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ORIGINAL ARTICLE

Elective replacement of intravenous cannula in neonates—a randomised trial

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Abstract

Peripheral intravenous cannula (PIVC) insertion is one of the most common invasive procedures performed in neonates and is frequently associated with adverse events. There are no studies in the neonatal population looking at the possibility of reducing the risk of PIVC-related complications by elective replacement of PIVC. A randomised, non-blinded, control trial was conducted in a tertiary level neonatal unit in Melbourne, Australia, to examine rates of extravasation in neonates with elective replacement of PIVC as compared to standard practice. Neonates born at 32 weeks of gestation or more were randomly assigned to have their PIVC replaced electively (every 72–96 h) or when clinically indicated in a 1:1 allocation ratio after parental consent. Primary outcome studied was rate of extravasation. Secondary outcomes included rates of phlebitis, leakage or spontaneous dislodgement of PIVC. One hundred thirteen infants were enrolled. Extravasation was noted in 33 (60%) of standard practice group vs. 28 (48.3%) of elective replacement (RR 0.80, CI 0.57–1.13, $p = 0.21$) infants. Time to first extravasation was similar between the groups (hazard ratio 0.69, CI 0.42–1.15). Extravasation events per 1000 IV hours were also similar between groups. Similar results were seen by both intention to treat and per protocol analyses. There was an increase in leaking rates (HR1.98, CI 1.03–3.81, $p = 0.04$) in the elective group, while phlebitis and spontaneous dislodgement rates were similar to standard group.

Conclusion: Elective replacement of PIVC in neonates is not associated with reduction in extravasation rates.

Trial registration: This trial has been registered with the Australian and New Zealand Clinical Trials Register. Identifier: ACTRN12615000827538.

What is Known:
- *The reported incidence of extravasation injury is as high as 70% in the neonatal and paediatric population and has an association with cannula dwell time.*
- *Adult studies have done to look at the possibility of reducing intravenous cannula-related complications with routine replacement of the cannulas but no similar studies have been done in the neonatal population.*

What is New:
- *Routine replacement of intravenous cannula in neonates between 72 and 96 h of use does not reduce the rate of extravasation injuries.*
- *There might be some added complications associated with such a practice.*

Keywords Extravasation · Infiltration · Phlebitis · Resite

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Abbreviations

CI	Confidence interval
HR	Hazards ratio
IV	Intravenous
PIVC	Peripheral intravenous cannula
RD	Risk difference
RR	Relative risk

Introduction

Peripheral intravenous cannula (PIVC) insertion is one of the most common procedures performed in a neonatal unit. Almost all neonates admitted require intravenous access, with many requiring multiple PIVC resites during their admission [3]. Despite its routine nature, peripheral cannulation is not without risks [1, 3, 4, 7, 19]. Extravasation injury is the most common complication of PIVC use with a higher incidence in patients less than 1 year of age [4, 9, 16, 19]. In the neonatal population, the reported incidence of extravasation is as high as 70% [3, 8, 18, 19]. The risk is even higher with very low birth weight babies due to poor venous integrity [12] and flexible subcutaneous tissue [19]. Phlebitis is another common complication and results from mechanical, chemical or infective inflammation of the intimal layer of the vein [12, 19]. The incidence of phlebitis in neonates can be as high as 23% and is five times higher than the general paediatric population [2, 5]. Long term sequelae of extravasation and phlebitis can include significant tissue damage, scarring, necrosis, nerve damage and contractures [13]. Prevention of these adverse outcomes in the neonate is therefore a critical aspect of their care. Duration of PIVC use is a factor that has been shown to increase the risk of PIVC associated injuries with rates of extravasation and phlebitis injuries being higher when PIVC use was greater than 72 h, and the rates more than doubled when PIVC remained in situ for longer than 96 h [16]. There has been no randomised study however that addresses the need for elective replacement of PIVC in neonates. Some local guidelines suggest that resiting the PIVC every 48–72 h can reduce the likelihood of phlebitis but studies supporting this have not been conducted [11]. The primary aim of our study was to determine if the rate of extravasation is reduced with elective replacement of PIVC in neonates.

Methods

Study site and participants

We conducted a single centre, prospective, randomised control trial at the (tertiary level) neonatal unit of Monash Children's Hospital, Melbourne, Australia. Neonates who were born at or after 32 completed weeks of gestation (based on maternal early scan or last menstrual period) that would require a PIVC for at least 72 h were considered eligible for the study. Infants who required more than one concurrent PIVC, a central venous catheter, or those who did not require PIVC for at least 72 h were excluded. Infants were enrolled only when the research team was available.

Consent

The institutional human research ethics committee approved the study and written informed consent was obtained from parents before infants were recruited. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12615000827538).

Randomisation

Randomisation was performed by an independent research nurse using an online program and individual allocations were given to the investigators in sealed sequentially numbered opaque envelopes. When an eligible patient's PIVC was either planned to be used beyond 72 h, or approaching 72 h of use, consent was obtained to enrol into the study, if a member of the research team was available. After consent was obtained, a member of the research team picked up the next numbered envelope and patient allocation occurred. Caregivers (nursing staff) were not blinded to the allocation.

Intervention

Infants were randomly assigned to have their PIVC electively resited every 72 to 96 h or earlier if complication arose (elective group) or whenever clinically indicated by presence of complications (standard group) in a 1:1 allocation ratio. All cannulas in both groups were inserted by medical staff, mainly neonatal registrars. If there were difficulties with insertion by the registrar, the fellow and then consultant were involved in the cannula insertion accordingly.

The standard procedure to insert PIVC in the unit includes choosing the appropriate site of insertion (generally dorsum of hand, foot, skin antisepsis) with 2% chlorhexidine and 70% alcohol swab stick, Steristrips and Tegaderm (3M, NSW, Australia) to secure the PIVC, and using appropriate size splints to immobilise the joint above insertion. Local unit protocol does not recommend elective replacement of PIVC. Further, central line insertions are recommended in the unit protocol for prolonged need for PIVC for antibiotics or parenteral nutrition use, based on clinician discretion.

After enrolment, the time, date, location, number of attempts and designation of medical staff (registrar, fellow, consultant) inserting the PIVC was documented. The unit uses an electronic patient record system where this information is maintained. Case records were also reviewed to record the

participant's gestation, birth weight, admission diagnoses and initial indication for PIVC. The IV cannulation procedure was performed using 24 gauges BD Insyte Autoguard IV catheter (Becton, Dickinson & Co, NJ, USA). Standard universal precautions including the use of vein finder devices, when needed were used for performing the procedure. An appropriate size splint was used to secure the PIVC. Patency of the cannula was maintained with 6 hourly normal saline flushes if continuous infusion was not given.

Data collection and outcome measures

A standardised extravasation (primary outcome) and phlebitis grading system were used [6]. For the purposes of this study, we did not differentiate between extravasation and infiltration. Parameters for extravasation assessment included pain/tenderness, swelling, skin blanching, delayed capillary refill, absent peripheral pulsation and blistering of skin at insertion site [6]. Parameters used for phlebitis assessment included pain/distress with flushing the cannula, erythema, induration, palpable venous cord or pyrexia [10]. Nursing staff was trained to use the grading systems prior to commencement of the study. They were required to perform hourly PIVC checks as per unit protocol and complete study records once per shift (8 hourly) or at the time of complication, whichever came first. The records also required nursing staff to input the type of infusate given and if blood products, antibiotics or other medications were given. When a complication occurred or was suspected, nursing staff alerted medical staff for assessment. The date, time and indication of PIVC removal were also recorded. Participants completed the study when they no longer required a PIVC.

Data analysis

Data were entered into an electronic database, then imported and analysed using Stata/IC 12.1 (StataCorp, College Station, TX). All data were assessed for normality. Continuous data was described using mean (SD) if normally distributed or median (IQR) if distribution was skewed. Differences in baseline characteristics of the infants were compared between the trial groups to assess the randomisation. The primary and secondary outcomes were assessed by both intention to treat and per protocol analyses. We determined the relative risks, risk difference and 95% confidence intervals (CI) for any extravasation event per patient. We then calculated the rate of primary and secondary outcomes per 1000 intravenous hours per patient. The cox-proportional model (after assumptions were checked), including a cluster term to deal with the repeated outcomes was then used to determine the hazard ratios and 95% CI for difference between study groups. Lastly, Kaplan-Meier failure curves for time to first extravasation were determined. A p value < 0.05 (two-tailed) was regarded as significant.

Sample size

Sample size was based on the primary outcome studied, extravasation. The current extravasation rate in our neonatal population was estimated to be 50%. A minimum sample size of 104 (52 in each group) would be required in order to show a 60% decrease of extravasation injury (from 50 to 20%) between groups, with 80% power at an alpha level of 0.05. Ten percent extra participants were recruited to account for potential losses from withdrawal of consent or protocol violations.

Results

Participants

Between August 2015 and July 2017, out of seven hundred thirty-three infants eligible, 113 were enrolled and randomised (Fig. 1). Infants were not enrolled due to various reasons including unavailability of parent or research staff, parental refusal, infant deemed difficult to cannulate or clinically unstable by treating team, late clinical decision for ongoing PIVC use and language barrier. Of the 113 infants enrolled, none withdrew consent following randomisation. Fifty-five participants were randomised to the standard group, and 58 participants were randomised to the elective replacement group (intention to treat analysis). We studied a total of 118 PIVC in the standard group and 156 PIVC in the elective group. In the standard group, 46 (83.6%) participants had their PIVC replaced when clinically indicated while 9 (16.4%) were excluded because 6 did not reach at least 72 h of PIVC use, and 3 required more than one PIVC after randomisation. These 9 participants were not included in the per protocol analysis. In the elective replacement group, 45 (77.6%) participants had their PIVC replaced at 72 to 96 h of use while 9 (15.5%) did not because 5 had more than maximum unsuccessful attempts at elective replacement and 4 had lack of staff for elective replacement or replacement occurred early. These 9 patients were analysed in the standard group in the per protocol analysis. Four (6.9%) infants did not reach at least 72 h of PIVC use and they were excluded from the per protocol analysis.

Participant and PIVC characteristics are shown in Table 1. The groups were evenly matched for participant characteristics except a lower risk for sepsis (based on maternal risk factors and infant bloods) at admission in the standard group (55.6%) as compared to 75.9% in the elective group ($p = 0.01$). In the characteristics related to participants' PIVC use, the only difference noted between the groups was the higher

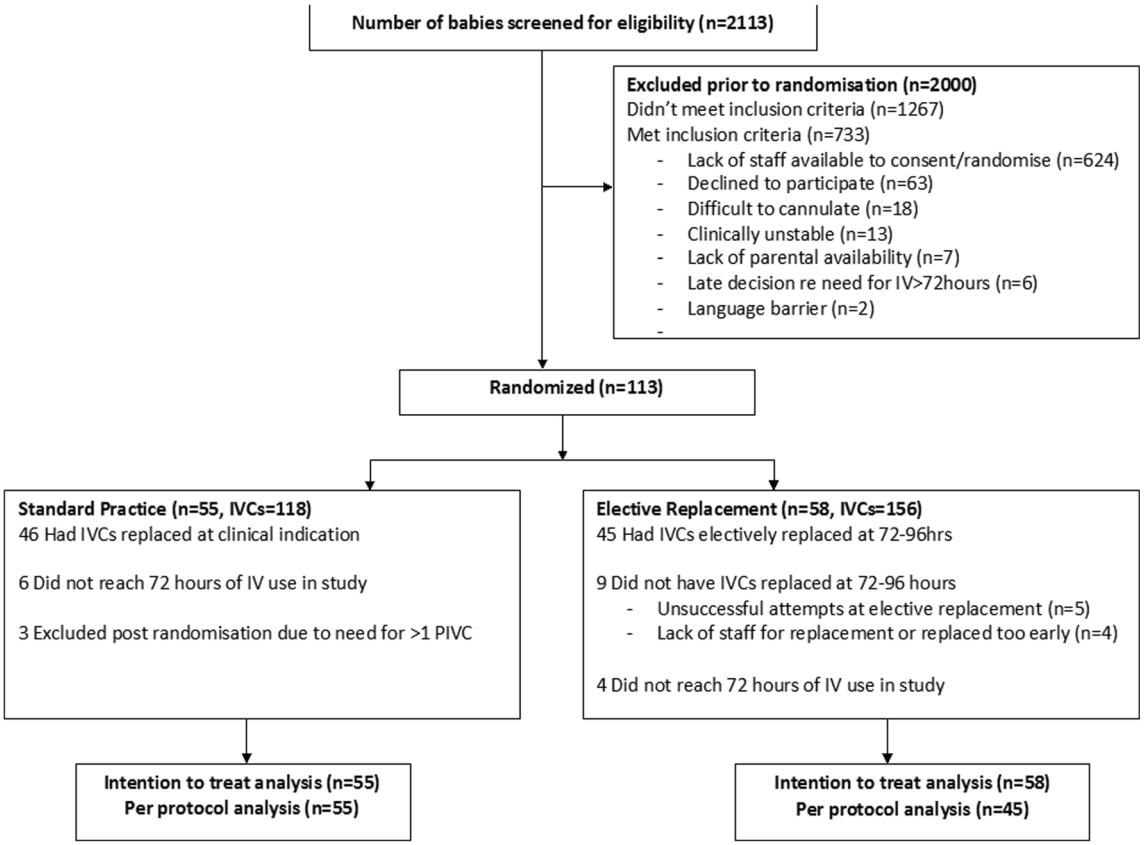

Fig. 1 Consort diagram

number of attempts during resite (3 (2–4) in the elective group vs. 1(1–3) in the standard group, $p = 0.002$) as expected due to the intervention.

Primary outcome measures (Table 2)

The primary outcome studied was the rate of extravasation between the two groups. Thirty-three out of 55 participants experienced PIVC extravasation in the standard group and 28 out of 58 participants experienced PIVC extravasation in the elective group. Hence, there was a 20% reduction (60% vs. 48.3%) in extravasation risk per patient with elective replacement (RR 0.8, 95% CI 0.57 to 1.13, $p = 0.21$). All episodes of extravasation were managed conservatively without need for irrigation or surgery. Similarly, there was a non-significant reduction of 9% (95% CI 0.55 to 1.5, $p = 0.70$) in the extravasation hazard per 1000 IV hours with elective replacement. We also tested the data with per protocol analysis. The overall risk of extravasation was similar after elective replacement (32 in standard arm vs. 24 in elective arm), with a relative ratio of 0.92 (95% CI 0.65 to 1.30, $p = 0.63$). Extravasation events per 1000 IV hours were also similar, by per protocol analyses (HR 1.14 (95% CI 0.66 to1.96). Lastly, from the Kaplan-Meier failure estimates, we found that the time to first extravasation was not significantly different between the groups (Hazard ratio 0.69 (95% CI 0.42–1.15, $p = 0.20$)) (Fig. 2).

Secondary outcomes (Table 3)

The secondary outcomes measured were the rates of other complications from PIVC use. Comparing the two groups, there was an insignificant increase HR − 1.93 (95% CI 0.83 to 4.51, $p = 0.13$) in phlebitis events per 1000 IV hours of use with elective replacement. This risk was shown to be 2.6 times (95% CI 1.07 to 6.41, $p = 0.04$) as per protocol analysis. The hazard of leakage events was also increased by 98% (95% CI 1.03 to 3.81, $p = 0.04$) with elective replacement. The increased risk of phlebitis and leaking seemed to increase with every subsequent PIVC resited (low numbers to analyse objectively). Per protocol analysis also showed a two-fold increase (95% CI 1.08 to 3.94 $p = 0.03$) in hazard risk of leakage with elective replacement. The other complications that occurred in our study population included spontaneous dislodgement, blockage, bleeding from cannula site and accidental coverage of PIVC with meconium. The rates at which they occurred individually were low, at equal or less than 0.3 per 1000 IV hours. There was no case of cannula-associated bloodstream infection, after the intervention.

Table 1 Demographics

	Standard ($n = 55$)	Elective ($n = 58$)
Infant characteristics		
Gestation (weeks) (median, IQR)	35 (33–39)	36 (33–39)
Male (n, %)	34 (62)	30 (52)
Birth weight (g) (mean, SD)	2571 (947)	2708 (919)
Admission diagnosis (n, %)		
Respiratory distress	21 (38.2)	20 (34.5)
Risk of sepsis	30 (55.6)	44 (75.9)*
Hypoglycaemia	8 (14.6)	12 (20.7)
Prematurity	29 (52.7)	26 (44.8)
Jaundice	2 (3.6)	2 (3.4)
Fetal growth restriction	5 (9.1)	3 (5.2)
Postnatal age at inclusion (days) (median, IQR)	1 (1–1)	1 (1–2)
PIVC characteristics		
Previous PIVC use (n, %)	10 (18.2)	10 (17.2)
Duration of previous PIVC use (days) (median, IQR)	2 (1–2.5)	1 (1–2)
Infusates (n, %)		
Intravenous fluids	40 (72.7)	44 (75.9)
Parenteral nutrition	10 (18.2)	7 (12.1)
Antibiotics	42 (76.4)	50 (86.2)
Blood products	1 (1.8)	0 (0)
Level of experience of operator for first PIVC (n, %)		
Registrar	41 (74.6)	39 (67.2)
Fellow	5(9.1)	9 (15.5)
Unknown	9 (16.4)	10 (17.2)
Site of first PIVC (n, %)		
Hand	49 (89.1)	51 (87.9)
Foot	3 (5.5)	5 (8.6)
Forearm	2 (3.6)	1 (1.7)
Unknown	1 (1.8)	1 (1.7)
Time to first resite (h) (median, IQR)	63(48–88)	56 (43–74)
Total number of resites (median, IQR)	1 (0–2)	1 (1–2)
Number of attempts during resites (median, IQR)	1 (1–3)	3 (2–4)**
Duration of PIVC use in study (days) (median, IQR)	5 (3–6)	5 (4–6)
Duration of PIVC use in study (h) (median, IQR)	119 (90–151)	111 (99–148)

PIVC peripheral intravenous cannula. No significant differences between groups except *p value 0.01 and **p value 0.002

Discussion

This is the first randomised control trial that has been performed in the neonatal population for elective replacement of PIVC. The study showed no impact of elective replacement of PIVC every 72 to 96 h on risk of extravasation injury. Moreover, there was an increased risk of leaking around the IV site seen in those infants who had their PIVC electively replaced.

We included neonates who were born at 32 weeks of gestation or above. Neonates born at a more premature age are more likely to need a central venous catheter and are at higher risk of being clinically unstable. We also excluded patients who required more than one PIVC concurrently as it would be difficult to track and resite multiple PIVCs. The elective and standard groups were comparable for most infant demographics and PIVC characteristics. The elective group had a higher number of infants with possible risk of sepsis; however, there were no cases of culture proven sepsis across the groups. There were also a significantly higher number of resite attempts in the elective group as can be expected given the higher number of overall resites in that group.

The primary outcome of extravasation was assessed both by intention to treat and per protocol analyses, given the

Table 2 Primary outcome

	Standard	Elective	Crude ratio (95% confidence interval)	*p* value
Intention to treat analysis, participant numbers	55	58		
Any extravasation, per patient (*n*, %)	33 (60)	28 (48.3)	RR 0.80 (0.57 to 1.13) RD − 0.12 (− 0.30 to 0.07)	0.21
Extravasation event, per 1000 IV hours	7.8	6.1	HR 0.91 (0.55 to 1.5)	0.70
Per protocol analysis, participant numbers	55	45		
Any extravasation, per patient (*n*, %)	32 (58.2)	24 (53.3)	RR 0.92 (0.65 to 1.30) RD − 0.05 (− 0.24 to 0.15)	0.63
Extravasation event, per 1000 IV hours	7.3	6.5	HR 1.14 (0.66 to 1.96)	0.63

RR relative risk, *RD* risk difference, and *HR* hazard ratio (repeated outcomes, cox proportion model)

relatively high numbers of protocol violations in the elective group (13/58) [14]. Extravasation injury in the standard group occurred with a rate of 60%, which is within the range of 52 to 70% reported in neonatal literature [3, 8, 18, 19]. With elective replacement of PIVC, the extravasation risk was reduced by around 20%, but did not reached statistical significance. This was further confirmed with extravasation events per 1000 IV hours and the time to extravasation survival curves, both of which showed no significant improvement with elective replacement of PIVC. Randomised studies in adult population have shown a similar outcome with none of the studies/meta-analyses favouring elective PIVC replacement [15, 17]. The information generated by this first randomised study in neonates is very important nonetheless, given the different patient characteristics and much higher risk of extravasation in this population. In fact, in most adult studies, the primary outcome studied has been the incidence of phlebitis or composite outcome rather than extravasation. This might be due to lower rates of extravasation, given the much better vascular integrity of vessels in the older patient.

Elective replacement of cannula in neonates is complex in neonates. Five of 55 (10%) patients were unable to have the elective replacement performed (despite multiple attempts), making it a non-feasible option in some cases. Potentially, elective replacement may require additional painful procedures for infants, extra staff resources and costs of equipment. While these have been seen as a factor in some adult studies [15], it is unlikely to be a major factor in neonates, as in our experience, most infants did not need more than one resite.

In terms of secondary outcomes, the risk of phlebitis was increased in the elective replacement group, albeit only in the per protocol analysis. The cause of phlebitis in our study may be related to other factors that affect phlebitis risk such as method of securing the cannula or location of the PIVC, instead of the intervention itself [16]. The risk of fluid leakage from PIVC was also significantly increased with elective

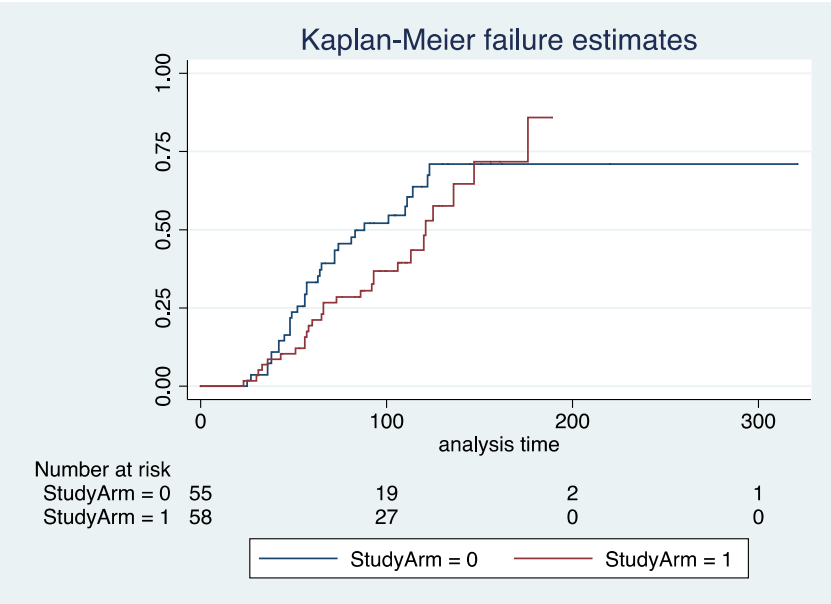

Fig. 2 Kaplan-Meier estimate for time to first extravasation and intention to treat analysis. Graph depicts the probability of failure from extravasation (y-axis) according to analysis time in hours (x-axis). Study arm 0 = standard group and 1 = elective group. Numbers at risk are also given at the analysis times of 0, 100, 200 and 300 IV hours

Table 3 Secondary outcomes

	Standard	Elective	Hazard ratio (95% confidence interval)	*p* value
Intention to treat analysis, participant numbers	55	58		
Phlebitis	1.3	2.2	1.93 (0.83 to 4.51)	0.13
Leaking	2.0	2.9	1.98 (1.03 to 3.81)	0.04
Spontaneous dislodgement	0.1	0.4	1.04 (0.18 to 6.10)	0.96
Per protocol analysis, participant numbers	55	45		
Phlebitis	1.0	2.3	2.62 (1.07 to 6.41)	0.04
Leaking	2.1	2.9	2.10 (1.08 to 3.94)	0.03
Spontaneous dislodgement	2.7	3.1	0.46 (0.04 to 4.59)	0.51

Outcomes shown as *n* per 1000 IV hours. Hazard ratio (repeated outcomes, cox proportion model)

replacement in this study. In literature, the rate of leaking reported ranges between 2 to 27.6% and the use of PIVC in lower extremities has been identified as a significant risk factor [3, 12]. It is possible that frequent replacement of PIVC reduces options of suitable locations for further insertions thus leading to placement of PIVC in locations, which may leak more frequently. This did not, however, lead to any difference in culture proven sepsis rates or extended use of PIVC.

The study has limitations. This is a relatively small study conducted in a single centre with 80% power, with a number of protocol deviations. Hence, the results are probably not generalisable. However, the difficulty seen in adhering to protocols is representative of the issues that exist in conducting pragmatic clinical studies in busy neonatal units—difficult access, lack of research staff and resources to resite every PIVC in a timely manner. It was also observed that the standard group had a median first PIVC dwell time of 63 h obviating the need for an elective replacement at 72 h in many cases, making the analysing of true differences between groups difficult. An urgent research priority that this data seems to highlight is better understanding of the reasons for poor PIVC life in neonates. On balance, it is probably not prudent to recommend elective replacement of PIVC to avoid complications in neonates based on our data, and we recommend a larger trial to study this intervention.

Conclusions

Elective replacement of peripheral intravenous cannula does not seem to reduce the risk of extravasation injury in neonates. Although limited by a small sample size in this study, future studies should assess the benefits of such an intervention against the potential increased risk of phlebitis and leaking in this infant population.

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Authors' contributions Li Yen Chin: Dr. Chin formulated the research question along with Drs. Van Haltren, Davies-Tuck and Malhotra. She helped with study design and ethics submission, recruited participants, collected and initially analysed data. She also wrote the first draft of the manuscript.

Timothy Walsh: Dr. Walsh helped with study design, recruited participants, collected and analysed data. He also helped in editing the manuscript.

Karen Van Haltren: Dr. Van Haltren formulated the research question along with Drs. Chin, Davies-Tuck and Malhotra, helped with study design and ethics, recruited participants and collected data. She also helped in editing the manuscript.

Laura Hayden: Dr. Hayden helped recruitment of participants, collected and helped in data analysis. She also helped in editing the manuscript.

Miranda Davies-Tuck: Dr. Davies-Tuck formulated the research question along with Drs Chin, Van Haltren and Malhotra. She was the statistician involved in study design, and analysis of the data. She also helped in editing the manuscript.

Atul Malhotra: Dr. Malhotra formulated the research question along with Drs. Chin, Van Haltren and Davies-Tuck. He also helped in study design and ethics submission, recruited participants, collected and analysed data, and critically reviewed and edited the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Formal ethics approval was sought, approved (15200B) and informed consent was obtained before recruitment of each participant.

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