International Journal of Nursing Studies 107 (2020) 103504

Contents lists available at ScienceDirect

International Journal of Nursing Studies

journal homepage: www.elsevier.com/ijns

The RESPECT trial–Replacement of peripheral intravenous catheters according to clinical reasons or every 96 h: A randomized, controlled, non-inferiority trial

Patricia Vendramim[a,*], Ariane Ferreira Machado Avelar[b], Claire M Rickard[c], Mavilde da Luz Gonçalves Pedreira[b]

[a] Specialist in pediatric intensive care, M.Sc., Ph.D. in Health Science of Federal University of Sao Paulo, 258 Aimberê, St. Sao Paulo, Brazil
[b] Federal University of Sao Paulo, Brazil
[c] Griffith University - Australia, Australia

ARTICLE INFO

Article history:
Received 12 April 2019
Received in revised form 6 December 2019
Accepted 8 December 2019

Keywords:
Catheterization
Peripheral
Catheters
Indwelling
Phlebitis
Nursing

ABSTRACT

Background: Peripheral intravenous catheters are widely used for infusion therapy. To prevent phlebitis, routine catheter replacement at 72 or 96 h remains widely practiced.

Objective: To investigate the non-inferiority of clinically indicated peripheral intravenous catheter replacement compared with routine replacement every 96 h to prevent phlebitis. Phlebitis severity, catheter indwelling time, and other catheter failure types were also compared.

Setting: Multi-center trial in wards at two hospitals in Sao Paulo, Brazil.

Design: The REplacement of PEripheral intravenous CaTheters according to clinical signs or every 96 h (RESPECT) trial was a Randomized, non-blinded, controlled, non-inferiority trial.

Participants: 1319 patients were enrolled with the following inclusion criteria: aged ≥18 years, expected peripheral intravenous therapy for ≥96 h; peripheral intravenous catheters inserted in the selected wards, intensive care units, or surgical centers; and informed consent provided. Exclusion criteria were: bloodstream infection and/or sepsis, neutrophil count of ≤1000/mm^3, and simultaneous use of more than one peripheral intravenous catheter. Recruitment occurred within 96 h of peripheral intravenous catheter insertion. Randomization was performed using a computer-generated, concealed list.

Methods: As intervention, clinically indicated replacement group patients underwent peripheral intravenous catheter removal only at the end of therapy or in the presence of phlebitis, infiltration, occlusion, displacement, accidental removal, or bloodstream infection. Routine 96-h replacement group patients (control) had their catheters replaced every 96-h, unless clinical reasons required earlier replacement. The primary outcome was Phlebitis and the analyses were carried out on intention-to-treat and per-protocol bases.

Results: Demographic and clinical variables were similar between groups, with the exception to type of admission ($p = 0.025$) more frequent in clinically indicated patients and surgical on routine replacement group. Of the 1319 patients, 119 (9.0%) developed phlebitis with no between-group difference ($p = 0.162$); these patients used 2747 peripheral intravenous catheters, being that 134 presented phlebitis. Phlebitis/1000 catheter-days, was 14.9 in the clinically indicated group and 23.8 in the routine replacement group ($p = 0.006$). The survival analysis showed no significant between-group difference in the occurrence of the first phlebitis episode.

Conclusions: Clinically indicated peripheral intravenous catheter replacement was not inferior to routine (96 h) replacement regarding phlebitis occurrence, and was associated with significantly less phlebitis per 1000 days.

Trial registration: Registered with www.clinicaltrials.gov (NCT02568670)

* Corresponding author.
E-mail addresses: patvendramim@gmail.com (P. Vendramim), ariane.machado@unifesp.br (A.F.M. Avelar), c.rickard@griffith.edu.au (C.M. Rickard), mpedreira@unifesp.br (M.d.L.G. Pedreira).
https://doi.org/10.1016/j.ijnurstu.2019.103504
0020-7489/

What is already known about the topic

- Peripheral intravenous catheters were routine removed and re-sited in a time-based protocol to prevent phlebitis.
- Removing peripheral intravenous catheters when clinically indicated did not increase phlebitis rates in specific populations.
- Variations on phlebitis rates are identified in different populations and higher rates can be verified in developing countries.

What this paper adds

- Indwelling time was not a risk factor for phlebitis, even in a more extended period of 96 h.
- The majority of the phlebitis episodes were classified in less severe grades and indwelling time has no significant impact on phlebitis grades
- The RESPECT trial reinforces the relevance of providing a nursing care based on patient individual clinical needs rather than routine based interventions to reduce adverse events as phlebitis.

1. Introduction

Compared with other catheter types, peripheral intravenous catheters, promote faster, less invasive venous access for the implementation of infusion therapy while also providing less risk to the patient. (Hadaway, 2012; Vizcarra et al., 2014; Ansel et al., 2017; Chopra et al., 2015) Despite their broad use, however, peripheral intravenous catheter insertions are not exempt from failures, including the potential of harming the patient. (Rickard et al., 2015; Fernandez-Ruiz et al., 2014; Scales, 2005) One of the most significant potential adverse events associated with the use of peripheral catheters, especially in adult patients, is the development of phlebitis.

Phlebitis is defined as endothelial inflammation that may be caused by mechanical, chemical, or infectious agent irritations. Phlebitis is also a risk factor for infection. The potential to damage the vascular integrity due to fibrin deposition and thrombus formation may precede a biofilm development and the infectious process. (Magerote et al., 2011; Zhang et al., 2016; Dunda et al., 2014; O'Grady et al., 2011)

The essential risk factor for any catheter failure is the presence of the device in the endothelium. However, prolonging the device's indwelling time at the same insertion site is still an unresolved issue, especially in developing countries and was described as such in the latest guideline published in 2011 of the Centers for Disease Control and Prevention (Atlanta, GA). (O'Grady et al., 2011)

Historically, peripheral intravenous catheters have been recommended to be routinely changed every 24–96 h. For a long time, it was adopted routine removing and re-siting catheters in a time-based protocol to prevent phlebitis. (Uslusoy and Mete, 2008; Washington and Barrett, 2012)

The Infusion Nurses Society, in the 2016 Infusion Therapy Standards of Practice (Infusion Nurses Society 2016) discouraged the systematic replacement of peripheral catheters and recommended their replacement as clinically indicated. This recommendation was based on the results of a systematic review published by Webster et al. (2015) that also recommended catheter replacement only at therapy completion or in the presence of inflammation, infiltration, and occlusion, as a means of minimizing insertion procedures. As an implication for research, the Webster et al. (2015) study suggested that their recommendation should be supported by a critical evaluation of results from developing countries and that the trials in these countries' health systems would add external validity to the main (Australian) studies included in their review.

Therefore, we aimed to verify the non-inferiority of the replacement of peripheral intravenous catheters based on clinical indications, compared with their routine replacement every 96-h, on the occurrence of phlebitis and other peripheral catheter-related complications.

2. Methods

This randomized, controlled, non-blinded, non-inferiority trial was conducted at two hospitals in São Paulo, Brazil. One was a general tertiary care hospital (HA) and the other was a university hospital specializing in cardiovascular and pulmonary diseases (HB). At both hospitals, we recruited patients admitted to the adult clinical and surgical units (240 beds, combined). The study was approved by the Committees of Ethics in Research in Brazil and was registered, on July15, 2015, with clinicaltrials.gov (NCT02568670). Written, informed consent from all participants before enrolment was obtained.

Patients were included in the study if they met the following inclusion criteria: ≥18-years-old; expected catheter use for ≥96 h; catheters inserted in the select wards, intensive care units, or surgical centers; and provided informed consent. The exclusion criteria included the presence of bloodstream infections and/or sepsis, neutrophil counts of ≤1000/mm^3, and simultaneous use of more than one catheter. Patient recruitment was performed from November 3, 2015 to August 30, 2016 by the research team, and occurred within 96 h of catheter placement. Patient randomization was performed using a computer-generated randomized list that was stored only with the principal researcher, who sent the sequence to the recruiters by a message app which was concealed until each patient's study entry. Randomization was 1:1 ratio between groups and stratified in 6 patients at a time, by ward and hospital.

The sample size calculation was based on a 5% prevalence of phlebitis, as cited by the Infusion Nurses Society. The study was designed with an 80% power with a 3% non-inferiority margin, based on the results obtained in an equivalence randomized trial of peripheral intravenous catheter routine versus clinically indicated replacement. (Rickard et al., 2012) As a result, the sample was estimated to require 1305 patients, divided into two groups. One group underwent peripheral catheter removal only when clinically indicated, i.e., at the end of infusion therapy or due to pain or discomfort; evidence of phlebitis, infiltration, extravasation, or occlusion; inadvertent catheter displacement or removal; or a suspected bloodstream infection. The second group underwent routine peripheral catheter removal every 96-h, regardless of the absence of complications or failures. The follow-up period ended at the conclusion of intravenous therapy or removal of the fifth catheter. Fig. 1 shows a flow diagram of the study. (Schulz et al., 2010) Correct group allocation and treatment was audited by the chief investigator.

All catheter insertion, maintenance, and removal procedures were performed by the bedside nursing teams at the hospitals (not researchers), after receiving previous training to practice standardization. The venipuncture procedure consisted: preinsertion skin disinfection with a 70% alcohol sachet, no-touch technique insertion and procedure glove use; catheter chosen, as appropriate, from among Insyte Autoguard®, Saf-t-Intima, and Nexiva (all, Becton Dickinson, Franklin Lakes, NJ, USA) catheter systems. Various gauges of needles were used along with the unrestricted use of different brands of accessories and semipermeable transparent dressings. The dressings were replaced, in both study groups, only when necessary (e.g., when soiled or loose) and the valve connectors were changed only when receiving blood products or when blood was visible in the line. Phlebitis and non-phlebitis diagnosis,

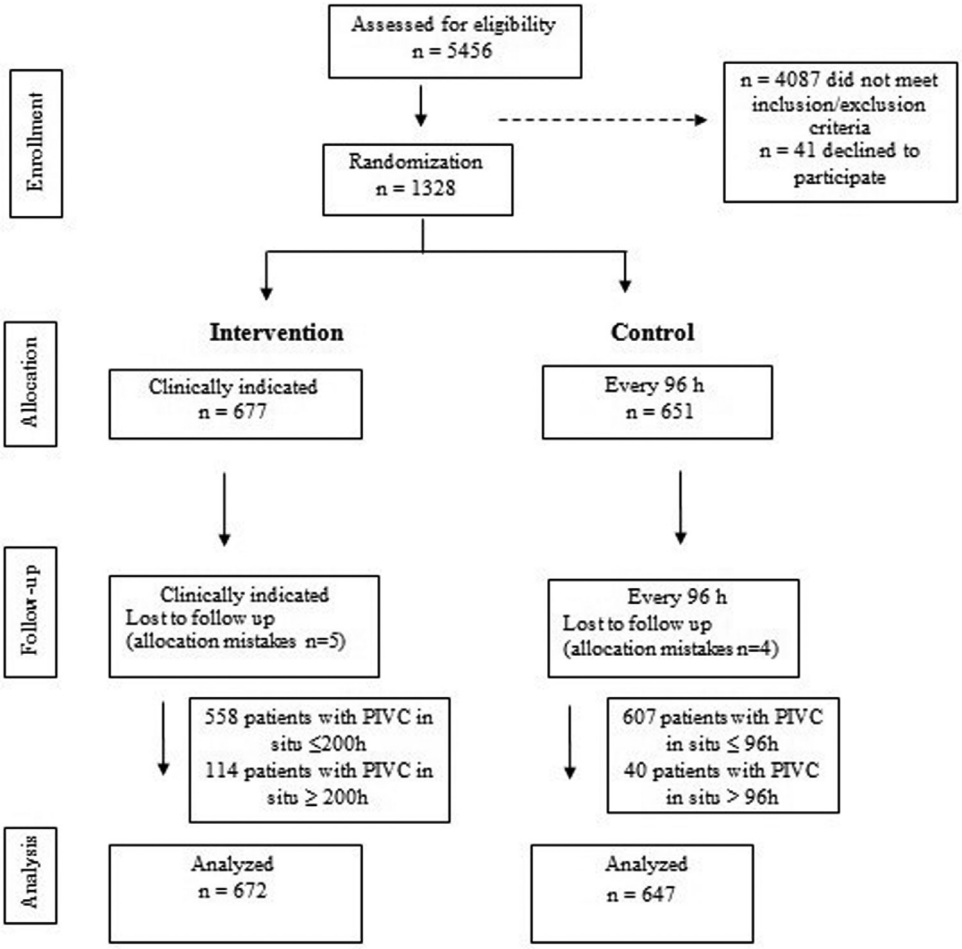

Fig. 1. CONSORT diagram profile flow.

as well as any decision to remove catheters in both groups were made by registered nurses from wards.

The main study outcome was phlebitis. Secondary endpoints included peripheral catheter indwelling time (h); number of catheter insertions per patient; and non-phlebitis catheter failures, including pain, occlusion, inadvertent catheter removal, infiltration, extravasation, and catheter-associated bloodstream infection. We also evaluated the severity of phlebitis classified according the Infusion Nurses Society phlebitis scales (2011), (Infusion Nurses Society 2011) ranging from grade 0 to 4.

All statistical analyses were performed using Stata software, version 14 (StataCorp, College Station, TX); a significance level of 5% was used for all analyses. The cumulative number of patients developing phlebitis was determined relatively to the total number of patients in each study group; the incidence rate was defined as the number of patients with phlebitis per 1000 catheter-days. The number of catheter-days was estimated using the number of catheter-hours.

The non-inferiority evaluation involved several analyses. The intention-to-treat group included the total number of patients, their respective numbers of catheters, and catheter-days. The non-inferiority analysis considered the upper limit of the 95% confidence interval for the absolute risk difference, without exceeding the predefined margin of 3.0% for non-inferiority. Additionally, it was used tests to incidence measures, relative risks, risk difference and incidence ratio, with an alpha value of 0.05.

The per-protocol analysis was performed by catheters and catheter-days and was calculated after excluding 28 of the 97 catheters that remained in place for >96 h, as they had ≥120 h of indwelling time in the routine replacement group. From a perspective of pragmatic studies, we included those routine replacement patients with catheters remaining up 120 h in the per-protocol analysis, since it is common for patients under a routine replacement policy to allow slight extensions to allow for inserter availability or patients receiving one last dose. As this analysis involved the exclusion of some peripheral intravenous catheters, the power of the test was re-calculated to detect non-inferiority in the sample obtained.

For the intention to treat analysis and Kaplan–Meyer curves, patients with total catheter therapy (all catheters) >200 h (8.33 days) were excluded to guarantee risk proportionality (Schoenfeld test $p = 0.06$ and parallelism in proportionality analysis); 1165 participants were included (558 patients in clinically indicated replacement group and 607 in routine replacement group).

3. Results

The two study groups included 1319 patients, with 672 (50.9%) participants in the clinically indicated replacement group and 647 (49.1%) in the routine 96-h replacement group. These patients used 2747 catheters, including 1356 (49.4%) in the 96-h replacement group and 1391 (50.6%) in the clinically indicated replacement group. The number of catheters used, per patient, ranged from 1 to 5. Specifically, 614 patients (46.5%) required a single catheter, 361 (27.4%) required 2, 196 (14.9%) required 3, 94 (7.1%) required 4, and 54 (4.1%) patients required 5 catheters. There was no

Table 1
Patient baseline demographics and clinical and PIVC characteristics.

	Clinically indicated		96-h		Total		*p*-value
	n = 672	%	*n* = 647	%	*n* = 1319	%	
Sex							
Female	333	49.6	329	50.9	662	50.2	0.638[a]
Male	339	50.4	318	49.1	657	49.8	
Age (y)							
Mean	59.7		59.9		59.8		0.848[b]
Standard deviation	20.9		20.1		20.5		
Minimum	18.0		18.3		18.1		
Maximum	101.5		100.8		101.5		
Median	61.9		61.3		61.7		
Skin color							
White	589	87.6	569	87.9	1158	87.8	0.590[a]
Brown	15	2.2	18	2.8	33	2.5	
Black	14	2.1	12	1.9	26	2.0	
Yellow	15	2.2	9	1.4	24	1.8	
Red	0	–	1	0.2	1	0.1	
Not informed	39	5.8	38	5.9	77	5.8	
Hospital							
Tertiary care hospital	594	88.4	572	88.4	1166	88.4	0.993[a]
University hospital	78	11.6	75	11.6	153	11.6	
Type of admission							
Surgical	83	12.4	108	16.7	191	14.5	0.025[a]
Clinical	589	87.6	539	83.3	1128	85.5	
PIVC characteristics							
Type of catheter							
Nexiva®	436	65.0	396	61.2	832	63.1	0.092[a]
Insyte®	188	27.9	215	33.2	403	30.5	
Saf-T-Intima®	46	6.8	32	5.0	78	6.0	
Other	2	0.3	4	0.6	6	0.4	
Catheter gauge							
24	116	17.3	92	14,2	208	15,8	0.235[a]
22	478	71.1	468	72,3	946	71,7	
20 or less	78	11.6	87	13,4	165	12,5	
Catheter insertion site							
Forearm	331	49.2	307	47.5	638	48.3	0.274[a]
Hand	134	20.0	127	19.6	261	19.8	
Cubital fossa	71	10.6	74	11.4	145	11.0	
Wrist	56	8.3	73	11.3	129	9.8	
Upper arm	63	9.4	45	7.0	108	8.2	
Other	17	2.5	21	3.2	38	2.9	
Catheter mode of use							
Intermittent	392	58.3	375	58.0	767	58.2	0.891[a]
Continuous	280	41.7	272	42.0	552	41.8	

[a] Chi-square association test.
[b] Bartlett test (>0.05) PIVC, Peripheral intravenous catheter.

significant difference in the per-patient numbers of peripheral catheters used between the 2 groups ($p = 0.339$).

Table 1 shows that the included patients comprised mostly elderly, white individuals. The population included similar numbers of males and females and an average age of about 60 years; there were no significant demographic differences between the two groups, with the exception to type of admission ($p = 0.025$) more frequent in clinically indicated patients and surgical on routine replacement group.

Nexiva® catheters, inserted using a 22-ga needle into the right forearm, were most frequently used for intermittent infusions. There were no significant differences between the groups, with respect to the catheters used, except more frequent insertions into the left arm were noted in the clinically indicated group (Table 1).

According to drugs infused through the studied catheters the most prevalent were antimicrobials (1208; 44.0%), with higher proportion in the clinically indicated group (707; 50.8%; $p < 0.001$). The other difference identified, were sodium phenytoin (21; 1.5%; $p = 0.003$) and clarithromycin (69; 5.1% $p = 0.003$) infusions with higher proportion in the every 96-h group.

Table 2 presents the phlebitis results as intention to treat and per protocol analyses. During the study, there were 134 (4.8%) cases of phlebitis in 119 (9.0%) patients; 99 patients experienced 1 case, 16 experienced 2 cases, and 1 patient experienced 3 episodes of phlebitis. It was verified that 80 cases of phlebitis were associated with the first catheter, 31 with the second catheter, 17 with the third, 5 phlebitis with in the fourth, and 1 with the fifth catheter.

For the intention to treat analysis and Kaplan–Meyer curves, 1165 participants were included, 558 patients in the clinically indicated replacement group and 607 in routine replacement group, which resulted in 110,436 catheter-hours. Specifically, 56,384 catheter-hours (mean 131.6 h therapy/patient, median 111,7 h, range 0.1–743.2 h) were observed in the clinically indicated replacement group and 54,053 catheter-hours (mean 99.6 h therapy/patient, median 89.0 h, range 0.8–392.6 h) in the routine replacement group ($p < 0.001$, Mann-Whitney test). The average per catheter dwell time was 66.0 h/catheter in the clinically indicated replacement group and 50.1 h/catheter in the every 96-h group. Regarding catheter-days, the results showed a total of 4602 catheter-days, being 2349 catheter-days in the clinically indicated replacement group and 2252 catheter-days in the routine replacement group (Table 2).

Still in the intention to treat analysis, 116 patients experienced phlebitis, being 54 in the clinically indicated group and 62 in the 96-h group. These data, resulted in a relative risk of developing

Table 2
Phlebitis and phlebitis severity according to removal of the peripheral intravenous catheter by clinical indication and every 96-h.

Phlebitis and phlebitis severity	Clinically indicated (N = 672 patients / 1391 PIVCs)		Every 96-h (N = 647 patients / 1356 PIVCs)		Total (N = 1319 patients / 2747 PIVCs)		Risk (95% CI)	p value
Phlebitis (ITT)	55 (n)	8.2 (%)	64 (n)	9.9 (%)	119 (n)	9.0 (%)		0.162[b]
Patients ≤200 h[e]	558		607		1165			
Phlebitis ≤200 h[e]	54		62		116			
Relative risk of phlebitis							0.83 (0.59 to 1.17)	
Absolute risk difference					−1.7% (−4.8 to 1.4)			
Phlebitis/1000 PIVC-days (95% CI)	14.9 (11.5–19.4)		23.8 (18.7–30.4)		18.7 (15.6–22.4)			0.006[b]
Incidence rate ratio							0.63 (0.43 to 0.91)	
Absolute risk difference							−8.90 (−15.95 to −1.86)	
Hazard ratio - 200 h[e]							0.81 (0.56 to 1.16)	0.248[c]
Phlebitis (PP)	62 (n)	4.4 (%)	72 (n)	5.3 (%)	134 (n)	4.8 (%)		0.324[b]
PIVC ≤120 h[f] in Every 96-h group	1391		1328		2719			<0.001[a]
Phlebitis per PIVC ≤120 h[g] in Every 96-h group	62		70		132			
Relative risk							0.85 (0.61 to 1.18)	
Absolute risk difference							−0.8% (−2.4 to 0.8)	
Phlebitis/1000 PIVC-days (95% CI)	16.2 (12.6 a 20.8)		26.0 (20.6 a 32.8)		20.3 (17.1 a 24.0)			0.004[b]
Incidence rate ratio							0.62 (0.44 to 0.89)	
Absolute risk difference							−9.78 (−17.08 to −2.47)	
Severity of phlebitis per PIVC (N = 2.745)	n	%	n	%	n	%		
Grade 1	25	40.3	29	40.3	54	40.3		0.626[d]
Grade 2	32	51.6	34	47.2	66	49.3		
Grade 3	4	6.5	8	11.1	12	9.0		
Grade 4	0	–	0	–	0	–		

[a] Chi-square.
[b] One-sided Fisher's test.
[c] Log-rank test.
[d] Fisher's exact test.
[e] excluding patients with PIVC indwelling times ≥200 h.
[f] excluding patients with PIVC indwelling times ≥120 h in the 96-h group.

Table 3
Secondary outcomes (per intention to treat analysis).

Complications (except phlebitis)	Clinically indicated		96-h		Total		ARD (95% CI)	*p* value[a]
	N	%	N	%	N	%		
No. of PIVCs	1391	51.16	1328	48.84	2719	100.0		
Any complication (except phlebitis)	709	51.0	547	41.2	1256	46.2	9.8% (6.1 to 13.5)	<0.001
Pain	362	26.2	280	21.4	642	23.9	4.7% (1.5 to 7.9)	0.004
Occlusion	91	6.6	81	6.2	172	6.4	0.4% (−1.5 to 2.2)	0.686
Dislodgement or inadvertent removal	142	10.3	110	8.4	252	9.4	1.9% (−0.3 to 4.1)	0.100
Infiltration	249	18.0	179	13.7	428	15.9	4.3% (1.6 to 7.8)	0.002
Extravasation	0	0.0	1	0.1	1	0.01	−0.1% (−0.2 to 0.1)	0.303
CABSI	0	–	0	–	0	–	–	–

ARD, Absolute risk difference; PIVC, peripheral intravenous catheter; CABSI, Catheter-associated blood stream infection; CI, confidence interval.
[a] One-sided Fisher's exact test.

phlebitis of 0.83 in the clinically indicated removal group that was not significantly different from the 96-h removal group; however, the clinically indicated removal was considered not inferior to the routine removal every 96-h, with an absolute risk difference of −1.7% (−4.8 to 1.4) for the occurrence of phlebitis (Table 2).

However, the rate of phlebitis/1000 days in the clinically indicated removal group was lower than that in the routine removal group, indicating a phlebitis incidence rate ratio of 0.63 (0,43 to 0,91).

The hazard ratio showed that, the risk of phlebitis in the clinically indicated replacement group was 0.81 that of the 96-h replacement group. There was a 19.0% relative reduction in the probability of the occurrence of phlebitis due to clinically indicated peripheral catheter replacement, compared with 96-h replacements; the reduction was not statistically significant (Table 2).

By per protocol analysis, there were 132 phlebitis cases, of which 62 were in the clinically indicated replacement group and 70 in the 96-h replacement group.

The null hypothesis, that is, the clinically indicated removal is inferior to routine removal was rejected, with an absolute risk difference of −0.8% (−2.4 to 0.8) for the occurrence of phlebitis; this was within the pre-defined non-inferiority margin of 3% (95% CI). (Table 2)

The incidence of phlebitis in the clinically indicated replacement group was lower than in the routine replacement group and the phlebitis incidence ratio was 0.62 (0.44 to 0.89), representing a significant, 38.0% relative risk reduction (Table 2).

Table 2 also shows that approximately 90% of the phlebitis episodes were classified as Grades 1 and 2; 9% were Grade 3. There were no statistically significant differences in the distribution of phlebitis grades between the two groups; none of the phlebitis episodes was identified as Grade 4.

To compare the time to the first phlebitis episode in the two groups, a Kaplan–Meier survival analysis was performed, per intention to treat, excluding the 154 patients with overall all-catheter dwells installed for >200 h to promote risk proportionality. As shown in Fig. 2, survival curves are correlates and intersect at some points, and the log-rank test ($p = 0.247$) suggests that the cumulative survival probability of the two groups is similar.

The analysis of the secondary outcomes, presented in Table 3, showed a prevalence of any complication (except phlebitis) with 10 percentage points higher in the clinically indicated group, as well as, individually analyzed, pain ($p = 0.004$) and infiltration ($p = 0.002$), were almost 5 percentage points higher in the clinically indicated group than in the 96-h replacement group.

4. Discussion

The study findings pointed that, the upper limit of the absolute risk reduction confidence interval (per protocol analysis) remained within the predefined non-inferiority margin of 3% (−2.4 to 0.8), as well as intention to treat analysis (−4.8 to 1.4), showing that peripheral intravenous catheter replacement based on clinical indications did not increase the phlebitis risk.

In addition, were found similar incidences in both studied groups intention to treat analysis (1.7 percentage points higher) and per-protocol analysis (0.9 percentage points higher) in the 96-h replacement group, without statistical difference.

This finding corresponds with the results of other randomized controlled studies of clinically indicated versus routine 72 h peripheral catheter removal conducted in Australia (2012) and China (2017). In those studies, the phlebitis incidences (per intention to treat) were 7% and 12%, respectively, with no statistical differences between the groups. (Rickard et al., 2012; Xu et al., 2017) Of the Latin American sites in a recent global peripheral catheter study, one-third had clinically indicated (not-time based) catheter removal policies; our data supports standardization of this policy in our region. (Alexandrou et al., 2018)

In the present study, the between-group differences in phlebitis rate per 1000 days were significantly difference, with the highest incidence in the routine catheter removal group (23.8 versus 14.9 events/1000 days). Conversely, Rickard et al. (2012) presented lower rates and no statistical difference between the groups in the Australian study with rates of 13.8/1000 catheter-days (clinically indicated removal) and 13.11/1000 catheter-days (routine removal). Similarly, the study of Xu et al. (2017) from China did not find significantly different phlebitis rates between groups, despite observing higher rates than in the present study.

The difference in our study may reflect the longer average overall (all peripheral catheter) treatment duration in the clinically indicated group, perhaps related to the higher proportion of clinical patients rather than surgical in this group. While it is possible that a routine replacement policy may 'prompt' clinicians to reassess and cease treatment, this does not seem to explain our results since clinically indicated patients had comparable numbers of catheters fail and require replacement, during therapy. Previous studies did not find different overall dwell time between study groups. (Rickard et al., 2012; Xu et al., 2017)

Although dozens of patients had overall (all-catheter) indwelling times up to more than 400 h, patients with overall indwelling times >200 h ($n = 154$) were excluded from the catheter survival curve analysis, to maintain risk proportionality. Although they chose not to exclude outlying patients from their analyses, the Rickard et al. (Rickard et al., 2012) trial found similar results. Xu et al. (2017) verified a significant difference in survival from phlebitis ($x^2 = 10.482$, $p = 0.001$) between treatment groups. The observed difference was presumed to be due to some patients in the clinically indicated group had remained with peripheral catheter over a long period, without developing phlebitis; consequently, not promoting between-group risk proportionality, may have influenced their result. (Xu et al., 2017)

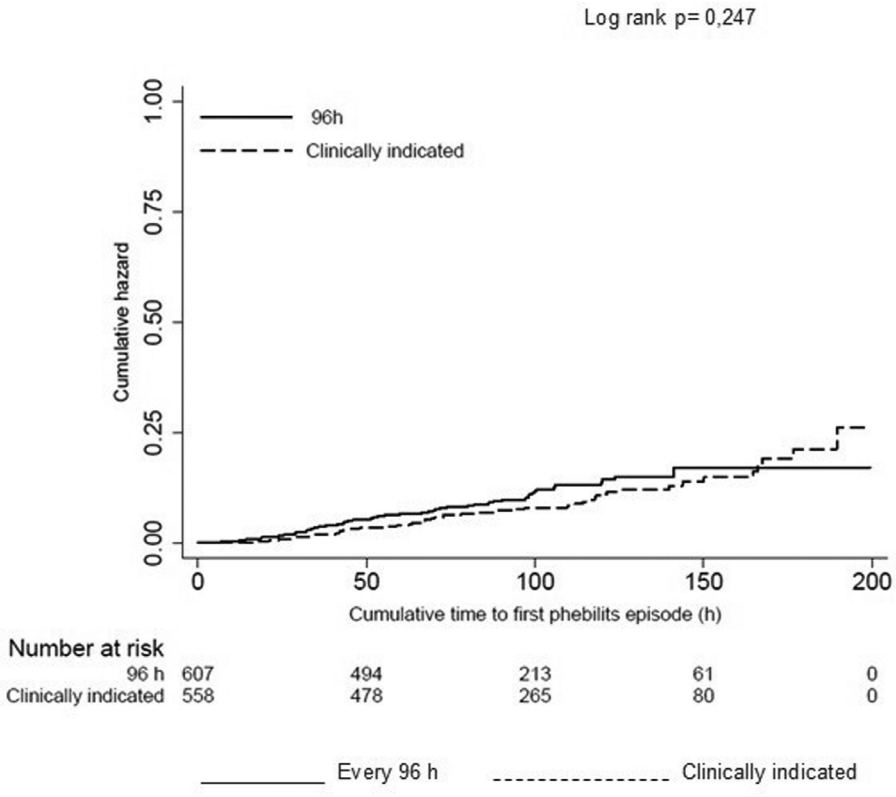

Fig. 2. Kaplan–Meier analysis of survival from phlebitis per-intention to treat.

The phlebitis severity findings showed that peripheral catheter indwelling time did not influence severity and that Grade 2 phlebitis was the most prevalent, followed by Grades 1 and 3. These observations suggest that phlebitis severity was not excessive, particularly since there was no evident progression to Grade 4. Other studies corroborate this finding, reporting approximately 10% of phlebitis cases reaching Grade 3. (Urbanetto et al., 2016; Urbanetto et al., 2017)

Approximately half of the patients (n = 614) in the present study received the insertion of only one catheter during their hospitalization, which is the desired outcome. In addition, more than 28% required only two catheter insertions. Combined, approximately 74% of the patients required only one or two catheter insertions (equivalent performance in both groups). Thus, a mean 2.08 catheter insertions per patient (2.09 in the routine removal group and 2.06 in the clinically indicated removal group) were required for overall study population. Other studies, with similar objectives, demonstrated mean catheter insertions of 1.6–1.7 per patient in the clinically indicated removal group and 1.9 in the routine removal group. (Rickard et al., 2012; Rickard et al., 2010) However, in these studies there were more catheters inserted per patient. In addition, previous studies reported the clinically indicated removal groups to have mean dwell times of 99/96 h and routine removal groups 70/48 h. Nevertheless, these studies tested a 72–96 h routine removal time frame and in our study, 96-h routine interval may have explained our finding of no between-group difference. (Rickard et al., 2012; Xu et al., 2017)

During the conduct of the present study, removing peripheral catheters routinely was more prone to protocol violations than when removing the catheter when clinically indicated, despite the routine period being part of the usual protocol at the study sites. Other studies presented similar pragmatic situations with different approaches regarding protocol adherence. (Rickard et al., 2012; Xu et al., 2017) This may indicate that patients' conditions and needs were taken into account in the decision to remove catheters. Additionally, existing literature (Murayama et al., 2018; Tanabe et al., 2016) shows that with technological developments associated with infusion therapy-related supplies and devices, the average indwelling time has tended to increase without increasing failure rates. Thus, prolonging the indwelling time does not seem to be the key factor for risk increase, but rather, poor practices in insertion and maintenance. (Helm et al., 2015)

The predominant clinical reasons for removing peripheral catheters were pain or discomfort (23.9%) and/or infiltration (15.9%), followed by inadvertent removal (9.4%) and some of these were significantly higher in the clinically indicated group. Apart from phlebitis, these complications are described in the literature as the main contributors to the infusion failures that challenge practitioners in their desire to promote quality care and minimize harm to patients. (Tanabe et al., 2016)

A Brazilian clinical study that analyzed complications resulting from peripheral catheter use, in adults, verified an infiltration rate of 11.9% for the overall study population. Comparing catheters that showed infiltration with those that did not, antimicrobial infusion was identified as a contributor, and in the present study the modes of catheters utilization and the type of medications infused are important issues to be addressed in future analyses on impact on phlebitis and other catheter related complications. Additionally, a third puncture attempt resulted in a 6-fold increase in the risk of developing infiltration. On the other hand, the use of 20 G catheter reduced this risk. The survival analysis, after the third day of catheter indwelling time, showed that the cumulative infiltration risk was reduced by half for patients treated using integrated catheters, compared with single over-needle ones. (Johann et al., 2016)

A cross-sectional study describing insertion characteristics, as well as catheter maintenance and removal, reported that 90% of inserted catheters are removed prematurely, i.e., before the sched-

uled replacement time or the end of therapy, due to complications and care failures. (Alexandrou et al., 2018) A range of strategies have been researched in attempts to achieve better patient care outcomes related to catheters, including the use of bundles, checklists, and risk scores. (Carr et al., 2017; Ray-Barruel and Rickard, 2018; Holder et al., 2017; Ray-Barruel et al., 2018) Peripheral intravenous catheter insertion and maintenance can be enhanced with the use of improved supplies and devices; improving the best practice training and qualifications of the team, including adherence to hand hygiene protocols and frequent assessment of the catheter insertion site; frequent flushing; improving dressing maintenance; and encouraging patient and family engagement in the treatment. (Ansel et al., 2017; Holder et al., 2017) Importantly, infusion therapy best practices are not limited to the use of state-of-the-art technology. Essentially, they also account for the use of clinical reasoning to guide the professional's decisions and to demonstrate outcomes within levels of excellence and add value to the patient's experience. (Ansel et al., 2017; Holder et al., 2017)

The use of clinical indications to dictate peripheral intravenous catheter removal necessarily implies a modification to our conception of peripheral infusion, especially in hospitalized patients. Studies that reinforce the use of prevention measures are a priority to support clinical decisions in this environment. The idea that catheters are short-term indwelling devices and, therefore, are associated with minimal infection risk needs to be abolished. When catheters are inserted to support treatment, the professional must use all available resources to mitigate complications and prevent infection. Investing efforts in deciding the best insertion site, appropriate catheter gauge, and stabilizing and securing the catheter, comprise a more desirable practice. The concept of innocuous and disposable peripheral catheters should be definitively discarded. (Ray-Barruel et al., 2018; Rickard and Ray-Barruel, 2017; Stevens et al., 2018; Roszell et al., 2018)

5. Limitations

Peripheral intravenous catheter insertion, maintenance, and removal activities were purposely delegated to the nursing staff to reflect their application in practice and have a more pragmatic characteristic of this trial. On the other hand, it also facilitated protocol violations, especially with regard to maintaining catheter placement for only 96 h in that group. Another limitation was the inability to blind the study.

6. Conclusion

Patients with peripheral intravenous catheters removed by clinical indications presented less phlebitis episodes than those submitted to catheter removal every 96 h, pointing to rejection the inferiority of clinically indicated replacement. Phlebitis severities were similar between the study groups, and pain and infiltration were more associated to catheters removed by clinical indications.

Funding organization(s) and funding support

The Becton Dickinson Company (Brazil) provided vascular and infusion supplies (including catheters and needless connectors) and covering cost of statistical assistants employed by the researchers. The company had no involvement in the design, conduct, analysis or reporting of the study.

This study was conducted as part of the doctoral program at Paulista Nursing School, Federal University of Sao Paulo – UNIFESP. The study was funded by a grant from the National Council for Scientific and Technology (No. 308281/2015-2).

Declaration of Competing Interest

The author(s) have no potential conflicts of interest to disclose.

Acknowledgments

We appreciate the head nurses and all clinical nurses who were working in the research wards and we are grateful to the team of research nurses and we also thank Maria Carmen Martinez for the statistical analyses.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijnurstu.2019.103504.

References

Alexandrou, E., Ray-Barruel, G., Carr, P.J., Frost, S., Inwood, S., Higgins, N., et al., 2018. Use of short peripheral intravenous catheters: characteristics, management, and outcomes worldwide. J. Hosp. Med. 13 (5). doi:10.12788/jhm.3039.

Ansel, B., Boyce, M., Embree, J.L., 2017. Extending short peripheral catheter dwell time. a best practice discussion. J. Infus. Nurs. 40 (3), 143–146. doi:10.1097/NAN.0000000000000137.

Carr, P.J., Higgins, N.S., Cooke, M.L., Rippey, J., Rickard, C.M., 2017. Tools, clinical prediction rules, and algorithms for the insertion of peripheral intravenous catheters in adult hospitalized patients: a systematic scoping review of literature. J. Hosp. Med. 12 (10), 851–858. doi:10.12788/jhm.2836, Epub 2017 Sep 6.

Chopra, V., Flanders, S.A., Saint, S., et al., 2015. The michigan appropriateness guide for intravenous catheters (MAGIC): results from a multispecialty panel using the rand/ucla appropriateness method. Ann. Intern. Med. 163 (6 Suppl), S1–S340. doi:10.7326/M15-0744.

Dunda, S., Demir, E., Mefful, O., Grieb, G., Bozkurt, A., Pallua, N., 2014. Management, clinical outcomes, and complications of acute cannula-related peripheral vein phlebitis of the upper extremity: a retrospective study. Phlebology 30 (6), 381–388. doi:10.1177/0268355514537254.

Fernandez-Ruiz, M., Carretero, A., Diaz, D., et al., 2014. Hospital-wide survey of the adequacy in the number of vascular catheters and catheter lumens. J. Hosp. Med. 9 (1), 35–41. doi:10.1002/jhm.2130.

Hadaway, L., 2012. Short peripheral intravenous catheters and infections. J. Infus. Nurs. 35 (4), 230–240. doi:10.1097/NAN.0b013e31825af099.

Helm, R.E., Klausner, J.D., Klemperer, J.D., Flint, L.M., Huang, E., 2015. Accepted but unacceptable: peripheral IV catheter failure. J. Infus. Nurs. 38 (3), 189–203. doi:10.1097/NAN.0000000000000100.

Holder, M.R., Stutzman, S.E., Olson, D.M., 2017. Impact of ultrasound on short peripheral intravenous catheter placement on vein thrombosis risk. J. Infus. Nurs. 40 (3), 176–182. doi:10.1097/NAN.0000000000000214.

Infusion Nurses Society, 2011. Infusion nursing standards of practice. J. Infus. Nurs. 34 (1Suppl), S1–92.

Infusion Nurses Society, 2016. Infusion nursing standards of practice. J. Infus. Nurs. 39 (1 Suppl), 1–157.

Johann, D.A., Danski, M.T.R., Vayego, S.A., Barbosa, D.A., Lind, J., 2016. Risk factors for complications in peripheral intravenous catheters in adults: secondary analysis of a randomized controlled trial. Rev. Lat. Am. Enfermagem. 24, e2833. doi:10.1590/1518-8345.1457.2833.

Magerote, N.P., Lima, M.H.M., Silva, J.B., Correia, M.D.L., Secoli, S.R., 2011. Relation between phlebitis and peripheral intravenous catheter removal. Texto & Contexto - Enfermagem. 20 (3), 286–292.

Murayama, R., Takahashi, T., Tanabe, H., Yabunaka, K., Oe, M., Komiyama, C., Sanada, H., 2018. Exploring the causes of peripheral intravenous catheter failure based on shape of catheters removed from various insertion sites. Drug Discov. Ther. 12 (3), 170–177. doi:10.5582/ddt.2018.01024.

O'Grady, N.P., Alexander, M., Burns, L.A., et al., 2011. Guidelines for the prevention of intravascular catheter-related infections. Am. J. Infect. Control 39 (4 Suppl 1), S1–S34. doi:10.1016/j.ajic.2011.01.003.

Ray-Barruel, G., Rickard, C.M., 2018. Helping nurses help PIVCs: decision aids for daily assessment and maintenance. Br. J. Nurs. 27 (8), S12–S18. doi:10.12968/bjon.2018.27.8.S12.

Ray-Barruel, G., Cooke, M., Mitchell, M., Chopra, V., Rickard, C.M., 2018. Implementing the i-decided clinical decision-making tool for peripheral intravenous catheter assessment and safe removal: protocol for an interrupted time-series study. BMJ Open 8, e021290. doi:10.1136/bmjopen-2017-021290.

Rickard, C.M., Ray-Barruel, G., 2017. Peripheral intravenous catheter assessment: beyond phlebitis. Lancet Haem. 4 (9), E402–E403. doi:10.1016/S2352-3026(17)30145-X.

Rickard, C.M., McCann, D., Munnings, J., McGrail, M.R., 2010. Routine resite of peripheral intravenous devices every 3 days did not reduce complications compared with clinically indicated resite: a randomized controlled trial. BMC Med. 8, 53. doi:10.1186/1741-7015-8-53.

Rickard, C.M., Webster, J., Wallis, M.C., et al., 2012. Routine versus clinically indicated replacement of peripheral intravenous catheters: a randomized controlled equivalence trial. Lancet 380 (9847), 1066–1074. doi:10.1016/S0140-6736(12)61082-4.

Rickard, C.M., Marsh, N., Webster, J., et al., 2015. Securing all intraVenous devices effectively in hospitalized patients— the save trial: study protocol for a multicentre randomised controlled trial. BMJ Open 5 (9), e008689. doi:10.1136/bmjopen-2015-008689.

Roszell, S.S., Rabinovich, H.B., Smith-Miller, C.A., 2018. Maintaining short peripheral catheter patency. A comparison of saline lock versus continuous infusion in the acute care setting. J. Infus. Nurs. 41 (3), 165–169. doi:10.1097/NAN.0000000000000276.

Scales, K., 2005. Vascular access: a guide to peripheral venous cannulation. Nurs. Stand. 19 (49), 48–52. doi:10.7748/ns2005.08.19.49.48.c3935.

Schulz, K.F., Altman, D.G., Moher, D.CONSORT Group, 2010. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ 340, c332.

Stevens, C., Milner, K.A., Trudeau, J., 2018. Routine versus clinically indicated short peripheral catheter replacement: an evidence-based practice project. J. Infus. Nurs. 41 (3), 198–204. doi:10.1097/NAN.0000000000000281.

Tanabe, H., Takahashi, T., Murayama, R., Yabunaka, K., Oe, M., Matsui, Y., Arai, R., Uchida, M., Komiyama, C., Sanada, H., 2016. Using ultrasonography for vessel diameter assessment to prevent infiltration. J. Infus. Nurs. 39, 105–111. doi:10.1097/NAN.0000000000000159.

Urbanetto, J.S., Peixoto, C.G., May, T.A., 2016. Incidence of phlebitis associated with the use of peripheral iv catheter and following catheter removal. Rev. Lat. Am. Enfermagem 24, e2746. doi:10.1590/1518-8345.0604.2746.

Urbanetto, J.S., Muniz, F.O.M., Silva, R.M., Freitas, A.P.C., Oliveira, A.P.R., Santos, J.C.R.D., 2017. Incidence of phlebitis and post-infusion phlebitis in hospitalized adults. Rev. Gaúcha Enferm. 38 (2), e58793. doi:10.1590/1983-1447.2017.02.58793.

Uslusoy, E., Mete, S., 2008. Predisposing factors to phlebitis in patients with peripheral intravenous catheters: a descriptive study. J. Am. Acad. Nurse Pract. 20 (4), 172–180. doi:10.1111/j.1745-7599.2008.00305.x.

Vizcarra, C., Cassut, C., Corbitt, N., Richardson, D., Runde, D., Stafford, K., 2014. Recommendations for improving safety with short peripheral catheters. J. Infus. Nurs. 37 (2), 121–124. doi:10.1097/NAN.0000000000000028.

Washington, G.T., Barrett, R., 2012. Peripheral phlebitis a point-prevalence study. J. Infus. Nurs. 35 (4), 252–258. doi:10.1097/NAN.0b013e31825af30d.

Webster, J., Osborne, S., Rickard, C.M., New, K., 2015. Clinically-indicated replacement versus routine replacement of peripheral venous catheters. Cochrane Database Syst. Rev. (8), CD007798 doi:10.1002/14651858.CD007798.pub4.

Xu, L., Hu, Y., Huang, X., Fu, J., Zhang, J., 2017. Clinically indicated replacement versus routine replacement of peripheral venous catheters in adults: a nonblinded, cluster-randomized trial in china. Int. J. Nurs. Pract. 23 (6). doi:10.1111/ijn.12595.

Zhang, L., Cao, S., Marsh, N., et al., 2016. Infection risks associated with peripheral vascular catheters. J. Infect. Prev. 17 (5), 207–213.