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ORIGINAL RESEARCH: CLINICAL TRIAL

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Benefits of the application of heat and pressure on peripheral venous cannulation in adults: A randomized controlled trial

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Abstract

Aim: To evaluate the effectiveness of the application of topical heat, high pressure or a combination of both on antebrachial venous cannulation.

Design: A cross-over clinical trial blinded for haemolysis analysis.

Methods: This cross-over clinical trial with two periods was performed in the Clinical Trial Unit of Hospital Universitario de La Princesa (Madrid) during June–July of 2017 in 59 healthy adults who were randomly allocated to one of three interventions: (1) Using dry topical heat for 7 min produced by two hot seed bags ($N = 21$), (2) Applying controlled pressure from a sphygmomanometer inflated to 100 mmHg ($N = 18$) and (3) combining heat and pressure ($N = 20$) in one period out of two. All interventions were contrasted to standard clinical practice in the other period. The comparator involved a standard tourniquet around the upper arm to restrict venous blood flow. The primary outcome was effectiveness measured as vein cannulation at first attempt. Secondary outcomes were vein perception, pain, haemolysis in blood samples and adverse events.

Results: All the interventions were more effective than comparator. Vein perception was optimized in about all individuals. Moreover, pain relief was significantly higher when high pressure was applied. Haemolysis was not affected in any of the three interventions. In addition, no serious adverse events appeared.

Conclusion: High pressure is determined to be the most effective in vein catheterization, pain relief, vein perception and quality of blood sample inalterability. Moreover, it is safe considering that only one adverse event appeared.

Impact: Vein cannulation is a very common invasive technique, where repeated failures have been registered. Thus, we consider it relevant to develop interventions to achieve venous catheterization at first attempt to alleviate the pain and anxiety associated with this technique. We advocate using high pressure intervention for emergency, due to swiftest method and feasible in case of lacking resources, such as sphygmomanometers in the ambulance.

Protocol registration: The study protocol was registered in ClinicalTrial.gov Identifier: NCT04027218.

Name of the trial: ECYPVEN-H/17

Interventions can be extrapolated to healthy young adults, adults and patients who have healthy vein status perception. Pressure intervention could be an alternative to heat intervention when performing vein cannulation due to its lower risk of transient paresthesia for older people who often suffer from arterial hypertension.

KEYWORDS

dry heat, heating, nursing, pain, patient safety, peripheral venous catheterization, tourniquet, venipuncture

1 | INTRODUCTION

Peripheral vein cannulation (PVC) is one of the most frequently performed invasive interventions in hospital environments (up to 70–80%) (Milutinović et al., 2015) and is one of the most common what can cause pain. However, after its implementation, the initial pain significantly decreases (Fink et al., 2009). Moreover, anxiety is reported as a factor (about 20%) which complicates PVC as a result of causing vasoconstriction. Once an initial attempt has failed, nearly all patients experience a sympathetic activation that makes subsequent attempts particularly complicated (1.36–2.34 additional attempts) (Fink et al., 2009; Yamagami et al., 2017). Although PVC should be technically easy, failed attempts have been described (26%) (Ravik et al., 2017); which may increase costs due to using additional supplies. Additionally, extra time is required from the nurse and the subject (Fink et al., 2009; Lenhardt et al., 2002).

2 | BACKGROUND

Pain relief may contribute to successful PVC (Péculo, 2010). Therefore, previous studies have used different approaches to ease the pain associated with venipuncture, such as local anaesthetic (Péculo, 2010), cold sprays producing vasoconstriction (Barbour et al., 2018; Mace, 2016), lidocaine intradermal increase complexity of palpation veins (Rüsch et al., 2017), valsalva maneuver increasing risks of expected vaso-vagal syncope (Suren et al., 2013) and music therapy requiring previous self-selected music (Hsieh et al., 2014; Shabandokht-Zarmi et al., 2017). Therefore, although those alternatives are effective for pain relief, many failed attempts occurred after applying cold or pharmacological therapies which overall result in prolonged PVC procedure and increased adverse events. The implementers were distributed equivalently and, as a result, their skills as well (Rüsch et al., 2017).

Moreover, to reduce pain reducing the attempts, ultrasound-guided intravenous catheterization and dry heat technique with non-controlled pressure were effective for PVC at first attempt. However, the ultrasound-guided intravenous catheterization increased risk of nerve (up to 2.4%) or artery (up to 9.8%) puncture (Salleras-Duran & Fuentes-Pumarola, 2016), whereof none of them occurred or the expected erythema after the application of heat (Fink et al., 2009; Yamagami et al., 2017).

Additional factors have been considered due to their potential worsening of vein perception and cannulation such as obese, the extremes of age, chronic patients, receiving chemotherapy infusion, rolled veins, low visibility/palpability veins, inadequate skill level in the technique (De la Torre-Montero et al., 2014; Yamagami et al., 2017) and different skin types such as dark (Eilers et al., 2013; Fink et al., 2009; Sachdeva, 2009).

Venipuncture is performed for obtaining blood samples that are used for the analysis of different parameters such as potassium (Makhumula-Nkhoma et al., 2019), cholesterol, aspartate aminotransferase (Thomas, 2002), creatinine,, iron, lactate dehydrogenase, billirrubin and glucose (Lippi et al., 2008). The extraction method was described as the major contributor for haemolysis (Plumhoff et al., 2008), which affects the accuracy of some diagnostically relevant analytical determinations that are based on 60%–80% of medical decision-making, therefore of patient safety (Farrell & Carter, 2016; WHO, 2002). Considering all the above mentioned methods, it seems that no reference method is available for PVC at first attempt which can be safely applied to most patients and in distinct clinical situations. Nevertheless, the dry heat technique with non-controlled pressure was effective for first attempt cannulation safely (Fink et al., 2009), however, the effective pressure of the applied tourniquet were not investigated in PVC (Sabri et al., 2013; Yamagami et al., 2017).

3 | THE STUDY

3.1 | Aim

The aim of this study was to compare the outcomes of the most frequently used technique for intravenous cannulation (using a standard tourniquet around the upper arm to restrict venous blood flow) with each of the following techniques: (1) The application of dry topical heat; (2) the application of high pressure via a sphygmomanometer cuff; or (3) a combination of both. We applied these techniques because the dry heat technique was effective and safe in previous studies, however, the effective and safe pressure of the applied tourniquet in PVC, with and without heat, was unknown. These alternatives may be easily transferred to normal clinical practice.

The primary outcome was to assess PVC successfully at first attempt because of the impact on secondary outcomes, which were

set according to relevance to patient safety. As secondary outcomes, we analysed its effects in vein perception, pain, blood haemolysis and adverse events according to skin types. Our objectives were also set in previous studies but for different interventions, which allow comparisons among them (except for haemolysis, skin types, adverse events and relationship with pain). We hypothesized that at least one of the three interventions would be more advantageous than the PVC techniques at first attempt applied in the current clinical practice.

3.2 | Study design

This study was a cross-over clinical trial with two periods, two sequences, single-centre and blinded for haemolysis analysis to evaluate the effectiveness—measured as PVC at first attempt—and safety of three interventions based on the application of: (1) dry heat; (2) high pressure; and (3) dry heat and high pressure in healthy adult volunteers. Participants were randomly assigned to one of the three interventions and clinical practice application—a common comparator of the three interventions—in a 1:1 ratio due to the two periods of the bioequivalence trials where this study was conducted.

3.3 | Setting and sample

Our study population comprised 59 healthy young adults from both sex (20 men & 39 women). Participants were recruited among subjects in bioequivalence trials for the present study in the Clinical Trial Unit of Hospital Universitario de La Princesa (Madrid) in June 2017. They were informed about the aims and intervention of this study and signed the informed consent form the night before admission. The trial was carried out between June–July of 2017.

Inclusion criteria were the following: eligible 18–55 years old participants (Ischemic Heart Disease|National Heart, Lung, and Blood Institute (NHLBI), n.d.), fluid intake was limited to a volume equal to or less than 500 ml and fasted 6–8 hr before PVC (Berman et al., 2016). Exclusion criteria: participants with grade one in assessment of vein perception (optimal vein perception) by Venous International Assessment (VIA) scale, smokers, body mass index (BMI) <18.5 or ≥30, who had any disease, blood test, urinalysis or physical examination showing disorders with clinical relevance and subjects receiving treatment for any other disease apart from contraceptives.

We enrolled 62 subjects. However, the study was conducted in 59 participants what was considered sufficient based on two-sided calculation for paired intervention-comparator groups (Sample Size & Power Calculator, 2012) that estimated that a sample of 60 participants (alfa risk of 5%, power of 80% and assuming a drop out of 12% based on experience) was needed to detect a statistical significance difference of 21% effectiveness by any of three interventions related to clinical practice. We set a 95% of effectiveness to be more favourable than the first attempt of the comparator being 74% (null hypothesis) (Lapostolle et al., 2007).

Twelve sealed envelopes were allocated six times to cover the size of each sample. Six envelopes contained an intervention for the first entry while six consisted of the comparator in the first entry as described in Figure 1. The envelopes were allocated by the principal investigator in the first admission day and were saved to apply the remaining intervention/comparator in the second admission day. The study was performed in five groups due to the capacity of the Clinical Trials Unit. The unnecessary envelopes due to exclusion or drop-out were not re-used. Nurses performed PVC according to the randomized procedure assigned to each healthy volunteer.

3.4 | Study interventions

Those allocated to intervention 1 were treated with two bags of carob seeds which were heated in a microwave at 800 W for 30 s to reach a temperature of 34–35°C. Afterwards, both bags were lined up consecutively on a forearm from the most distal antebrachial vein to the most proximal vein (considered as antecubital fossa vein). This distribution stimulated venous flow throughout the forearm (Figure 1). Bags were placed for 7 min (Fink et al., 2009). After heating, a pressure tourniquet was applied according to CLSI GP41-A6 to increase vein stagnation (Lima-Oliveira et al., 2012).

For those allocated to intervention 2 a nurse placed an aneroid sphygmomanometer (215-BK2006, Quirumed ®, S.L., Valencia, Spain) in the forearm selected as optimal. Pressure was set at 100 mmHg (Silbernagl & Despopoulos, 2015). The radial pulse was monitored in each subject to confirm that it was lower than the systolic blood pressure (Silbernagl & Despopoulos, 2015). Those participants allocated to intervention 3 were treated with heat as described in intervention 1. Subsequently, pressure was applied as described in intervention 2.

For all participants, a comparator was allocated, which consisted of non-controlled pressure applied by an elastic compressor (Synthetic rubber-latex compressor tape, Unidix®, Madrid, Spain) according to CLSI GP41-A6. Moreover, when venipuncture failed at first attempt, the subsequent attempts were performed with the comparator technique. Therefore, all interventions received pressure application, which could be high controlled pressure, or non-controlled pressure in clinical practice. Figure 1. Dry heat, high pressure, combined intervention and comparator.

3.5 | Outcomes

Any intervention was considered effective when two actions were completed: PVC was successful at first attempt using a 20-gage diameter IV catheter (Jelco® ProtectIV® Plus Safety IV Catheter, Smiths Medical International, Ltd., Kent, UK) and an EDTA K2 blood

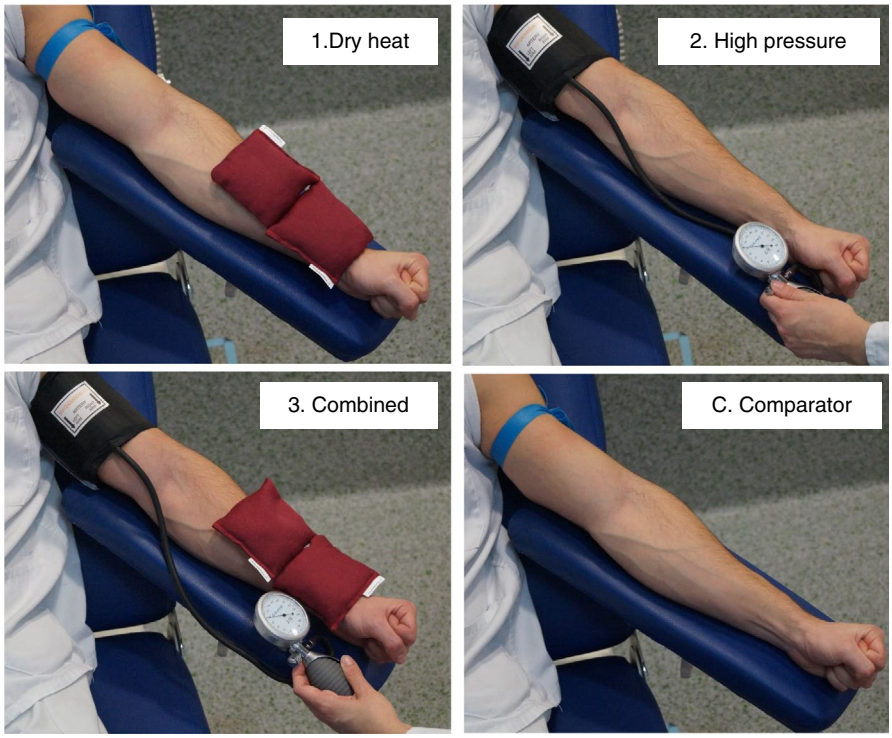

FIGURE 1 Dry heat, high pressure, combined intervention and comparator. 1. Dry heat intervention: when dry heat was performed, two bags were applied according to the criteria from the most distal forearm to the most proximal (as shown in pictures 1 and 3). After 7 min, both bags were removed to proceed to perform a vein stagnation by an elastic compressor according to CLSI GP41-A6; as comparator. 2. High pressure intervention: pressure was set at 100 mmHg using a sphygmomanometer and monitoring the radial pulse. 3. Combined intervention: first dry heat was performed with two bags were applied according to the criteria from the most distal forearm to the most proximal, second, to proceed to perform a vein stagnation by high pressure was set at 100 mmHg using a sphygmomanometer. C. Comparator (Clinical practice). In all three interventions and comparator, after a vein cannulation in antebrachial potential puncture site was achieved, the pressure (sphygmomanometer or compressor) and fist was released [Colour figure can be viewed at wileyonlinelibrary.com]

sample was extracted by Vacutainer™. Vein perception was assessed by VIA scale, which is considered as the 'self-reported visual observation or palpation of a venous pathway by a registered nurse' (De la Torre-Montero et al., 2014). Improvements of at least one grade in VIA were considered clinically relevant.

The condition of the skin was self-evaluated by the subjects on the inside of their forearm and the skin type was self-classified according to the Fitzpatrick's scale (Eilers et al., 2013). Pain was assessed by the Visual Analogue Scale (VAS) (Ferreira-Valente et al., 2011) expressed by round number values. Pain relief values of at least one number were considered clinically significant.

To determine haemolysis, the free haemoglobin absorbance was measured by NanoDrop® 2000 Spectrophotometer (Thermo Fisher Scientific Inc., Wilmington, USA) in 2 μl of plasma. Blood samples were centrifuged at 4°C for 10 min at 1900 *g* and then plasma was collected. The following equation was used to correct lipaemia (Appierto et al., 2014): (A414-A385) +0.16xA385. Additionally, a baseline correction factor at 750 nanometre wavelength was applied based on a previous pilot study (Simón-López & Luquero-Bueno, 2017). The analyst was blinded for blood sample extraction. Adverse events were registered and evaluated according to the World Health Organization (WHO) causality algorithm (Holloway & Green, 2003).

3.6 | Data collection procedure

All procedures were performed in the same room where the temperature and humidity were monitored by a digital thermometer (OH HAUS OH 503, Greutor, S.L., Barcelona, Spain). All subjects wore cotton pajamas and light was always artificial to harmonize visibility and thermoregulation respectively. Implementers were collaborating nurses who had at least 1 year of experience in PVC in the Clinical Trial Unit, skills to achieve cannulation in less than 5 min due to bioequivalence studies conditions, worked and had a similar career in hospital assistance.

3.6.1 | In the morning of first admission (first period):

Step 1. The elastic compressor offered by the Hospital Universitario de La Princesa (Madrid), was applied on both forearms of each individual as in usual practice according to the CLSI GP41-A6 venipuncture guide (Lima-Oliveira et al., 2012) to examine vein perception (step 2).

Step 2. Vein perception was assessed by VIA scale on both forearms with the elastic compressor applied.

Step 3. The forearm of each individual with the best vein perception was selected and registered for intervention or comparator application and PVC, excluding grade one due to exclusion criteria.
Step 4. Participants were randomly allocated to a sequence of one intervention with comparator.
Step 5. Different parameters such as systolic and diastolic blood pressure, heart rate (Monitor Carescape V100, General Electric, Milwaukee, United States of America), tympanic temperature (Genius 2, Covidien llc., Mansfield, United States of America) and weight (SECA 711, Seca gmbh & co., Hamburg, Germany) were measured immediately before the intervention.
Step 6. Assigned intervention or comparator was applied (see study interventions section). Each intervention was performed in seated volunteers. Moreover, a clenched fist was requested during interventions until PVC was performed.
Step 7. Immediately after any of the three interventions and before PVC, another VIA assessment was performed to determine if vein perception was increased. Although comparator was applied in the first admission, step 7 was not performed due to any expected changes in VIA assessment after comparator application.
Step 8. PVC was performed in the selected upper arm and an EDTA K2 blood sample was extracted.
Step 9. The anatomical area where the PVC was performed was registered for second admission.
Step 10. The condition of the skin was self-evaluated and classified according to the Fitzpatrick's scale.
Step 11. Pain was assessed by the VAS (Ferreira-Valente et al., 2011) no later than 2 hr from venipuncture to avoid disremembering.
Step 12. All volunteers were followed up for undesirable side effects during 72 hr after intervention and when any occurred, they were evaluated.

3.6.2 | In the morning of second admission (second period)

After 1 week of washout the following steps were performed:

Considering the registrations of step 3 and 9 of first admission to maintain conditions, from step 5 to step 12 were carried out chronologically as stated for first admission. Specifically, in step 6, the comparator was applied in second admission whereas an assigned intervention was implemented in first admission. Accordingly, step 7 was not performed.

Steps 1, 2, 3, 4, 9 and 10 were only examined during the first admission because the upper arm was established and the application in the opposite arm was considered as a deviation from the protocol. In the second period steps 3 and 9 were registered to prove the protocol adherence. With regard to step 10, a week was not sufficient to produce any changes in skin conditions.

According to these registrations, the arm where PVC was performed in first admission was imperative in second admission. The anatomical zone of the forearm was registered as: distal forearm (optimal zone), medium forearm, proximal forearm and flexure.

3.7 | Data analysis

Baseline characteristics were age, sex, ethnicity, BMI, mean blood pressure, tympanic temperature, heart rate and skin phototype. Clinical variables were effectiveness as main variable and anatomical zone, venous perception, pain, haemolysis and adverse events as secondary variables.

All analyses were performed using IBM SPSS® v23.0 (IBM Corp., Armonk, New York, USA). The results were expressed as incidence and odds ratio (OR), 95% CI and *p*-value. The abnormal distribution was confirmed with the Kolmogorov–Smirnov normality test ($p < 0.05$). For non-parametric data such as dichotomous paired groups, the Mc Nemar test was used to evaluate the effectiveness of the interventions. The Wilcoxon test was used to compare secondary variables between intervention and comparator. A stratification was performed according to antebrachial anatomical zone of intervention/comparator. A binary logistic regression model was carried out for effectiveness as the dichotomous non-parametric variable using dummies to compare the three interventions. OR was determined according to the following formula, apart from standard calculation in binary logistic regression: OR = effectiveness or adverse event cases in one group/effectiveness or adverse event cases in another group. To calculate the correlation between two quantitative non-parametric variables, a Spearman (rho) test was used. A two-tailed p-value lower than 0.05 was considered statistically significant.

3.8 | Validity and reliability of instruments

Twenty-gage diameter IV catheter, EDTA K2 tube and Vacutainer™ are commonly used along with certified systems (Lima-Oliveira et al., 2013, 2015). VIA scale is a validated classification of the peripheral venous system in terms of vascular access. It consists of five grades, where grade one represents optimal perception and grade five the worst perception. Vascular diameter measurements by ultrasound showed a decrease directly related to the observers' assessment in VIA scale between five grades (global $p < 0.005$). The following quadratic weighted kappa was obtained by three inter-evaluators: 0.77, 0.82 and 0.77, $p < 0.001$ respectively (good, very good and good level of agreement, respectively, by Landis and Koch criteria) (De la Torre-Montero et al., 2014).

VAS is a validated scale for acute perceived pain, defined as a recent onset. It consists of a 10-cm horizontal line, marked from 0–10 in each end where 0 represents 'no pain' and 10 'worst imaginable pain'. Statistically significant differences to detect pain intensity changes ($p < 0.001$) were obtained and inter-correlation for other rating scales ($r = 0.79–0.96$) (Ferreira-Valente et al., 2011). High intraclass-correlation of 0.97 between 1 min-difference measurements was described and of the dissimilar ratings 95% were up to 9 mm (Bijur et al., 2001).

Fitzpatrick's scale is a validated classification used to estimate the minimal erythema for initial dose in phototherapy (Sachdeva, 2009). It consists of six skin phototypes, type I refers to ivory white, VI to black and the intermediate types graded in colour, which is only

associated with skin sensitivity to reflected sunburn. Phototypes detected by participants' responses to burning and dermatologists correlated significantly (rho = 0.764, $p < 0.001$) (Eilers et al., 2013), participants with trained researchers and inter-researchers significantly agreed (kappa = 0.76 and kappa = 0.731, $p < 0.001$ respectively). Phototypes and melanin measurement were correlated significantly (rho = 0.89 $p < 0.001$) and substantially agreed (kappa = 0.65 $p < 0.001$) (Isa et al., 2016).

The haemolysis score and the red blood cell percentage were correlated ($r^2 > 0.998$) when the lipaemia factor correction was applied for different degrees of lipaemia (Appierto et al., 2014). Baseline correction factor was correlated better (rho = 0.753) than non-baseline correction (rho = 0.457) (Simón-López & Luquero-Bueno, 2017).

3.9 | Ethical considerations

The protocol and the informed consent fulfilled the Spanish law on clinical research and both were approved by the Ethics Committee for Clinical Research of Hospital Universitario de La Princesa (Madrid) The study was carried out according to the Declaration of Helsinki (World Medical Association, 2013).

4 | RESULTS

4.1 | Baseline demographic and clinical characteristics

Fifty-nine participants were included in the present study. All of the subjects completed the clinical trial (Figure 2). As shown in Table 1, before interventions, the groups were comparable in baseline characteristics. Accordingly, VIA grade V was more frequent in group 1 and 2 while IV was more frequent in group 3. Besides, indoor temperature and humidity (24.43°C [0.93] and 33.25% [5.28], respectively) were stable in the three intervention groups.

4.2 | Effectiveness

As shown in Table 2, PVC was significantly more effective with the application of any of the three interventions than comparator ($p < 0.001$). Accordingly, the most significantly effective intervention in PVC was intervention 2 ($p = 0.001$), followed by interventions 1 ($p = 0.002$) and 3 ($p = 0.004$).

The success rate for the three interventions was 0.983, 95% CI (0.949–1.017) and for comparator was 0.475, 95% CI (0.343–0.606). For those participants who failed at first attempt in the comparator group, the effectiveness arose to 0.968, 95% CI (0.902–1.034) using one of three interventions. There was only one subject that reported failure in intervention 3 and with comparator. No statistically significant differences were found in effectiveness between interventions 1 or 2 and 3 (Table 2).

When PVC was performed in the distal antebrachial zone, effectiveness was significantly higher for any of three intervention than for comparator ($p < 0.001$, Table 2); specifically, the intervention 3 ($p = 0.016$, Table 2). By contrast, there was no significant difference in effectiveness when interventions 1 or 2 were applied related to the comparator in the distal antebrachial zone ($p = 0.125$). Moreover, no significant differences were found in the flexure for any intervention or comparator (Table 2).

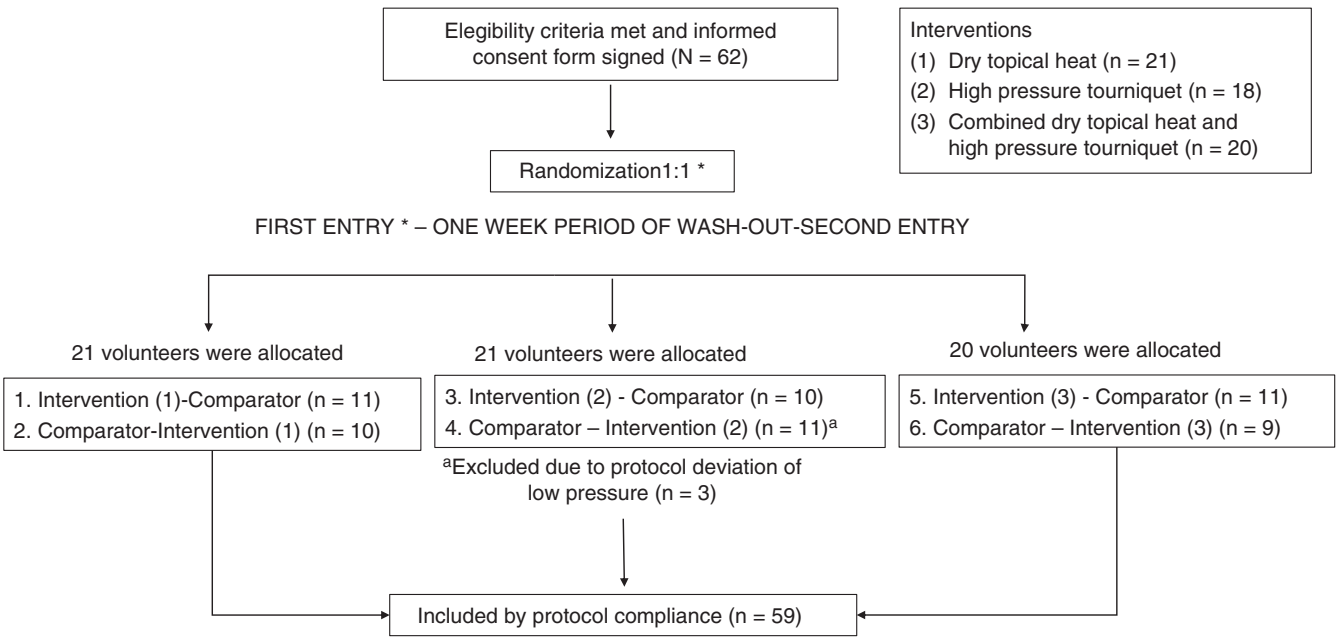

FIGURE 2 Participant flowchart. *: Randomization of intervention and sequence was performed only at first entry

TABLE 1 Baseline demographic and clinical characteristics of participants by intervention group

Variable	Dry topical heat (*N* = 21)	High pressure tourniquet (*N* = 18)	Combined (*N* = 20)
No. females (%)	17 (80.95)	11 (61.11)	11 (55.00)
Sequence IFC (%)	11 (52.40)	10 (55.60)	11 (55.00)
Age (years)	26.19 (3.91)	27.94 (6.57)	26.05 (7.16)
White (%)	12 (57.10)	12 (66.70)	13 (65.00)
Black (%)	1 (4.80)	0 (0.00)	0 (0.00)
Latin (%)	8 (38.10)	6 (33.3)	7 (35.00)
Body mass index (kg/m^2)	23.13 (2.94)	24.28 (2.72)	22.75 (2.45)
II grade VIA[a] (%)	4 (19.00)	4 (22.20)	7 (35.00)
III grade VIA[a] (%)	6 (28.60)	4 (22.20)	10 (50.00)
IV grade VIA[a] (%)	10 (47.60)	10 (55.60)	3 (15.00)
V grade VIA[a] (%)	1 (4.80)	0 (0.00)	0 (0.00)
Mean blood pressure (mmHg)	77.21 (7.13)	77.04 (6.99)	79.48 (8.52)
Heart rate (pulse/minute)	63.62 (11.36)	63.22 (12.68)	65.20 (9.66)
Tympanic temperature (°C)	36.00 (0.34)	35.78 (0.48)	35.93 (0.45)
Fitzpatrick skin type I (%)[b]	1 (4.80)	1 (5.60)	0 (0.00)
Fitzpatrick skin type II (%)[c]	2 (9.50)	2 (11.10)	1 (5.00)
Fitzpatrick skin type III (%)[d]	9 (42.90)	6 (33.30)	8 (40.00)
Fitzpatrick skin type IV (%)[e]	7 (33.30)	8 (44.40)	8 (40.00)
Fitzpatrick skin type V (%)[f]	1 (4.80)	1 (5.60)	3 (15.00)
Fitzpatrick skin type VI (%)[g]	1 (4.80)	0 (0.00)	0 (0.00)
After intervention application[h]			
Distal forearm (%)	14 (66.70)	10 (55.60)	14 (70.00)
Medial forearm (%)	3 (14.30)	5 (27.80)	5 (25.00)
Proximal forearm (%)	0 (0.00)	1 (5.60)	0 (0.00)
Flexure (%)	4 (19.00)	2 (11.10)	1 (5.00)
VIA change[i] in successful cases	21 (100.00)	17 (94.40)	19 (95.00)
Successful cases	21 (100.00)	18 (100.00)	19 (95.00)
After comparator application[h]			
Distal forearm (%)	9 (42.90)	7 (38.90)	13 (65.00)
Medial forearm (%)	5 (23.80)	3 (16.70)	2 (10.00)
Proximal forearm (%)	0 (0.00)	2 (11.10)	3 (15.00)
Flexure (%)	7 (33.30)	6 (33.30)	2 (10.00)
Successful cases	11 (52.40)	7 (38.90)	10 (50.00)

Note: Data are shown as mean (standard deviation) or number (percentage).

[a]IFC: Intervention in First Confinement. VIA: Venous International Assessment pre-intervention.

Fitzpatrick skin type:

[b]White Ivory,

[c]Easy white burnt,

[d]Moderately burned white,

[e]Toasted luster,

[f]Moderately toasted and

[g]black.

[h]The same forearm (right or left) was used for intervention and comparator.

[i]At least one grade was considered clinically significant.

4.3 | Secondary clinical outcomes

No association was found between baseline demographic characteristics and effectiveness for the three interventions or comparator ($p > 0.05$). Significant differences were found in VIA grades between each of the three interventions and the comparator (Table 3). Only one participant showed no change in VIA scale (intervention 2, $p = 3 \times 10^{-4}$). As shown in Table 3, all three interventions relieved

TABLE 2 Outcome measures of univariate and multivariate analysis of effectiveness

Groups	First attempt success one group/ first attempt success another group	OR[b] (95% CI)	*p* value[a]
Univariate analysis			
Interventions (*N* = 59)/Comparator (*N* = 59)	58 (98.30)/28 (47.45)	**2.07 (1.94–2.19)**	**1.8×10^{-9}**
High pressure tourniquet (*N* = 18)/Comparator (*N* = 18)	18 (100.00)/7 (38.88)	**2.57 (2.34–2.79)**	**0.001**
Dry topical heat (*N* = 21)/Comparator (*N* = 21)	21 (100.00)/11 (52.38)	**1.92 (1.70–2.13)**	**0.002**
Combined (*N* = 20)/comparator (*N* = 20)	19 (95.00)/10 (50.00)	**1.90 (1.87–1.92)**	**0.004**
Adjusted by anatomical antebrachial zone[c,d]			
Interventions (*N* = 7)/Comparator (*N* = 7)[c]	6 (85.71)/3 (42.85)	2.00 (0.88–4.45)	0.250
Interventions (*N* = 29)/Comparator (*N* = 29)[d]	28 (96.55)/13 (44.82)	**2.15 (2.08–2.21)**	**15×10^{-5}**
Adjusted by distal antebrachial zone[d]			
Combined (*N* = 12)/Comparator (*N* = 12)	12 (100.00)/5 (41.66)	**2.40 (2.12–2.68)**	**0.016**[a]
Multivariate analysis			
Dry topical heat (*N* = 21)/Combined (*N* = 20)[f]	21 (100.00)/19 (95.00)	85.00[e] (0.00-)	0.998[g]
High pressure tourniquet (*N* = 18)/Combined (*N* = 20)[f]	18 (100.00)/19 (95.00)	85.00[e] (0.00-)	0.998[g]

[a]Mc Nemar test unless other test is stated. Values are shown as number (percentage).

[b]OR: Odds ratio adjusted formula, unless otherwise stated. CI: Confidence interval.

[c]Flexure.

[d]Distal antebrchial.

[e]OR standard formula.

[f]Dummies are created as: one categorical variable/ reference categorical variable.

[g]Binary logistic regression by dummies. The rest of antebrachial zones are not shown due to insufficient variability data to calculate. No upper limit interval is shown due to insufficient variability information to calculate. Statistical significance was set at $p < 0.05$. Skewness was assumed by Kolmogorov–Smirnov ($p < 0.05$).

Statistically significant values were marked in bold.

TABLE 3 Clinical outcomes

Variables	Dry topical heat (*N* = 21)	*p* value	High pressure tourniquet (*N* = 18)	*p* value	Combined (*N* = 20)	*p* value
Univariate analysis						
VIA positive/negative changes[a]	21 (11)/0 (0)	[b]3×10^{-5}	17 (8.50)/0 (0)	[b]2×10^{-4}	20 (10.50)/(0)	[b]4×10^{-5}
VAS negatives/positive changes[c]	8 (7.88)/7 (8.14)	0.863[b,d]	11 (7.45)/3 (9.50)	0.205[b,d]	11 (8.59)/6 (9.75)	0.391[b,d]
Haemolysis absorbance (nm) negatives/positive changes[c]	9 (9.67)/11 (11.18)	0.502[b]	7 (11.14)/11 (8.45)	0.744[b]	5 (10.90)/15 (10.37)	0.059[b]

[a]Comparator in pre-intervention less postintervention.

[b]Wilcoxon test. Data are presented as number of positive or negative changes (averaged range)/number of negative or positive changes (averaged range), the rest of number not presented are ties.

[c]Postintervention less comparator. Abnormal distribution was assumed by Kolmogorov–Smirnov ($p < 0.05$). Statistical significant was set $p < 0.05$ unless other significance is stated.

[d]At least one grade negative change was considered clinically significant for pain, therefore no *p*-value significance was set.

pain and interventions 2 and 3 were significantly less painful than the comparator based on clinical significance. Moreover, none of the three interventions increased haemolysis. As Figure 3 shows, no significant correlation was found between pain and haemolysis in any of the three interventions.

During the study, 23.72% suffered one adverse event. From those, 92.85% was local erythema, which resulted in incidental severity, probable causality and inspection as a relief method (WHO, 2002) and 7.15% was transient paresthesia, which showed mild severity, definite causality and immediate removal of pressure as relieve method (WHO, 2002). Moreover, no significant differences in local erythema were found between interventions 1 and 3 ($p = 0.819$). Local erythema was present in phototypes II, IV and V. However, there was no significant association between erythema and skin phototypes (Eilers et al., 2013; Sachdeva, 2009) when heat was applied ($p = 0.063$).

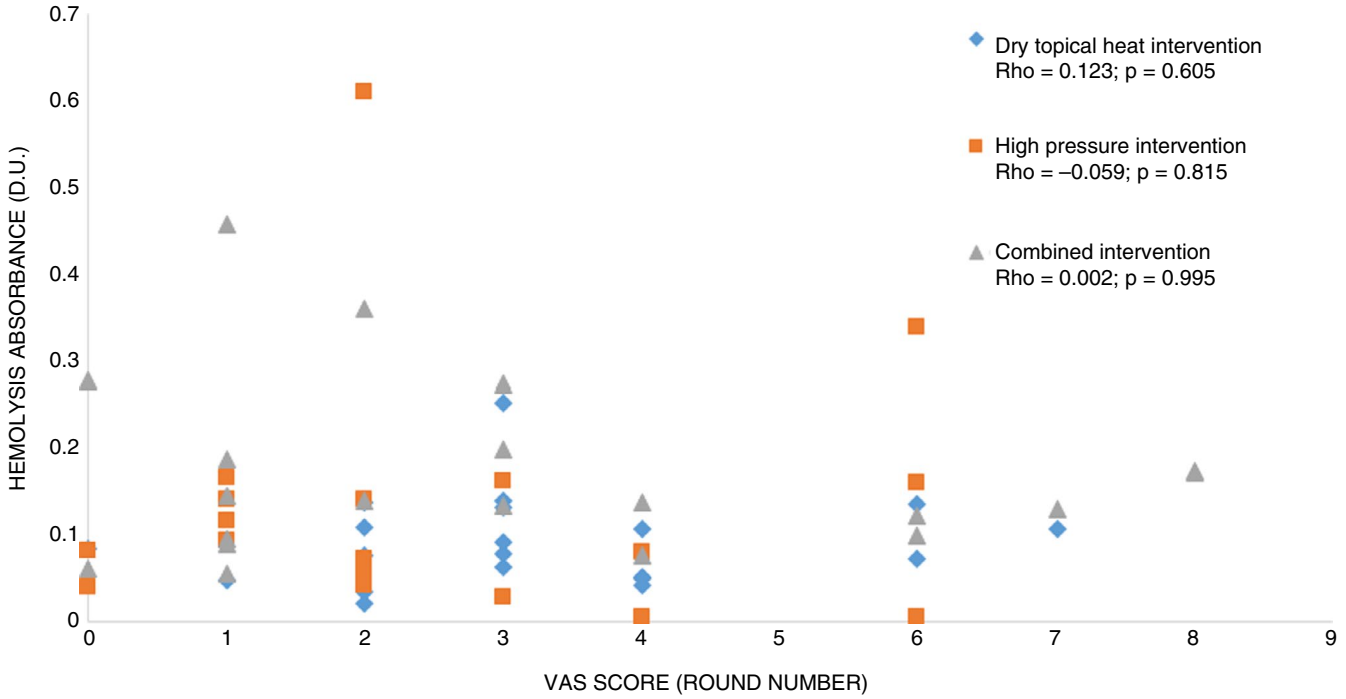

FIGURE 3 Relationship of pain and haemolysis according00 to intervention groups. Nomenclature of d.u.: dimensionless units. $p < 0.05$ was considered statistically significant; Rho was used. Abnormal distribution was assumed by Kolmogorov–Smirnov ($p < 0.05$). Absorbance dimensionless units were corrected for lipaemia and baseline correction factors whose wavelengths of absorbance data were at 385, 414 and 750 nanometres. The following equation was applied for lipaemia correction factor: (A414-A385) +0.16xA385 [Colour figure can be viewed at wileyonlinelibrary.com]

5 | DISCUSSION

PVC is one of the most frequently performed invasive techniques (Milutinović et al., 2015; Ravik et al., 2017). However, repeated failures and difficulties have been registered (Ravik et al., 2017). As a consequence, subjects suffer pain and the repeated failures increase their anxiety (Fink et al., 2009). Thus, we consider it relevant to develop interventions to achieve PVC at first attempt to alleviate the pain and anxiety associated with this technique (Fink et al., 2009; Shabandokht-Zarmi et al., 2017), without any unfavourable effects for the overall PVC procedure and safety. For instance, dry topical heat and high pressure are non-complex interventions and our results are comparable to those found in the literature according to venodilation and PVC at first attempt (Fink et al., 2009; Yamagami et al., 2017).

In our study, interventions 1, 2 and 3 were more effective than comparator. We applied dry heat for 7 min what resulted in 1.92 times more effective than comparator. Fink et al. showed that dry heat application for 7 min was 2.7 times more effective than moist heat for successful PVC (Fink et al., 2009). Moreover, our result with dry heat intervention is in line with Yamagami et al (Yamagami et al., 2017) where the combination of local warming for 15 min increased blood flow while the tourniquet application increased local vein stagnation. This overall caused higher venodilation than conventional pressure alone.

Interestingly, our results demonstrate that applying high pressure is 2.57 times more effective than the comparator. Thus, we showed that controlling the applied pressure to 100 mmHg by sphygmomanometer improved PVC at first attempt. In addition, this is the first study comparing fixed high pressure with the non-controlled pressure applied in clinical practice. As the clinical practice guide CLSI GP41-A6 establishes the use of an elastic compressor for tourniquet (Lima-Oliveira et al., 2012), it is not possible to control the applied pressure due to pressure fluctuations that depends on nurse strength and the elasticity of the compressor. Based on our data, we suggest that the half-life of the elastic compressor for tourniquet pressure should be considered previously to application. Specifically, our combined intervention was 1.90 times more effective than the comparator. However, high pressure with heat and PVC were not measured by studies in the literature; thus no comparison is possible with our result in combination with intervention effectiveness.

Furthermore, we found that the combined intervention in the distal forearm was more effective for PVC than the comparator. Nonetheless, we did not find noticeable benefit in PVC with any of the three interventions when they were carried out in the flexure. Therefore, the three interventions gave benefits in PVC, but even further benefits when the combined intervention was applied on the distal forearm. The vein diameters were different in distinct anatomical areas in previous studies that confirms our results (De la Torre-Montero et al., 2014; Yamagami et al., 2017).

PVC implies vein perception (De la Torre-Montero et al., 2014) which is a subjective component, thus it is not only affected by vein diameter (Yamagami et al., 2017). Accordingly, PVC must be

addressed considering the expertise of nurses and their criteria on palpation and visualization for vein perception. Therefore, in this study, nurses with a wide expertise participated in the three intervention groups, in contrast with other studies where only oncology or anaesthetist nurses participated (Fink et al., 2009; Lenhardt et al., 2002). Vein perception changes at least one grade in VIA scale. Only 1.7% of the sample got a venipuncture at first attempt without visualizing any change of grade through VIA and none resulted in a worse vein perception. Thus, our interventions can be used by any nurse and may even be helpful for nurses with lower experience in PVC. Regarding the improvement of vein perception, the ultrasound-guided technique requires additional training and supplementary devices that are not needed in our interventions. Moreover, it is non-feasible in departments with limited sources. Despite the uncertain accessibility to the seed bags involved in this study, aneroid sphygmomanometers are available for nurses in hospitals, health care centres and ambulances.

Regarding pain, our results showed that intervention 2 was more effective to relieve pain than 3, both clinically significant related to the comparator. Despite intervention 1 was not clinically significant, it was less painful than the comparator. A previous study showed that dry heat was associated with significantly higher self-reported comfort of the participants, however, pain was not assessed (Fink et al., 2009), then we add information about pain in dry heat interventions (Fink et al., 2009; Yamagami et al., 2017). We have not found studies comparing the effect in pain of either high pressure or non-controlled pressure related to the common technique.

According to previous studies, the insertion time was reduced by 20 s ($p = 0.013$) in patients when applying heat (Lenhardt et al., 2002), the warming therapy entailed 15 min prior to cannulate (Yamagami et al., 2017) and dry heat was applied during 7 min if the cannulation was tested before (Fink et al., 2009). Therefore, warming could reduce insertion time and, overall, the longest interventions were 1 and 3 for including 7 min waiting period. On the contrary, 2 was the shortest intervention as no additional procedure was needed prior to PVC.

The age of our participants in each intervention was similar to other study population (Yamagami et al., 2017). By contrast, in another study with patients the average age was different (Fink et al., 2009). However, we consider that our results can be extrapolated to healthy young adults, adults and patients who have healthy vein status perception.

In addition, intervention 2 could be safely implemented for older people. Notwithstanding, interventions 1 and 3 could be more perilous due to causing burns induced by junction flattening between the epidermis and dermis when ageing (Nursing Times, n.d.). Accordingly, these people often suffer from arterial hypertension (Pinto, 2007). Intervention 2 reduces the risk of transient paresthesia being another confirmation of increasing the benefit-risk balance. Thus, we consider that pressure intervention could be an alternative to heat intervention when performing PVC due to its lower risks in patients (Fink et al., 2009).

Limited studies analysed pain in venipuncture in healthy adults, specifically using local anaesthesia by cream or intradermal injection (Péculo, 2010; Rüsch et al., 2017). Hence, we should use effective, pain relieving and non-pharmacological techniques for PVC among both patients and older people. Additionally, people with healthy veins could be also exposed to PVC due to possible allergic conditions (National Clinical Guideline Centre (UK), 2014).

Dry heat and/or pressure do not modify the quality of blood samples. Also, pain did not have an impact on haemolysis. These results show that our interventions allow an adequate blood sample collection for subsequent blood tests and equivalent suitability as current clinical procedure for blood extraction (Makhumula-Nkhoma et al., 2019).

In our study, no severe adverse events were found. To date, adverse events when high pressure application is involved have not been described, thus we added information about its safety and applicability on any skin type (Sachdeva, 2009).

For the implications on nursing practice, we recommend using the intervention 3 for difficult—grade IV or V in VIA scale—vein perception, especially when distal antebrachial PVC is required. Additionally, it is not tim—and money-consuming as only a microwave is needed for 7 min. We endorse the use of intervention 1 for nurses with lower experience in PVC. We advocate using intervention 2 for emergency, due to the short time required prior to PVC. Additionally, intervention 2 should be used in case of lacking resources, such as sphygmomanometers in the ambulance. We propose that intervention 2 should be favoured due to being the most effective, less painful, feasible and swiftest method. It can be safely used as it does not alter haemolysis and does not cause serious adverse events.

5.1 | Limitations and strengths of the trial

It was not possible to determine which of the three interventions was more effective in all anatomical zones. Our sample size ($N = 59$) was low; however, the intervention groups were comparable (interventions 1: $N = 21$, 2: $N = 18$ and 3: $N = 20$). Because effectiveness required two completed actions, we consider that this could overestimate failure rate.

Nevertheless, this study is the first randomized controlled study to compare the effect of high-pressure tourniquet with or without dry heat and the applied pressure in clinical practice. So far, this study is the first that evaluates the vein perception by a validated scale (De la Torre-Montero et al., 2014), highlighting the nursing assessment. Moreover, our study confirms that the applied heat or pressure and the perceived pain during PVC do not have an influence on the haemolysis of blood samples. Therefore, further research is necessary to determine minimal amount of time for dry topical heat application and minimal amount of pressure required both to achieve effectiveness.

6 | CONCLUSIONS

A PVC applying dry topical heat, high pressure or a combination of both are more effective to achieve PVC at first attempt compared

with the usual clinical practice in healthy adults. Furthermore, the application of 100 mmHg pressure via sphygmomanometer is considered an alternative to the application of heat for PVC at first attempt. In conclusion, it is more effective, less painful, increases vein perception, the swiftest aid and can be safely used due the low prevalence of paresthesia and no influence on the haemolysis of the blood samples.

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CONFLICT OF INTEREST

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Maria C Ovejero-Benito has a potential conflict of interest with Janssen-Cilag as lecturer.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict apart from those disclosed.

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AUTHOR CONTRIBUTIONS

All authors have agreed on the final version and meet at least one of the following criteria (recommended by the ICMJE):

1. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
2. Drafting the article or revising it critically for important intellectual content.

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