (Figure 1D, n=10).

When comparing the percentage loss in the concentration of dopamine measured from the laboratory setting simulated neonatal ward, in all diluent vehicles there was

a significant difference between the two SOPs over the time sampled ($p<0.05$, Figure 2). In all cases there was a signficant increase in the percentage of dopamine lost at -1 hour and -0.5 hour before changeover in the old SOP when compared to the new SOP ($p<0.05$, Figure 2).

Figure 3A shows representative clinical traces spanning a 12-hour period from 3 neonates who received dopamine infusions for 24 hours. Clear presence of rapid BP fluctuations was observed post infusion changeover. Figure 3B shows representative clinical traces over a 12-hour period from 3 neonates where dopamine infusions were administered for 12 hours after being prepared 30 minutes prior to infusion. No clear presence of rapid fluctuations was observed post infusion changeover.

Evaluation of the changes in clinical MAP response, during changeover using the old and new SOP, are shown in Figure 4. There was a signficant increase in the MAP observed at 0.5 and 1 hour when compared to -0.5 and -1 hour in the old SOP ($p<0.05$, n=13 Figure 4A). No signficant differences in the MAP were observed during changeover in the new SOP (Figure 4A, n=17). When comparing the changes in MAP between the old and new SOP, there was a significant difference between the two SOPs over the time sampled ($p<0.05$, 2-way ANOVA, Figure 4A). There was a signficant reduction in the MAP at -1 hour and -0.5 hour before infusion changeover in the old SOP when compared to the new SOP ($p<0.05$, Figure 4A).

The number of times the dose was titrated up during an infusion was compared, where a longer time was required for the first titrated dose ($p<0.001$, t-test, Figure 4B) and there was a decrease in the number of times the dose was titrated in the new SOP when compared to the old SOP ($p<0.001$, t-test, Figure 4C).

Figure 5A demonstrates the observed changes in the MAP and dopamine concentration (for a 1 kg neonate, prepared in 5 % glucose diluent vehicle) during the infusion changeover using the old SOP. Figure 5B demonstrates the observed changes on the MAP and dopamine concentration (for a 1kg neonate, prepared in 5 % glucose diluent vehicle) during the infusion changeover in the new SOP. The green dashed line indicates when a drug concentration would be classed as unsuitable based on British Pharmacopia guidelines, in which dopamine concentration drop below this mark in the old SOP after 14 hours, whilst the response never drops below this point on the new SOP.

Discussion

Our study shows that by preparing dopamine 30 minutes prior to infusion and limiting the infusion duration to 12 hours, rapid fluctuations observed during infusion changeover in a 24-hour administration cycle are minimised. This new SOP is suitable for robust delivery of dopamine to neonates of all weights that may be treated for hypotension and for any dilution vehicle that dopamine is regularly prepared in for infusion.

This study supports previous observational studies that have identified rapid fluctuations in the MAP during infusion changeover [5] [9-11] [29]. Although many approaches to understand the effect observed at changeover have been taken, namely in evaluation and altering the practice of infusion changeover, these have yielded little improvement [14] [18] [19]. The concentration of dopamine during infusion has seldom been investigated as a cause and this study showcases the observed changes in dopamine concentration during infusion in a laboratory simulated

environment that replicates an infusion administered to a neonate within an incubator in an intensive care unit. To date only our previous study has shown that in a clinical environment dopamine stability varies [20], and this investigation adds further information covering a range of dilution vehicles and neonatal weights. These findings provide significant insight into the impact of dose variation during infusion changeover when a 24-hour dosing cycle is utilised. Although many studies on dopamine stability have been conducted [21-23] [26] [27], they have negated to use appropriate doses used in a clinical environment, explore the influence of dilution vehicle and clinical environment conditions of delivery. Our study indicates these parameters play a key role in reducing the stability of dopamine gradually over 24 hours, which leads to a significant variation during changeover resulting in rapid fluctuations in MAP.

Based on these observations, the guidelines by the British Pharmacopeia guidelines for medicines production indicate that any product that deviates > ±7.5% from the drug dose would be classed as unsuitable [30] and therefore based on Figure 3, 12 hours was defined as the safe timescale for dopamine infusions for the new SOP as the > ± 7.5% is breached at 14 hours as seen in Figure 2D. Additionally, most of the dopamine degradation was observed in the first 2 hours, and therefore it was logical to prepare the infusion 30-minutes prior infusion. The resultant changes assured that at no point was the dopamine concentration in the new SOP outside the British Pharmacopeia guidelines. Such changes to the new SOP also resulted in a reduction in the number of times the dose was titrated prior to changeover and the time taken to the first time the dose was titrated following changeover.

Despite great efforts being made to simulate neonatal ward conditions as accurately as possible in a laboratory setting, there are a few experimental design limitations

which can affect the interpretation of the data. These are highlighted in our previous publication and include the nature of the incubator utilised, which does not allow for maximal light, as utilised on the neonatal ward, therefore underestimating the degree of degradation [20]. Another important consideration is that our study is a very simple clinical model that does not fully mimic drug delivery of inotropes, as often they are co-administered with other compounds, formulations, or parenteral nutrition. Additionally, other factors such as the type of infusion tubing and materials may also influence the degree of stability.

Within our study we simulated the change in dopamine concentration as it was not possible to sample the infusion concentration at the varying timepoints within the clinical environment and match this directly with the change in MAP with the neonate. This type of matched observation would be of signficant advantage in understanding the context of dopamine concentration difference needed for a rapid fluctuation to be observed. Additionally, we have not fully explored the causes of dopamine's instability, however we have learnt through previous studies that light is not a major cause of this degradation [20]. Therefore, based on other studies and explored mechanisms, other variables such as oxygen and heat exposure may explain this degradation [21 22].

On surveying the hypotension guidelines from numerous NICU department within the UK (supplementary table 1), we obtained responses from one-third of NICUs. The data shows all these NICU currently administered immediately in a method that reflects the old SOP and therefore adoption of the new SOP can have significant impact in reducing the risk associated with rapid fluctuations during dopamine changeover. However, changing dopamine infusions every 12 hours can offer a

signficant change to practice, and requires the sterility of the infusion line to be broken twice as often.

This proposal only focused on understanding the changes in dopamine infusions, however these represent only a small element of the hypotensive therapeutics provided and therefore further studies are needed to understand whether other inotropes are stable in neonatal ward conditions when either administered individually or in combination. Additionally, there is a host of varying conditions in which neonates are cared for within an intensive care unit. Our studies have focused solely on the stability of dopamine for neonates nursed within incubators, however we have not explored if similar effects occur when using an open cot, radiant warmer or cooling mattress. Finally, future studies need to account for all the variations in neonatal intensive care conditions in which phototherapy and humidity is also influenced. Both parameters have been shown in other studies to influence the stability of inotropes [22 26] and therefore this would provide key insight on whether the new SOP can overcome rapid fluctuations in the MAP during changeover in any given environmental condition used.

Conclusions

Our studies highlight that a commonly used SOP for delivery of dopamine in hypotensive care of neonates in intensive care units is subjective to rapid fluctuations in the MAP following changeover of dopamine infusions. Using a simulated environment, these alterations in the MAP correlated with a loss in the dopamine concentration as a result of degradation over 24 hours. By adopting a new SOP where dopamine infusions were prepared 30 minutes prior to administration

and changed every 12 hours, both a reduction in rapid fluctuations in MAP and loss in the dopamine concentration due to degradation were minimised. Our new SOP has major implications to remove unwanted risk to neonates and should be implemented by clinical staff who are currently changing infusions of dopamine every 24 hours.

Acknowledgements

The authors would like to thank all the nursing staff in the Trevor Mann Baby Unit for their support in this research study.

Author Contributions

KK and PdS were responsible for the collection and analysis of the patient data. CLR and LR conducted and analysed the laboratory simulated neonatal ward conditions based experimental data. HR and BAP were responsible for study design, overall analysis of the study findings. PdS, KK and BAP wrote the manuscript and all authors approved the final version of the manuscript.

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FIGURE 1. Changes in dopamine concentrations in a simulated neonatal ward laboratory setting. (A) shows the percentage of dopamine loss relative to changeover time, when prepared in varying dilution vehicles in the old SOP. (B) shows percentage of dopamine loss relative to change over time, when prepared in varying neonate weights in the old SOP. (C) shows the percentage of dopamine loss relative to change over time, when prepared in varying dilution vehicles in the new SOP. (D) shows percentage of dopamine loss relative to change over time, when prepared in

varying neonate weights in the new SOP. Data shown as mean ± 95 % C.I., where *P<0.05.

FIGURE 2. Difference between the new and old SOP in percent of dopamine concentration loss from changeover when prepared in (A) 10 % glucose, (B) 5 % glucose, (C) 0.9 % sodium chloride and (D) 0.45 % sodium chloride in the laboratory setting simulated neonatal ward. Data shown as mean ± 95 % C.I., where *P<0.05.

FIGURE 3. Representative traces of mean arterial pressures from neonates receiving dopamine (A) for 24 hours before infusion changeover (old SOP) or (B) which was prepared 30 minutes prior to infusion and ran for 12 hours before infusion changeover (new SOP). The green line indicates the point where infusion changeover is conducted, and the red line indicates the mean arterial pressure (mmHg) over time in hours.

FIGURE 4. Difference in the MAP between the new and old SOP. (A) shows the difference in the mean arterial pressure. (B) shows the time following infusion changeover that the dose was required to be titrated and (C) shows the number of times the dose is titrated over 24 hours. Data shown as mean ± 95 % C.I., where *P<0.05 and ***P<0.001 between SOPs, $^{\dagger}P$<0.05 on the old protocol when compared to -0.5 and -1 hour.

FIGURE 5. Shows the changes in mean arterial pressure and percentage of loss in dopamine concentration based over a 48 hour period in the (A) old SOP and (B) new SOP. The green line indicates the British Pharmacopeia guidelines for medicines production which is > ±7.5%.