REVIEW

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Peripheral intravenous catheter securement: An integrative review of contemporary literature around medical adhesive tapes and supplementary securement products

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Abstract

Aim: To synthesise evidence related to medical adhesive tapes and supplementary securement products for peripheral intravenous catheters in adults, to prevent complications and device failure.

Design: Integrative review informed by Whittemore and Knafl and reported in accordance with the PRISMA 2020 statement.

Data sources.

The Cochrane Central Register of Controlled Trials, US National Library of Medicine National Institutes of Health, EMBASE/MEDLINE and Cumulative Index to Nursing and Allied Health were searched from 2000-21 September 2020.

Review Methods.

Studies enrolling hospitalised participants >16 years with peripheral intravenous catheters secured by medical adhesive tapes, or supplementary products (bandage, splint and sutureless securement device), were eligible. Quality appraisal was performed using Critical Appraisal Skills Program checklists.

Results: Nineteen studies met criteria, including 43,683 peripheral intravenous catheters. Quality appraisal identified high or unclear risk of bias in 58% of studies. Nonsterile tape was the most common intervention tested (14 studies), alone or in multiproduct combinations. Nonsterile tape directly over insertion sites was associated with increased PIVC failure and complications. Sutureless securement devices potentially reduce failure and complications. Multiproduct combinations were very common. Practice recommendations regarding other tapes and secondary securement products are challenging, due to conflicting, or lack of, evidence.

Conclusion: Tapes and secondary securement product evidence are limited, and over half of the studies are of low methodological quality. This review found nonsterile tape was associated with increased failure and complications; multiproduct dressing and securement bundles were prevalent; and significant evidence gaps exist particularly

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regarding bandages and splints. The results provide nurses with evidence of medical adhesive tapes and supplementary product effectiveness for peripheral intravenous catheter securement, and future research directions to reduce unacceptably high failure and complication rates. Larger rigorously conducted randomised controlled trials are needed to add to current evidence.

KEYWORDS

Intravenous, literature review, nurses, nursing, occlusive dressings, peripheral venous catheterization, securement device, surgical tape

1 | INTRODUCTION

Despite being one of the most common invasive medical devices, peripheral intravenous catheters (PIVCs) fail at unacceptably high rates, with around 50% failing before treatment is complete (Gunther et al., 2016; Marsh et al., 2018; Rickard et al., 2018). PIVC failure results in costs to both patients and healthcare institutions (Helm et al., 2015); for patients, pain and anxiety from reinsertions; and for healthcare institutions, financial burden of human and material resources to replace failed PIVCs, in addition to costs of treating PIVC complications (Helm et al., 2015). Ensuring optimal dressing and securement is an important nursing intervention, which aims to prevent PIVC failure and complications, thereby promoting patient safety. Many dressing and securement products are available to nurses; however, guidance on the most effective way to achieve clean, dry and intact PIVC dressings is lacking (Marsh et al., 2015; Rickard et al., 2018).

Adequate PIVC securement prolongs catheter longevity and prevents complications and is achieved by 1) fixing the catheter to skin to ensure correct position within the vein (Royal College of Nursing, 2016); 2) by reducing PIVC micromotion or pistoning within the vein (Marsh et al., 2018; Rickard et al., 2018); and 3) by providing a physical barrier between the insertion wound and environment (Ullman et al., 2015). Poor securement leads to early device failure due to complications including phlebitis, thrombosis, occlusion, infiltration, dislodgement and infection (Bolton, 2010; Rickard et al., 2018; Simin et al., 2019). Medical adhesive tapes provide additional securement for PIVCs as an adjunct to primary dressings or are used as the primary dressing itself (Beringer, 2008; Ter et al., 2015). They are made from paper, silk, cloth, silicone, foam or plastic; contain an adhesive, commonly acrylate-based, bonded to the tape material to ensure adhesion to the skin; and be sterile or nonsterile. Supplementary securement products can also be used to stabilise PIVCs and include: sutureless securement devices (SSDs, a stabilisation device with an adhesive footplate used in conjunction with a primary dressing to provide additional PIVC securement); elasticized, noncompression bandages (tubular, netting or rolled); and splints or armboards (to provide stability and reduce catheter movement in areas of flexion) (Malyon et al., 2014).

The use of tapes and other securement products is widespread in nursing practice with recent studies indicating 40–83% of PIVC dressings require reinforcement with medical adhesive tapes,

What does this paper contribute to the wider global clinical community?

- Despite being one of the most common invasive medical devices, peripheral intravenous catheters (PIVCs) fail at unacceptably high rates. Medical adhesive tapes and supplementary securement products are widely used in nursing practice; however, this use is not guided by strong evidence.
- 2. Themes emerging from this integrative review were: nonsterile tape directly over the PIVC insertion site is associated with poor PIVC outcomes; multiproduct PIVC dressing and securement interventions are very common; and evidence gaps exist in the literature, especially for bandages and splints/armboards.
- 3. The lack of high-quality evidence in this area hampers clinical practice recommendations, and efforts to add to the evidence base via rigorous randomised controlled trials should be a priority for researchers and funders.

bandages or other forms of securement to assist with keeping the PIVC in situ (Corley, Ullman, Mihala, et al., 2019; Marsh et al., 2018; Rickard et al., 2018). Recent observational studies indicate any additional PIVC securement with medical tapes, bandages or splints is strongly associated with fewer complications (Corley, Ullman, Mihala, et al., 2019; Larsen et al., 2020; Marsh et al., 2018). Highlighting the importance of effective securement in preventing PIVC failure and complications, a recent multicentre prospective observational study (n = 573 patients, 815 PIVCs, 1964 PIVC days) found significantly more adverse events were experienced by patients with poorly secured PIVCs (adjusted hazard ratio (HR) 4.93, 95% confidence interval (CI) 3.13 \pm 7.77, p<.001) (Miliani et al., 2017). However, the way in which supplementary securement products are used by clinicians is not grounded in strong evidence (Corley, Ullman, Marsh, et al., 2019), and ad hoc use of these products drives up PIVC maintenance costs, without clear benefit (New et al., 2014). Global clinical practice guidelines for intravascular device management (Gorski et al., 2021; Royal College of Nursing, 2016) recognise that effective PIVC stabilisation is important in

preventing complications and premature removal; however, only low-grade evidence guides the limited recommendations made regarding medical adhesive tapes and supplementary securement products to achieve this aim. Therefore, despite widespread use, it appears that little effort has gone into rigorously testing medical adhesive tapes and supplementary securement products as interventions to reduce PIVC failure.

Synthesis of evidence regarding these products is important as it will inform nursing practice and policy, so that secondary securements are used in a consistent and effective way. A combined dressing and securement intervention (or securement "bundle") could be an innovative and low-cost way of addressing currently high PIVC failure rates (Rickard et al., 2018). Indeed, the recent Infusion Therapy Standards of Practice (Gorski et al., 2021) advocate for adequately powered randomised controlled trials (RCTs) to test the concept of securement bundles for PIVCs. Effective PIVC dressing and securement is a key patient safety strategy to reduce preventable patient harm, experienced through unacceptable rates of PIVC failure.

2 | AIMS

The aim of this integrative review was to explore:

- what evidence exists regarding medical adhesive tapes and supplementary products, alone or in combination with other dressing and securement interventions, to secure PIVCs?
- 2. what are PIVC failure and complication rates when tapes and supplementary products are used for securement?
- 3. where do gaps lie in the existing evidence base?

3 | METHODS

The review approach was based on Whittemore and Knafl's five-stage review framework (Whittemore & Knafl, 2005): problem identification, literature search, data evaluation and analysis, and presentation of findings. This framework allows data from mixed methodologies to be combined, allowing for a thorough synthesis of the evidence base and also reducing bias and lack of rigour in the review (Hopia et al., 2016; Whittemore & Knafl, 2005). The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (201876) and is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement (http://prisma-statement.org/) (Supplementary File 1).

3.1 | Search strategy

In conjunction with a health librarian, a search strategy was developed using search terms based on MeSH headings, e.g. intravenous; catheterisation, peripheral; occlusive dressings; securement device;

tape; skin tape; bandage; stocking; splint; and armboard. Databases were systematically searched in September 2020: Cochrane Central Register of Controlled Trials (CENTRAL, US National Library of Medicine National Institutes of Health (PubMed), EMBASE and Cumulative Index to Nursing and Allied Health (CINAHL) Complete. Studies since the year 2000 were included to ensure a reflection of relevant contemporary practice. The search was limited to English language records. Reference lists of eligible studies and clinical trial registries (clinicaltrials.gov; controlled-trials.com; anzctr.org.au; and who.int/ictrp) were searched to identify additional studies.

3.2 | Types of studies

Studies eligible for inclusion were RCTs, randomised crossover trials, cohort studies (prospective and retrospective), observational studies (prospective and retrospective) or audits. Studies including healthy volunteers or animals were excluded.

3.3 | Types of participants

Participants >16 years with a PIVC admitted to a hospital setting.

3.4 | Types of interventions

Any study assessing the following interventions for the covering or stabilisation of PIVCs, with or without a primary dressing, was eligible for inclusion:

- Medical adhesive tape (sterile or nonsterile)
- Secondary securement method (tubular/rolled bandage, net stocking, splint/armboard and sutureless securement device)
- A combination of the above interventions

3.5 | Outcomes of interest

Studies assessing the effects of interventions on PIVC survival and complications were included in the review. These include device failure, individual device-related complications (phlebitis, infiltration, occlusion, dislodgement and infection), skin complications, dressing durability, patient and staff satisfaction, and cost.

3.6 | Quality appraisal

To assess the methodological quality of included studies, the Clinical Appraisal Skills Program (CASP) checklist relevant to individual study type (https://casp-uk.net/casp-tools-checklists/) was completed independently by two authors, with a third author resolving any discrepancies in quality assessment through discussion and consensus.

3.7 | Data extraction

Data were extracted from included studies using a purpose-designed data extraction form independently by two authors with a third author resolving any discrepancies through discussion and consensus. Fields extracted included author, setting, study aim, sample population, sample size, study methodology (including randomisation techniques and allocation concealment), intervention/s, outcome measures and study findings.

3.8 | Synthesis

According to Whittemore and Knafl's (Whittemore & Knafl, 2005) integrative review process, data from included studies were systematically categorised, compared and summarised by intervention, and presented as an integrated summary of the themes emerging from the evidence.

4 | RESULTS

4.1 | Search outcome

Database searches identified 532 titles, and five additional records were identified by handsearching reference lists. After 181 duplicates were removed, 356 titles and abstracts were reviewed for inclusion. Three hundred and twenty-seven articles were excluded. Full-text articles were retrieved for 29 records, and 10 articles were excluded due to the study intervention not including tape or any supplementary securement product, or not measuring an outcome of interest (Figure 1).

4.2 | Quality appraisal

Tables 1 and 2 display the quality assessment of each study. Risk of bias was deemed unclear or high in over half of the included studies, mainly due to unclear sampling technique, insufficient control of potential confounders and poor reporting of methods, cohort and results. External validity of the results was therefore questionable. Six included RCTs (75%) met criteria for valid study design and were deemed methodologically sound, while 4 of the included cohort studies (36%) had a focused study question, correct sampling technique and controlled bias and confounders. Reporting of results was not reliable with less than half of included studies (9 studies, 47%) comprehensively and precisely reporting findings. The generalizability of the results was poor or unclear, mainly due to poor descriptions of the included cohort in over half of the included studies (10 studies, 53%). Despite risks of bias identified, all studies were deemed suitable for inclusion in data synthesis, as they provide data on tapes and supplementary securement product use in clinical practice.

4.3 | Characteristics of included studies

Of the 19 studies meeting review criteria, eight were RCTs and 11 cohort studies. Data from 43,683 PIVCs were included, and study sample sizes ranged from 50 to 18,493 patients. Most studies (84%) were conducted in Australia or North America with one each from Spain, Brazil and United Kingdom. The evidence base around medical adhesive tapes and supplementary products for PIVC securement would be classified as containing mainly lower grades of evidence (National Health and Medical Research Council, 2009). Only two of the included studies were Level II evidence (large, well-designed

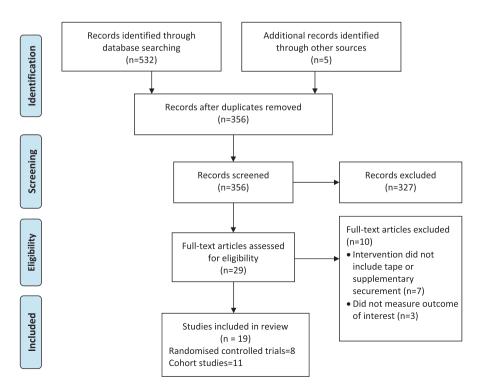


FIGURE 1 PRISMA flow diagram of study selection

TABLE 1 Quality appraisal of included randomised controlled trials using the Critical Appraisal Skills Program (https://casp-uk.net/casp-tools-checklists/)

Study ID	Is the basic study design valid for an RCT?	Was the study methodologically sound?	Were results reported comprehensively and precisely?	Will the results help locally?	Overall appraisal
Bahl 2021	Unclear	Unclear	Unclear	Unclear	Unclear ROB. Insufficient information from clinical trial registry to perform full ROB assessment
Bauzone-Gazda 2010	Yes	Yes	°Z	Unclear	Unclear ROB. Incomplete outcome reporting. Stopped early due to "enrolment issues" so not powered.
Bugden 2016	Yes	Unclear	Yes	Yes	Low ROB. Method of randomization unclear. PIVC failure censored at 48 hours
Chico-Padron 2011	Unclear	Yes	°Z	Yes	Unclear ROB. Results not comprehensively and precisely presented.
Corley 2019	Yes	Yes	Yes	Yes	Low ROB. Pilot study only so limited by small sample size
Marsh 2015	Yes	Yes	Yes	Yes	Low ROB. Pilot study only so limited by small sample size
Marsh 2018	Yes	Yes	Yes	Yes	Low ROB. Pilot only but intervention significantly decreased PIVC failure
Rickard 2018	Yes	Yes	Yes	Yes	Low ROB.

Note: RCT, randomized controlled trial; ROB, risk of bias; PIVC, peripheral intravenous catheter.

TABLE 2 Quality appraisal of included cohort studies using the Critical Appraisal Skills Program (https://casp-uk.net/casp-tools-checklists/)

Study ID	Was the study question focused; the cohort recruited correctly; and was bias/confounders controlled?	Are the results precise and reliable?	Are the results generalisable?	Overall appraisal
Bolton, 2010	Unclear	O Z	Unclear	Unclear ROB. No control of confounders, unclear outcome reporting.
Crowell 2017	°Z	OZ	Unclear	High ROB. No control of confounders.
Delp 2011	Yes	Yes	Yes	Low ROB.
Larsen 2020	Yes	Yes	Yes	Low ROB.
Marsh 2018A	Yes	Yes	Yes	Low ROB.
McNeill 2009	Unclear	°Z	Unclear	Unclear ROB. No control of confounders, unclear outcome reporting.
Penney-Timmons, 2005	No	No	Unclear	High ROB. No control of confounders, poor outcome reporting.
Royer, 2003	Unclear	°Z	Unclear	Unclear ROB. No control of confounders, unclear outcome reporting.
Schears, 2006	Unclear	Yes	Unclear	Unclear ROB. No control of confounders
Smith, 2006	Unclear	Unclear	Unclear	Unclear ROB. No control of confounders, unclear outcome reporting.
Salles 2007	Yes	°Z	Unclear	Unclear ROB. Minimal control of confounders, unclear outcome reporting.

Note: ROB, risk of bias.

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	Summary of findings	TA with dressing and nonsterile tape was not more effective in reducing failure than dressing and nonsterile tape alone.	PIVCs secured with sutureless securement device and nonsterile tape had higher rates of failure and complications, except for phlebitis, but were less costly compared with PIVC secured with a bordered dressing and nonsterile tape.	Tissue adhesive plus dressing and nonsterile tape reduced failure and dislodgement compared with dressing and nonsterile tape alone.	PIVCs with sterile tape and gauze had comparable failure and complication rates compared with transparent dressing.
	Outcome measures and results	PIVC failure: Comparable rates between groups (transparent dressing + tape, 38% v tissue adhesive 32%).	PIVC failure: Nonsignificantly higher in sutureless securement device group (38% v 28%, p = .138). Phlebitis: Significantly higher in bordered transparent dressing group (55% v < 13%, HR 8.04, 95%CI 1.02–63.59, p = .04). Infiltration/ extravasation: Comparable rates between groups (14% v 18%, HR .78, 95%CI .44–1.38, p = .390). Occlusion: Higher rates in sutureless securement device group (7% v 1%). Dislodgement: Significantly higher rates in sutureless securement device group (9% v 1%, HR .16, 95%CI .04–.72, p = .017). Skin complications: Adhesive residue on skin after dressing removal was minimal (<10%) and not significantly different. Dressing durability: No significant difference. Staff satisfaction: Higher in bordered transparent dressing group (56% v 36%). Cost: Sutureless securement device group USD\$5.65, bordered transparent dressing \$7.56.	PIVC failure: 10% lower (95% CI –18%-–2%; p = .02) in tissue adhesive group (17%) than control (27%). Phlebitis: Less in tissue adhesive group (3% vs 5%) but not statistically significant. Occlusion: Less in tissue adhesive group (8% vs 11%) but not statistically significant. Dislodgement: 7% lower in tissue adhesive group (95% CI –13% – 0%; p = .04). PIVC-related infection: No PIVC-related infections.	PIVC failure: No significant difference (sterile tape 33% v transparent dressing 38%, p = .74). Phlebitis: 24% in sterile tape group, 28% in transparent dressing group. Dislodgement: 5% in sterile tape group, 3% in transparent dressing group. Cost: \$24.82 per patient for transparent dressing, \$38.85 for sterile tape (materials/labour costs for dressing change).
	Interventions	 Transparent dressing + nonsterile tape Transparent dressing + nonsterile tape + tissue adhesive 	Bordered transparent dressing + nonsterile tape over extension tubing Sutureless securement device (Statlock) + nonbordered transparent dressing + nonsterile tape over extension tubing	 Tissue adhesive + bordered transparent dressing + nonsterile tape over dressing Bordered transparent dressing + nonsterile tape over dressing (control) 	Sterile tape at insertion site + gauze Transparent dressing
summary of findings	Participants [*]	trials n = 345 adults in emergency department	n = 302 adults in medical-surgical wards	n = 369 adults in emergency department	n = 50 hospitalised patients#
IABLE 3 SUMMARY	Author	Randomised controlled trials Bahl, 2021 USA n =	Bauzone Gadza et al, 2010 USA	Bugden et al, 2016 Australia	Chico-Padron et al., 2011 Spain

Summary of findings	PIVC failure and complications were not different between study arms, except for phlebitis, where sterile tape and a bordered transparent dressing had higher rates than a bordered dressing alone.	PIVCs secured with sutureless securement device and nonbordered dressing had less failure, phlebitis and occlusion than a nonbordered dressing alone. Tissue adhesive had less failure and complications overall but adverse skin events were seen in 1 in 5 patients in this group.	Only on multivariable analysis was integrated securement dressing use associated with reduced failure. All other complication rates similar between groups. Longer dwell time for integrated securement dressing.
Outcome measures and results	PIVC failure: 38% for Bundle 2, 25% for Bundle 1 and 24% for control. Incidence rate ratio/1000 PIVC days, compared to control, was 1.1 (95%CI .4-2.7) for bundle 1 and 2.1 (95%CI .9-5.1) for bundle 2. Phlebitis: 21% in control, 14% in bundle 1 and 15% in bundle 2. Significantly higher in Bundle 1 compared to control (p = .04). Infiltration/extravasation: 15% in control, 17% in bundle 1 and 18% in bundle 2. Occlusion: Nil in control group or bundle 1, but 6% in bundle 2. Dislodgement: 15% in control, 6% in bundle 1 and 12% in bundle 2. PIVC-related infection: No infections in any group. Skin complication: Incidence was 6 in 34 patients (18%) for control, 5 in 36 (14%) for bundle 2 and 4 in 33 (12%) in bundle 2. Patient/staff satisfaction: High in all study groups.	PIVC failure: Sutureless securement device group 22%, tissue adhesive group 14%, bordered dressing group 25% and control group 38%. Adjusted hazard ratio: sutureless securement device group (.61, 95% CI .20–1.91), bordered transparent dressing group (.52, 95% CI .15–1.78) and tissue adhesive group (.50, 95%CI .13–1.98). Phlebitis: Highest in control group 19% compared with sutureless securement device 6%, tissue adhesive 5%, bordered dressing 5%. Occlusion: Both sutureless securement device and tissue adhesive were 10%, bordered dressing 15% and control 29%. Dislodgement: Sutureless securement device, tissue adhesive and bordered dressing groups each 5%, control 0%. PIVC-related infection: No infection in any group. Skin complications: For tissue adhesive group, 4 events in 3 patients (14%). No skin complications in other groups. Patient/staff satisfaction: Overall high. On application, sutureless securement device group had lowest staff satisfaction (median score 7). On removal, scores ranged from 7.5–10, with sutureless securement device group at 8.	PIVC failure: No significant difference in proportion (p = .137); however, on multivariable analysis, integrated securement dressing significantly associated with less failure (HR .50, 95%CI .2989). Phlebitis: No significant difference (6% v 5%). Occlusion and infiltration: No significant difference (11% v 20%). Dislodgement: Same rates in each group (4% each). PIVC-related infection: No PIVC-related infections. Skin complications: Same rates of adverse skin events (4% each). Dressing durability: Longer in integrated securement dressing group (median 53.2 hrs v 47.8 hrs). Patient satisfaction: High in each group, both median 9 of possible 10.
Interventions	 Bordered transparent dressing + nonsterile tape over dressing ± extension tubing (control) Control + sterile tape over hub (bundle 1) Control + sterile tape over hub + tubular bandage (bundle 2) 	Sutureless securement device (Statlock) + nonbordered transparent dressing Bordered transparent dressing Tissue adhesive + nonbordered transparent dressing Nonbordered transparent dressing (control)	Bordered transparent dressing + nonsterile tape Integrated securement dressing
Participants [*]	n = 104 adults in general medical- surgical wards	n = 85 adults in general medical-surgical wards	n = 300 adults in general medical- surgical wards
Author	Corley et al, 2019 Australia	Marsh, Webster, Flynn, et al., 2015 Australia	Marsh et al., 2018 Australia

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	Summary of findings	No significant difference in study groups for failure or complications, except less occlusion in tissue adhesive group.	Sutureless securement device with dressing and nonsterile tape performed better than dressing alone.	No difference in failure rates for PIVCs secured with nonsterile tape over the compared with integrated or bordered dressings.	Sutureless securement device group more expensive but no difference in PIVC failure of rates.	(Continues)
	Outcome measures and results	PIVC failure: Equivalent rates in each arm: tissue adhesive 38%, bordered dressing 40%, sutureless securement device 41%, nonbordered dressing 43%. Phlebitis: Equivalent rates in each arm: tissue adhesive 25%, bordered dressing 22%, sutureless securement device 26%, nonbordered dressing 27%. Occlusion: Lower rates in tissue adhesive group (16%, HR. 89, 95%Cl 0:80–0.99, p = .027) bordered dressing 19%, sutureless securement device 23%, nonbordered dressing 22%. Dislodgement: Equivalent rates in each arm: tissue adhesive 7%, bordered dressing 9%, sutureless securement device 9%, nonbordered dressing 10%. PIVC-related infection: No difference between groups. Skin complications: Highest rate in the tissue adhesive group (4%). Dressing durability: No difference in dwell time of first dressing. Patient and staff satisfaction: High scores for each group Costs: Significantly higher per patient in experimental groups compared with control (all p<0.001; includes reinsertion costs and dressing replacement/reinforcement).	PIVC failure: Lower in sutureless securement device group (13% v 69%). Infiltration/ extravasation: Higher in bordered transparent dressing group (36% v 0%). Dislodgement: Not reported in sutureless securement device group, 8% in bordered transparent group "fell out" or removed by patient. Staff satisfaction: 94% "positive" feedback from staff. Cost: £175,140 per annum saving (includes reduction in failure rate and reinsertion costs [labour and materials]) in sutureless securement device group.	PIVC failure: 52% for bordered transparent dressing, 46% for integrated securement dressing and 52% for tape + transparent dressing $(p=.06)$.	PIVC failure: Comparable between groups (sutureless securement device 67% v Nexiva 66%) Cost: Higher in sutureless securement device group (USD\$6.37 v \$8.94 - material costs associated with insertion only)	
	Interventions	Tissue adhesive + nonbordered transparent dressing + nonsterile tape over extension tubing Bordered transparent dressing + nonsterile tape over extension tubing Sutureless securement device (Statlock or Griplock) + nonbordered transparent dressing Nonbordered transparent dressing + nonsterile tape over extension tubing (control)	 Nonbordered transparent dressing + sutureless securement device (Statlock) + nonsterile tape over extension tubing Bordered transparent dressing 	 Nonsterile tape over PIVC wings + transparent dressing Integrated securement dressing Bordered transparent dressing 	 Sutureless securement device (Statlock) Nexiva Closed Catheter System + bordered dressing 	
,	Participants [*]	n = 1697 hospitalised adults	studies n = 1000 PIVCs (audit), n = 43 PIVCs [#] (clinical evaluation)	n = 939 hospitalised patients**	n = 18,493 hospitalised patients**	
	Author	Rickard et al., 2018 Australia	Observational cohort studies Bolton, 2010 n = 1 United Kingdom r (Crowell et al., 2017 USA	Delp et al, 2011 USA	

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Author	Participants [*]	Interventions	Outcome measures and results	Summary of findings
Larsen et al., 2020 Australia	n = 200 adults with 396 PIVCs in cancer wards	 Nonsterile tape over dressing or extension tubing Tubular bandage 	Phlebitis: No association between nonsterile tape or bandage use Occlusion: Significant association with nonsterile tape (HR .46, 95%CI .2584, p = .012; univariable Cox regression) Dislodgement: Nonsterile tape associated with reduced rate (HR .06, 95%CI .0148, p = .008; multivariable Cox regression)	The use of nonsterile tape as an adjunct to the primary dressing was strongly associated with reduced dislodgement.
Marsh et al, 2018A Australia	n = 1000 adults with 1578 PIVCs in general medical- surgical wards	 Nonsterile tape over dressing or extension tubing Tubular bandage 	Phlebitis: Lower rates associated with nonsterile tape (HR .63; 95%CI .4882). Occlusion: Lower in PIVCs with nonsterile tape and tubular bandages (HR .46, 95%CI .3363; HR .49, 95% CI .3570). Dislodgement: Lower rates associated with nonsterile tape (HR .44, 95%CI .3163).	The use of nonsterile tape and tubular bandages were associated with less phlebitis, occlusion and dislodgement.
McNeill et al., 2009 USA	n = 80 PIVCs in hospitalised patients#	 "Standard care" Bordered transparent dressing + sutureless securement device (Hubguard) 	PIVC failure: Hubguard at insertion site + bordered transparent dressing (28%) "standard care" (62%). Infiltration/extravasation, occlusion and dislodgement: Hubguard + bordered transparent dressing reduced each (8% v 26%, 8% v 30% and 2% v 50%, respectively).	Less PIVC failure and complications with a sutureless securement device at the hub covered with a bordered dressing, compared with "standard care".
Penney-Timmons, 2005 USA	n = 1345 PIVCs in hospitalised patients#	 "Standard care" Bordered dressing + sutureless securement device (Hubguard) + nonsterile tape over dressing 	Phlebitis: Compared with standard care, lower rates in Hubguard group (<1% v 3%). Cost: Significantly less Hubguard group (annual cost of \$367,200 v \$555,840 (includes materials for insertion and securement only).	Less phlebitis and cost in PIVCs secured with a sutureless securement device at the hub compared with "standard care".
Royer, 2003 USA	n = 122 adult patients on medical-surgical ward with 146 PIVCs	Sterile tape at hub + nonbordered transparent dressing (control) Sutureless securement device + nonbordered transparent dressing	PIVC failure: Lower rate in sutureless securement device group (15% v 41%) Phlebitis: Comparable rates (Tape 1% v sutureless securement device 0%) Occlusion: Lower rate in sutureless securement device group (7% v 28%) Dislodgement: Lower rate in sutureless securement device group (12% v 16%)	Lower failure and complications rates in PIVCs secured with a sutureless securement device and nonbordered dressing.
Salles et al., 2007 Brazil	n = 120 adult patients in surgical ward	 Nonsterile tape at hub (control) Transparent dressing 	Dislodgement: Lower rate in transparent dressing group (3% v 15%) Skin complications: Less in nonsterile tape group (13% v 26%) Cost: Lower cost in nonsterile tape group (US\$.56 v \$6.29)	Fewer skin complications in the nonsterile tape group; however, dislodgement and cost was higher.
Schears, 2006 USA	n = 10,164 patients# with 15,004 PIVCs	TapeSutureless securement device	PIVC failure, phlebitis and cost: Lower in sutureless securement device group (17% v71%, p = .0001; 1% v 4%, p = .001; and USD\$432,000 v \$450,000, respectively)	Sutureless securement device reduced failure, phlebitis and cost compared with tape.

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	*			
Author	Participants	Interventions	Outcome measures and results	Summary of findings
Smith, 2006 USA	n = 659 adult hospitalised patients	hospitalised patients • Nonsterile tape hospitalised patients • Sutureless securement device (Statlock) + nonbordered transparent dressing • Sutureless securement device (Hubguard)	PIVC failure: Statlock had the lowest rate (48%, Hubguard 91%, nonsterile tape 92%)	Statlock had less PIVC failure compared with Hubguard and nonsterile tape.

BOLD denotes interest in the integrative results of adults/children separately; BOLD denotes interventions of interest in the integrative review; PIVC, peripheral intravenous some studies did not report number of participants and only present number of PIVCs; catheter; HR, hazard ratio; CI, confidence interval RCTs); 6 RCTs had either small sample sizes or were underpowered pilot trials; and the remaining 11 studies were observational in nature and included such study designs as prospective cohort, prepost observational, audit and clinical evaluation.

There was high heterogeneity of study interventions tested in the included studies. Across included studies, 45 different interventions were tested (Table 3). Two-thirds were multiproduct (bundled) combinations, with 38 individual components including tapes (61%), SSDs (29%) or bandages (8%). The most commonly tested intervention was nonsterile tape (directly over the insertion site; or over the primary dressing to provide extra securement to the dressing or to secure extension tubing), followed by SSDs and sterile tape. Detailed descriptions of study interventions and how they were applied were lacking in some included studies. No studies exploring the use of splints or armboards were found in this review of evidence.

All review outcomes of interest were reported in one or more of included studies; however, outcome definitions were inconsistent between studies, potentially hampering interpretation of results. PIVC failure was the most reported outcome with three quarters (14 studies) reporting this, followed by dislodgement and phlebitis (13 studies each, 68%), occlusion (10 studies, 53%) and infiltration/extravasation (9 studies, 47%). Table 3 describes population, interventions and findings of included studies.

4.4 | Evidence summary by theme

4.4.1 | Nonsterile tape directly over the PIVC insertion site is associated with poor PIVC outcomes

The PIVC insertion site is a wound, which can allow for entry of microorganisms locally and into the bloodstream; therefore, it is important that any product used at the insertion site is sterile (Gorski et al., 2021; Marsh, Webster, Flynn, et al., 2015). In four of the included studies (Salles et al., 2007; Schears, 2006; Smith, 2006), nonsterile tape was placed directly over the insertion wound and functioned as the only means of PIVC dressing and securement. This practice of placing nonsterile tape directly over the insertion wound is not uncommon, with one in five catheters globally secured in this way, more commonly in low-income regions and also in paediatrics patients (Corley, Ullman, Mihala, et al., 2019). Varying application techniques were used including a chevron pattern around the PIVC hub and the use of multiple tape strips to achieve the aim of PIVC securement. Regardless of how the nonsterile tape was applied, higher rates of failure and complications were found in PIVCs secured by this method when compared with all comparator interventions (Salles et al., 2007; Schears, 2006; Smith, 2006). For example, one study (Schears, 2006) assessed PIVC failure and phlebitis with nonsterile tape at the insertion site compared with an SSD and found higher rates of each in the nonsterile tape group (71% v 17%, p = .0001; and 4% v 1%, p = .001, respectively).

While the lower purchase price of nonsterile tape may make this a low-cost securement option, this must be weighed against the cost of any complications arising from this practice. In a small cohort study (Salles et al., 2007), material costs per patient for nonsterile tape compared with a transparent dressing were calculated, and the former was found to be less expensive (US\$.56 v \$6.29). However, Schears (Schears, 2006) factored in additional costs arising from PIVC failure as well as material costs and found SSDs more cost effective than nonsterile tape alone.

4.4.2 | Multiproduct PIVC dressing and securement interventions are common

Great diversity existed in the multiproduct dressing and securement interventions used in the included studies (Figure 2). Extra reinforcement to existing PIVC dressings is commonplace in nursing practice (Corley, Ullman, Mihala, et al., 2019; Marsh et al., 2018; Rickard et al., 2018); however, the way in which these products are used is not informed by strong evidence and appears to be based on personal preference or work area culture. The common practice by nurses of reinforcing PIVC dressings with supplementary securement products is yet to be explained in a qualitative exploration of why this practice occurs, but this understanding is important when developing evidence-based strategies to optimally dress and secure PIVCs. The "bundling" of interventions is a concept, which has been identified in the literature as requiring further investigation (Corley, Ullman, Mihala, et al., 2019; Gorski et al., 2021; Rickard et al., 2018) and should include evidence-based interventions rather than *ad hoc* usage of tapes and supplementary products.

Nonsterile tape

Nonsterile tape was the most prominently featured component of multiproduct study interventions and was almost exclusively placed over the primary dressing to provide extra dressing securement or to secure extension tubing. Two observational cohort studies found that reinforcement of the primary dressing with nonsterile tape was significantly associated with fewer complications, specifically less occlusion (HR .46, 95%CI .33–.63; and HR .46, 95%CI .25–.84, p = .012)(Crowell et al., 2017), dislodgement (HR .44, 95%CI .31–.63; and HR .06, 95%CI .01–.48, p = .008) (Larsen et al., 2020; Marsh et al., 2018) and phlebitis (HR .63; 95%CI .48–.82) (Marsh et al., 2018).

One study (Crowell et al., 2017) bundled the use of nonsterile tape to secure PIVC wings under the primary sterile transparent dressing and compared this securement method with a bordered transparent dressing and an integrated securement dressing and found no statistically significant difference in failure between groups (52%, 52% and 46%, respectively, p = .06).

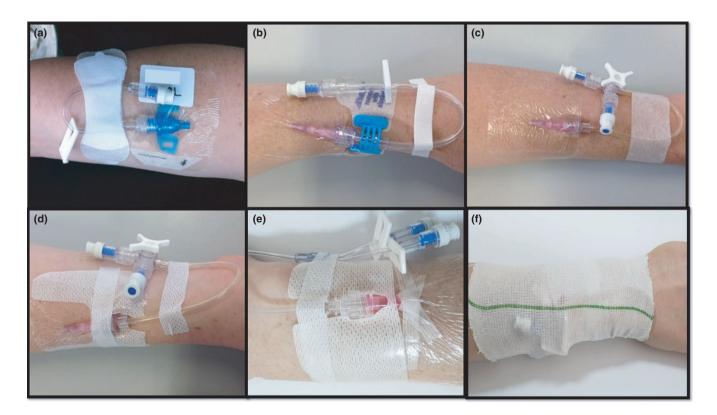


FIGURE 2 Examples of medical adhesive tape and supplementary securement product use in PIVC maintenance. (2a), sutureless securement device (GripLok); (2b), sutureless securement device (Statlock) and nonsterile tape; (2c,d), nonsterile tape securing the primary dressing and/or the extension tubing; (2e), sterile tape at insertion site and nonsterile tape over primary dressing; (2f), tubular bandage over PIVC

Sterile tape

Sterile tape may be placed under the primary dressing to add stability and securement directly at the PIVC hub thereby reducing micromotion of the catheter and fixing the catheter more firmly to the skin. The effect of sterile tape placed at the PIVC hub (in either a chevron pattern or laid straight over), covered with either a gauze or bordered transparent dressing, on PIVC failure is unclear with only 3 small studies assessing this intervention (Chico-Padron et al., 2011; Corley, 2019; Royer, 2003). Two small underpowered RCTs (Chico-Padron et al., 2011; Corley, 2019) found no difference in failure rates when comparing sterile tape and dressing with transparent dressing alone; however, when tested in a small observational study against SSD and transparent dressing (Royer, 2003), failure rates were higher in the sterile tape group (41% v 15%) in addition to higher rates of occlusion and dislodgement (28% vs 7%, and 16% vs 12%, respectively). A small RCT (Chico-Padron et al., 2011) found no difference in PIVC complication rates when using sterile tape and gauze compared with a transparent dressing; however, another small RCT showed significantly less phlebitis with sterile tape at the PIVC hub compared with bordered transparent dressing alone (14% vs 21%, p = .04) (Corley, 2019). Sterile tape shows promise to add extra security directly at the PIVC hub but requires further testing to determine its effectiveness in preventing PIVC failure and complications.

To maintain patient safety, extra tape at the insertion site requires extra surveillance to detect any increase in adverse skin events or infection. Tape under the dressing could act as a fomite and increase infectious complications (Harris et al., 2012; Redelmeier & Livesley, 1999). Furthermore, the exposure of skin to additional tape and adhesive could result in an increase in medical adhesive-related skin injuries (MARSI) through mechanical and chemical processes, resulting in skin tears, bruising, blisters, contact dermatitis, erythema and pain (Broadhurst et al., 2017; Thayer, 2012; Ullman et al., 2019). A small pilot RCT (Corley, 2019) measured both these potential complications, finding no increase in adverse skin events with the use of sterile tape at the PIVC hub and no PIVC-related infection in any group.

Sutureless securement devices

SSDs were developed to provide additional central stability at the insertion site without the use of sutures (Marsh, Webster, Flynn, et al., 2015). Their pupose is to reduce micromotion of the catheter within the vein, thereby preventing such complications as phlebitis, infiltration/extravasation and occlusion, and to fix the PIVC firmly to the skin to prevent dislodgement (Frey & Schears, 2006; Ullman et al., 2015). Types tested in included studies were: StatLock IV stabilization device (BD, Franklin Lakes, New Jersey, USA), Hubguard (Centurion Medical Products, Williamston, Michigan, USA), and GripLok (TIDI, Neenah, Wisconsin, USA). SSDs were a common component in the bundled dressing and securement interventions, were generally used in conjunction with a sterile transparent dressing, as recommended in clinical practice guidelines (Gorski et al., 2021) and often had nonsterile tape applied over the dressing for added security.

An SSD combined with transparent dressing was associated with fewer PIVC complications (compared with transparent dressing alone with or without nonsterile tape over the primary dressing), specifically phlebitis (Bausone-Gazda et al., 2010; N. Marsh, Webster, Flynn, et al., 2015; Penney-Timmons, 2005; Royer, 2003), infiltration/extravasation (Bolton, 2010; McNeill et al., 2009) and occlusion (N. Marsh, Webster, Flynn, et al., 2015; McNeill et al., 2009; Royer, 2003). However, the effect of SSDs on dislodgement in the included studies was unclear with a reduction in one study (McNeill et al., 2009), no difference between groups in another study (C. Rickard et al., 2018) and an increase in dislodgement reported in 2 studies (Bausone-Gazda et al., 2010; N. Marsh, Webster, Flynn, et al., 2015). Less PIVC failure was reported when SSDs were combined with a transparent dressing (N. Marsh, Webster, Flynn, et al., 2015; Royer, 2003; Smith, 2006); however, the largest RCT conducted to date (Rickard et al., 2018) did not support the findings of these smaller studies

Synthesis of data on the effect of SSDs on PIVC failure and complications is hampered by differing study design and sample size, along with inconsistencies in outcome definition. From the available evidence, SSDs appear to either reduce or have similar rates of PIVC failure compared with transparent dressings alone. Furthermore, SSDs may be useful at reducing some complications (phlebitis, infiltration/extravasation and occlusion); however, their effect on dislodgement is unclear.

Material costs of SSDs were reported to be higher compared to that of comparator interventions (Bausone-Gazda et al., 2010; Delp & Hadaway, 2011). However, when factoring in the savings associated with fewer reinsertions in the SSD group due to decreased failure, in addition to fewer costs associated with treating complications, SSD use was found to be more cost effective (Bolton, 2010; C. Rickard et al., 2018; Schears, 2006).

Bandages

Covering the PIVC with a bandage is common in clinical nursing practice (Corley, Ullman, Mihala, et al., 2019; New et al., 2014) to protect the insertion site and PIVC from accidental and intentional removal; however, only 3 of the included studies described a multiproduct intervention, which included a bandage component (Corley, 2019; Larsen et al., 2020; Marsh et al., 2018). Clinical practice guidelines recommend tubular bandages over rolled bandages (Gorski et al., 2021), so the insertion site can be easily and frequently inspected, and each of the 3 included studies included a tubular bandage. One study with a small sample size (n = 104) described the effects of a tubular bandage on PIVC failure and complications (Corley, 2019). This study found no difference in failure rates in the study arm consisting of a tubular bandage over a PIVC secured with sterile tape and covered with a bordered transparent dressing, compared with the other two study arms, which did not include a bandage. A large observational cohort study (Marsh et al., 2018) found the addition of a tubular bandage to the primary dressing was associated with significantly less dislodgement; however, in a small underpowered RCT, a tubular bandage did not have any effect on PIVC complication rates (Corley, 2019).

4.4.3 | Evidence gaps exist in the literature

This review revealed a lack of high-grade evidence in the literature regarding medical adhesive tapes and supplementary securement products for PIVCs. There was limited evidence on the use of bandages (tubular, net or rolled) to cover the PIVC site, so firm clinical practice recommendations cannot be made. Splints and armboards can be used to immobilise PIVCs, placed at a point of flexion such as the wrist or antecubital fossa (Gorski et al., 2021), and are used commonly in paediatric settings (Dalal et al., 2009; Malyon et al., 2014); however, no studies testing splints or armboards were identified in the literature search. The lack of consistency in outcome definitions made synthesis of the available evidence difficult, and standardized definitions should be used.

5 | DISCUSSION

When making PIVC securement decisions, nurses are tasked with an array of products and practices without high-quality evidence to inform practice. In this integrative review, we demonstrated that the literature consists of mainly low-level evidence at high or unclear risk of bias, due to small sample size, and poor reporting of patient selection, outcome measures and results. Themes emerging from the literature were: nonsterile tape directly over the PIVC insertion site is associated with poor PIVC outcomes; multiproduct PIVC dressing and securement interventions are very common; and evidence gaps exist in the literature, especially for bandages and splints/armboards. The lack of high-quality evidence in this area hampers clinical practice recommendations and efforts to add to the evidence base should be a priority.

The most common intervention tested in the included studies was nonsterile tape, which was used in different ways, including directly over the insertion wound, under the sterile primary dressing to secure the catheter wings, over the primary dressing to add extra securement or over the extension tubing attached to the PIVC. Nonsterile tape directly at the insertion wound is not recommended (Corley, Ullman, Mihala, et al., 2019; Gorski et al., 2021) and is associated with increased failure and complications. A secondary analysis of a large global PIVC data set also found this practice, which is more prevalent in lower income countries, was associated with increased PIVC site complications, specifically 4-fold higher odds of pain and tenderness, palpable vein cord and vein streak; and double the odds of swelling at the insertion site (Corley, Ullman, Mihala, et al., 2019). Nonsterile tape rolls are not designed for single patient use, are carried from patient to patient and are often visibly contaminated (Harris et al., 2012). These multiuse tapes are a vector for microorganisms (Cady & Gross, 2011; Harris et al., 2012; Redelmeier & Livesley, 1999), significantly increasing the risk of PIVC insertion site and bloodstream infection when used directly over the PIVC insertion wound. This practice contradicts modern infection prevention strategies and is not in accordance with modern evidenced-based nursing. Targeted efforts are needed to deimplement this practice

by explicitly outlining the safety risks associated with nonsterile tape use under the primary dressing in global clinical practice guide-lines and hospital policies. This will be challenging in developing countries in which access to transparent dressings is hindered by affordability and availability. Importantly, the financial cost of complications associated with this practice must be taken into account when considering moving from nonsterile tape to more advanced PIVC dressings, as significant cost savings can be made by avoiding preventable complications.

Nonsterile tape as an adjunct to the primary dressing is very prevalent in nursing practice (Alexandrou et al., 2018; Marsh et al., 2018; New et al., 2014; Russell et al., 2014). In fact, two thirds of interventions tested in the included studies used a combination of dressing and secondary securement products to secure the PIVC. This demonstrates that a single dressing or securement product may not be regarded by clinicians as providing adequate PIVC stability and that nurses may lack confidence in the dressing and securement products available (Marsh et al., 2018). The concept of a multiproduct dressing and securement intervention (a securement bundle) to address PIVC failure was first discussed by Rickard et al. (Rickard et al., 2018) after their 4-arm RCT testing 3 dressing and securement interventions against standard care failed to find a significantly better product to prevent PIVC failure than a simple nonbordered transparent dressing with nonsterile tape on the extension tubing. The authors purported that a securement bundle, consisting of a number of different dressing and securements to keep PIVCs well secured, required further investigation, and some work has been done in this area. Corley and co-authors (Corley, Ullman, Mihala, et al., 2019) interrogated a large global data set to find dressing and securement options associated with fewer PIVC complications and then developed two evidencebased securement bundles in a pilot RCT (Corley, Ullman, Marsh, et al., 2019). This study, included in this review, found it was safe and feasible to test these securement bundles in a larger definitive trial. A bundled approach to dressing and securement is also advocated by a recent clinical practice guideline as a potential solution aimed at reducing PIVC failure and complication rates (Gorski et al., 2021).

Tubular bandages are frequently used by nurses in clinical practice (Marsh, Webster, Flynn, et al., 2015; Miliani et al., 2017) to provide extra PIVC security, as they can prevent PIVC attachments "catching" on bedding or clothing. Despite being strongly associated with reduced PIVC complications (Larsen et al., 2020; Marsh et al., 2018), only one small RCT to date has assessed their effect on PIVC failure (Corley, 2019). If a bandage is used to cover the PIVC site, it must be easily removed by nursing staff to perform regular site assessments to detect, and act on, any complications at the earliest opportunity (Gorski et al., 2021).

The effect of dressing and securement interventions on PIVC-related infection is unclear, largely due to the low rate of PIVC-related bloodstream infections, which is reported as .1% (.5 infections per 1000 PIVC days) (Maki et al., 2006). However, given that 2 billion PIVCs are purchased each year (Rickard & Ray-Barruel, 2017), PIVC-related infection represents a large burden on patients and healthcare institutions. The large sample size required to test

the effect of dressing and securement interventions on PIVC-related infection makes it difficult to conduct adequately powered trials in this area. Indeed, a recent Cochrane review of devices and dressing to secure PIVCs identified a lack of evidence in this area (Marsh, Webster, Flynn, et al., 2015). Overall, there is a significant gap in the existence of high-quality evidence, and at present, there is no strong evidence that one dressing and securement intervention is more effective than any other in preventing PIVC-related infection.

Inconsistency in, or lack of, definitions of outcome measures was common in the included studies. Providing a synthesis of the evidence is made difficult if outcome definition is not standardized. In the current review for example, 13 studies reported phlebitis, with four providing no outcome definition and the remaining nine using five different outcome definitions for phlebitis. In a systematic review of phlebitis assessment measures (Ray-Barruel et al., 2014), 71 different scales were identified with no scale undergoing rigorous testing. Efforts to investigate standardized outcome definitions in PIVC research, perhaps by global professional bodies, should be a priority so that nurses can draw meaningful conclusions about intervention effectiveness and practice recommendations.

This integrative review has some limitations. First, to provide a contemporary review reflective of current clinical practice, only studies published from 2000 onwards were included. Additionally, we limited the literature search to English language records, peerreviewed records (not grey literature) and specific study designs, all of which may have contributed to selection bias. Finally, synthesis of the data and a summary of intervention effect was made difficult by the low or uncertain methodological quality, with unclear sampling technique, poor description of the study cohort, variation in the definition of outcome measures and imprecise reporting of results evident in around half of the included studies.

6 | CONCLUSION

The lack of high-quality evidence in this area hampers clinical practice recommendations, and efforts to add to the evidence base should be a priority for researchers and funders. The use of nonsterile tape directly over the PIVC insertion site should be deimplemented, as this practice is strongly associated with increased failure and complications. Rigorous efficacy trials testing the use of medical adhesive tapes and supplementary products in a bundled securement intervention are urgently required to determine whether these simple and inexpensive interventions reduce the high rates of PIVC failure.

6.1 | Relevance to Clinical Practice and Future Research

The current evidence base regarding medical adhesive tapes and supplementary securement products for PIVCs is limited and conflicting. It is therefore difficult to make firm practice recommendations

regarding the effects of these interventions on PIVC failure and complications. As a result of this inconsistent evidence, nurses make choices about dressing and securement type based on local hospital policies, tradition and personal belief. One practice on which there is consensus is the use of nonsterile tape directly over the insertion wound, with all studies assessing this intervention concluding that it increases PIVC failure and complications (Crowell et al., 2017; Salles et al., 2007; Schears, 2006; Smith, 2006).

Further large-scale rigorous RCTs are urgently needed to inform clinical practice. Planning and reporting of these future trials must follow the CONSORT statement (Schulz et al., 2010) to ensure methodological rigour and transparency. The concept of a securement bundle, where multiproduct dressing and securement interventions consisting of primary and secondary securement such as tapes and bandages, warrants testing in an adequately powered rigorous RCT to determine its effect on PIVC failure and complications.

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CONFLICT OF INTEREST

AC's employer on her behalf has received an investigator-initiated research grant from Cardinal Health (unrelated to the current project).

NM reports investigator-initiated research grants and speaker fees provided to her employer from vascular access product manufacturers (Becton Dickinson, 3 M, Eloquest Healthcare and Cardinal Health) and a consultancy payment for expert advice from Becton Dickinson for clinical feedback related to peripheral intravenous catheter placement and maintenance (unrelated to the current project).

AJU's former employer on her behalf received speaking fees and investigator-initiated research grants to support XXs research, from intravascular device product manufacturers (3 M, Becton Dickinson, Cardinal Health) (unrelated to the current project).

CMR's current or former employer received on her behalf investigator-initiated research grants from Becton Dickinson-Bard, Cardinal Health, Eloquest, and consultancy payments for educational lectures/expert advice from 3 M and Becton Dickinson-Bard (unrelated to the current project).

AUTHOR CONTRIBUTIONS

AC, NM, AJU and CMR contributed to study conception and protocol development. AC and NM performed the literature search. AC, NM, AJU and CMR performed data extraction and quality assessment, and were involved in data synthesis. AC prepared the first draft and coordinated manuscript preparation. All authors were involved in data interpretation, critical review of manuscript drafts and approval of final manuscript.

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