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Review

Comparative efficacy of various antimicrobial lock solutions for preventing catheter-related bloodstream infections: A network meta-analysis of 9099 patients from 52 randomized controlled trials

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ABSTRACT

Objectives: It remains uncertain which catheter lock solution (CLS) to prevent catheter-related bloodstream infections (CRBSI) works best and is safest for patients. This study was performed to compare the efficacy of different CLSs for the prevention of CRBSI and ranked these CLSs for practical consideration.
Methods: The PubMed, Web of Science, Embase, and MEDLINE databases, earlier relevant meta-analyses, and the reference lists of included studies were searched. The primary outcome was CRBSI; secondary outcomes were catheter-related thrombosis and exit-site infections. A network meta-analysis was performed to estimate odds ratios (ORs) with 95% confidence intervals (CIs).
Results: A total of 52 randomized controlled trials involving 9099 patients and evaluating 13 CLSs (single and combinations) were included. With regard to the quality of the evidence, the risk of bias was typically low or unclear (45 out of 52 trials, 86.5%). In the network meta-analysis, saline (OR 8.44, 95% CI 2.19–32.46), gentamicin + citrate (OR 2.92, 95% CI 1.32–6.42), ethanol (OR 5.33, 95% CI 1.22–23.32), and cloxacillin + heparin (OR 2.07, 95% CI 1.19–5.49) were associated with a greater effect on CRBSI than heparin.
Conclusions: This network meta-analysis showed that minocycline–ethylenediaminetetraacetic acid (EDTA) seemed to be the most effective for the prevention of CRBSI and exit-site infection, and cefotaxime + heparin seemed to be the most effective for catheter-related thrombosis.

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Introduction

The central venous catheter (CVC) is an essential device for intensive care, hemodialysis, and home parenteral nutrition. However, the presence of a CVC raises the risk of catheter-related complications, e.g., catheter-related bloodstream infection (CRBSI), catheter-related thrombosis (CRT), and exit-site infections (Brandt et al., 2018; Sofroniadou et al., 2017). This may increase morbidity, hospitalization, medical costs, and even mortality (O'Grady et al., 2011; Olaechea et al., 2013; Leistner et al., 2013). The economic burden of CRBSI in the USA alone has been estimated to be more than $23 billion annually (Dudeck et al., 2015). In four European countries (France, Germany, Italy, and the UK), it was shown to account for 14 400 deaths with associated annual costs of between €35.9 and €163.9 million (Tacconelli et al., 2009). In China, the average economic loss per case of CRBSI is about ¥30 713 (Yinghong et al., 2018). This trend poses a great challenge for health systems in both developed and developing countries.

Measures to reduce CRBSI include impregnated catheters (Gnass et al., 2004), catheter lock solutions (CLSs) (Rijnders et al., 2018; Barcellos et al., 2017), antimicrobial dressings (Kawamura et al., 2014), and education of health care workers (Musu et al., 2017). In recent years, some meta-analyses have demonstrated that the use of CLSs can reduce CRBSI (Zacharioudakis et al., 2014; Liu et al., 2013; Labriola et al., 2007; Zhao et al., 2018). However, previous pairwise meta-analyses have not determined which CLS is most beneficial and safest for patients with CRBSI.

Toward this goal, the network meta-analysis makes it possible to enable simultaneous comparison of multiple interventions. The network meta-analysis generates evidence through direct and indirect comparisons within a network of trials and enables inference about every possible comparison between a pair of interventions in this network, even if some comparisons have never been directly evaluated in a trial (Higgins and Welton, 2015). It appears that no network meta-analysis comparing CLSs for the treatment of CRBSI has yet been performed. Therefore, the aim of this study was to perform a systematic review and network meta-analysis to compare the effectiveness of different CLSs in terms of preventing CRBSI.

Methods

Search strategy and selection criteria

The PubMed, Web of Science, Embase, and MEDLINE databases were searched, from the date of their inception to February 6, 2019. The references in the included studies and relevant systematic reviews/meta-analyses were also searched to identify additional relevant studies. The search strategy was developed by one author (JHT), who has more than 10 years of experience as an information specialist. The full search strategy is described in the Supplementary material (Appendix pp. 39–40). Randomized controlled trials (RCTs) comparing CLSs with heparin or other different CLSs for the treatment of patients with CRBSI were included. The RCTs included patients from any inpatient hospital setting with a CVC in place. Studies that evaluated patients with catheters in the vein for ≤48 h and patients with pacing wires were excluded.

Literature selection and data extraction

Literature search records were imported into EndNoteX8 literature management software (Thomson Reuters, New York, NY, USA). Two authors (HC and RJW) independently reviewed the title and abstract of the studies and excluded those that did not meet the inclusion criteria. Then the remaining studies were identified by reviewing the full text. In the case of repeatedly published studies, only the report with the most informative and complete data was included. Any disagreements were resolved by discussion or through consultation with a third independent examiner (HJL). Excluded trials and the reasons for their exclusion were listed and examined by the third reviewer (HJL).

Two authors (FPD and JJR) independently extracted the data from each included RCT according to a pre-designed Excel sheet created in Microsoft Excel 2016 (Microsoft Corp, Redmond, WA, USA). The items extracted contained study characteristics (author, year of publication, journal, sample size, type of design, country, duration of trial), participant characteristics (age, details of intervention, day of catheter insertion, site, sex ratio), characteristics of the CLSs (catheter lock time, type of catheter, number of catheters), and outcomes (CRBSI, CRT, exit-site infection). One author (FPD) performed the data extraction and entry, and another (JHT) was in charge of examining the data.

Risk of bias in individual studies

Risk of bias was assessed by two authors (FPD and QW) according to the Cochrane Handbook version 5.1.0 (Higgins and Green, 2011). Each study was classified as having a low, unclear, or high risk of bias.

Data analysis

Full details of the statistical approaches applied are provided in the protocol (https://doi.org/10.1136/bmjopen-2019-030019).

A random-effects network meta-analysis model was used to synthesize the study effect sizes. Relative odds ratios (ORs) with 95% confidence intervals (CI) for dichotomous outcomes are presented in the results for each pairwise and network comparison. The additional uncertainty expected in future studies owing to heterogeneity was evaluated using the I^2 index within each pairwise comparison (Salanti et al., 2014). The consistency was assessed by examining the agreement between direct and indirect treatment effects in all closed loops and by assuming loop-specific heterogeneity using the loop-specific approach, which assumes a common heterogeneity parameter for all comparisons within the same loop. The node-splitting analysis method was used to evaluate the presence of inconsistency for any treatment contrast in the network, because it assesses whether the direct and indirect evidence on a specific node is in agreement (Riley et al., 2011).

Additionally, loop and design inconsistencies were accounted for and a global Wald test conducted to evaluate inconsistency in the entire network by fitting a design-by-treatment interaction model. The surface under the cumulative ranking curve (SUCRA) and the mean ranks were used to rank the treatments for each outcome. Network meta-analyses were conducted using the "mvmeta" and "network" packages in Stata SE 15.0.

This study is registered in the PROSPERO database (number CRD42019121089).

Small-study effects and sensitivity analyses

Comparison-adjusted funnel plots for each outcome were evaluated to explore the potential small-study effects in the network. Focus was placed on comparisons of all interventions that might be prone to small-study effects. Sensitivity analyses were then conducted for the outcomes in which studies with a sample size of 100 or less and those with a high risk of bias were excluded in order to assess the robustness of the findings (van Valkenhoef et al., 2016).

Assessment of clinical assumptions

The validity of network meta-analysis is based on the transitivity assumption that there is a balance in the distribution of effect modifiers across the different types of direct treatment comparisons (Chaimani and Salanti, 2012). Therefore, it is necessary to evaluate the transitivity assumption (i.e., distribution of patient and study characteristics that are potential modifiers of treatment effects and are sufficiently similar in different sets of trials before an indirect comparison). Thus, the transitivity assumption was assessed by comparing the distribution or frequency of potential effect modifiers across treatment comparisons.

Results

Characteristics and risk of bias of the included studies

A total of 52 studies (Supplementary material Appendix pp. 31–38) with 9099 patients were available for network meta-analysis (Figure 1). The characteristics of the included studies are presented in Table 1. In total, 4537 participants were randomly assigned to the treatment group and 4562 were randomly assigned to the control group. Of the sample population, 4202 (46.2%) were female. The median duration of the CRBSI was 19 months. Five studies randomly assigned participants to three or more groups, and 43 (82.7%) of the 52 studies were heparin-controlled trials.

The risk of bias assessment is presented in the Supplementary material (Appendix pp. 4–10). The studies with a high risk of bias, low risk of bias, and unclear risk of bias are marked in red, green, and yellow, respectively. Thirty-nine studies used a computer-generated random number list for random sequence generation and 28 studies used allocation concealment. Overall, 50% of the included studies were considered low risk, 36.5% unclear risk, and 13.5% high risk.

Evaluation of clinical assumptions

All patients had a diagnosis of CRBSI, and some had diagnoses of CRT and exit-site infection. The distribution with regard to age, sex, and CRBSI diagnosis was comparable between studies (Table 1). Thus, the transitivity assumption is tenable for this dataset.

Pairwise meta-analysis

The results of the pairwise meta-analysis and heterogeneity estimates are presented in the Supplementary material (Appendix pp. 25–26). The forest plot for CRBSI indicated that taurolidine–citrate, ethanol, citrate, minocycline–ethylenediaminetetraacetic acid lock solution (EDTA), gentamicin + citrate, gentamicin + heparin, vancomycin + heparin, cloxacillin + heparin, Cathasept, saline, and taurolidine were more efficacious than heparin (I^2 = 45.4%). The forest plot for CRT indicated that cefotaxime + heparin was more efficacious than heparin (OR 3.63, 95% CI 1.49–8.86, I^2 = 19.8%). The forest plot for exit-site infection indicated that citrate was more efficacious than heparin (OR 3.59, 95% CI 1.73–7.45, I^2 = 23.3%). According to I^2, it was not necessary to perform subgroup analyses or meta-regression, as I^2 was <50% for all outcomes.

Network meta-analyses

Primary outcome—CRBSI

Figure 2a shows the network plot of the treatment comparisons for CRBSI. The results of the network meta-analysis for CRBSI are presented in Table 2. A total of 43 RCTs (8073 participants) were analyzed for CRBSI. The results of the network meta-analysis indicated that saline (OR 8.44, 95% CI 2.19–32.46), gentamicin + citrate (OR 2.92, 95% CI 1.32–6.42), ethanol (OR 5.33, 95% CI 1.22–23.32), and cloxacillin + heparin (OR 2.07, 95% CI 1.19–5.49) were most effective in the prevention of CRBSI. Saline (OR 8.90, 95% CI 1.43–55.58), gentamicin + citrate (OR 7.07, 95% CI 2.57–16.91), and cloxacillin + heparin (OR 2.82, 95% CI 2.02–21.50) were associated with a greater effect on CRBSI than citrate. There was no statistically significant difference between the other CLSs for CRBSI (Table 2). According to the SUCRA, EDTA (84.4%) and cloxacillin + heparin (84.2%) ranked in the top two positions for effectiveness on CRBSI, followed by citrate (77.2%) and taurolidine–citrate (62.1%) (Supplementary material Appendix p. 21).

Secondary outcome—CRT

Figure 2b shows the network plot of the treatment comparisons for CRT. Nineteen RCTs (2651 patients) provided data for the analysis of CRT. In the comparisons between CLSs, vancomycin + heparin (OR 4.11, 95% CI 1.39–12.14), heparin (OR 6.46, 95% CI 1.31–31.70), co-trimoxazole (OR 5.52, 95% CI 2.14–12.63), citrate (OR 5.89, 95% CI 1.68–20.58), and cefotaxime + heparin (OR 9.13, 95% CI 4.81–16.00) were more effective in the prevention of CRT than Cathasept. Meanwhile, cefotaxime + heparin was more effective than vancomycin + heparin, taurolidine–citrate, saline, polygeline, heparin + sterile bag,

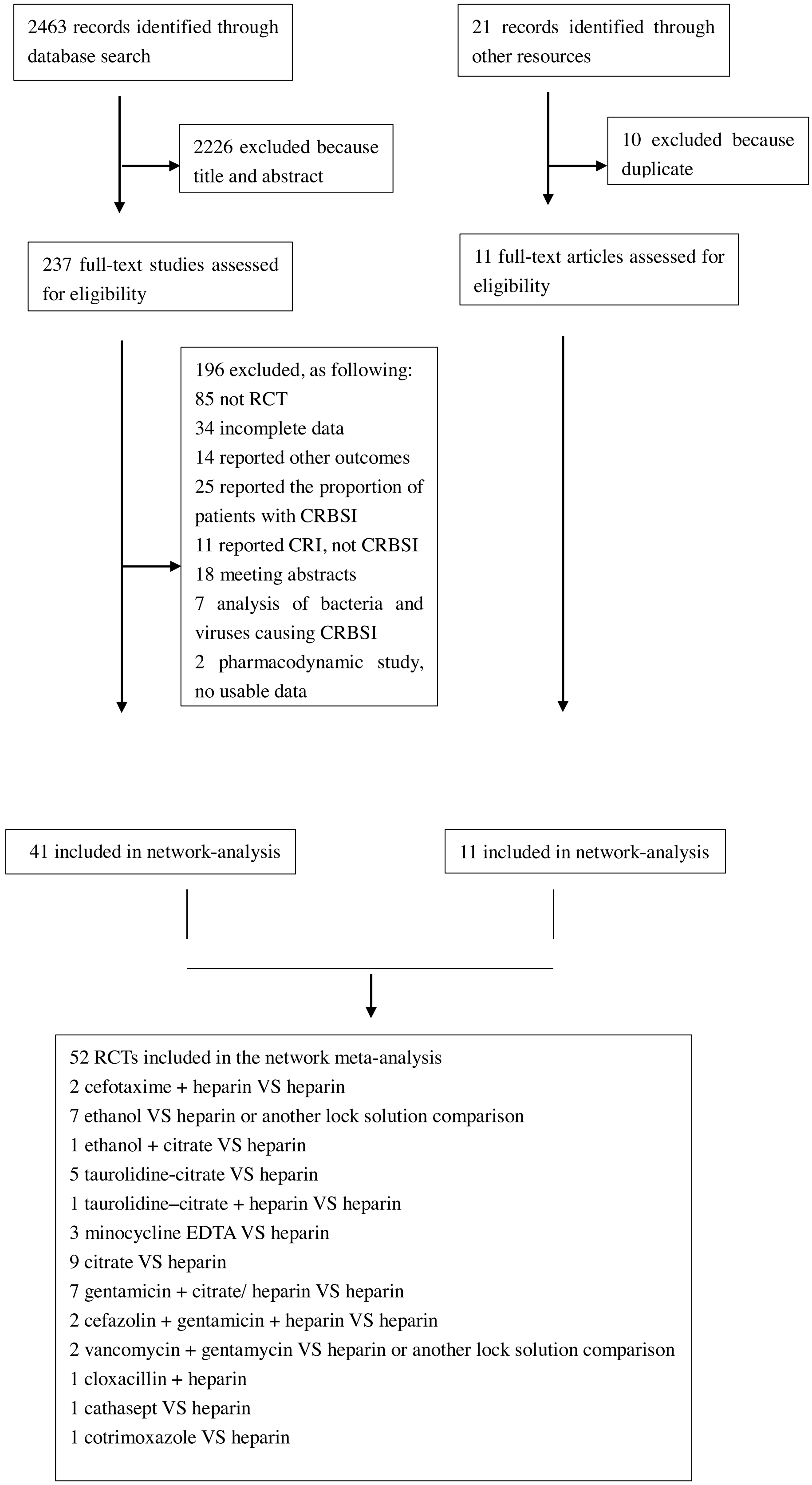
2463 records identified through database search
21 records identified through other resources
2226 excluded because title and abstract
10 excluded because duplicate
237 full-text studies assessed for eligibility
11 full-text articles assessed for eligibility
196 excluded, as following:
85 not RCT
34 incomplete data
14 reported other outcomes
25 reported the proportion of patients with CRBSI
11 reported CRI, not CRBSI
18 meeting abstracts
7 analysis of bacteria and viruses causing CRBSI
2 pharmacodynamic study, no usable data
41 included in network-analysis
11 included in network-analysis
52 RCTs included in the network meta-analysis
2 cefotaxime + heparin VS heparin
7 ethanol VS heparin or another lock solution comparison
1 ethanol + citrate VS heparin
5 taurolidine-citrate VS heparin
1 taurolidine–citrate + heparin VS heparin
3 minocycline EDTA VS heparin
9 citrate VS heparin
7 gentamicin + citrate/ heparin VS heparin
2 cefazolin + gentamicin + heparin VS heparin
2 vancomycin + gentamycin VS heparin or another lock solution comparison
1 cloxacillin + heparin
1 cathasept VS heparin
1 cotrimoxazole VS heparin

Figure 1. xxx.

Table 1
Study and patient characteristics.

No.	Study ID	Country	Treatment group (T)	Control group (C)	T/C	Age (T/C) (years)	Female/ male (T/C)	Type of CVC	Number of catheters	Catheter insertion site	Duration of trial (months)
1	Saxena 2006	Saudi Arabia	Cefotaxime + heparin	Heparin	58/ 55	78.0 ± 19/75.5 ± 17	22/36 23/32	TCC	119	SC: 32 JU: 97	24
2	Slobbe 2010	Netherlands	Ethanol	Saline	226/ 222	51.7/49.8	96/130 97/125	TCC	449	SC: 5 JU: 432 FV: 2	36
3	Betjes 2004	Netherlands	Taurolidine–citrate	Heparin	39/37	58.3 ± 16.3/ 50.3 ± 20.4	NR	NTCC	76	JU: 44 FV: 14	NR
4	Zwiech 2016	Poland	Taurolidine–citrate + heparin	Heparin	24/29	57.1 ± 14.46/ 56.2 ± 11.98	12/14 13/11	NTCC	53	NR	NR
5	Dümichen 2012	Germany	Taurolidine–citrate	Heparin	35/36	7.9/8.5	19/16 13/23	CVC	71	NR	NR
6	Campos 2011	Brazil	Minocycline EDTA	Heparin	92/ 95	54.5 ± 16.86/ 55.5 ± 15.35	57/35 51/44	NTCC/ TCC	187	SC: 15 JU: 172	NR
7	Sanders 2008	New Zealand	Ethanol	Heparin	32/ 28	52.4 ± 2.3/ 47.2 ± 2.7	15/17 12/16	TCC	65	NR	NR
8	Buturović 1998	USA	Citrate/polygeline	Heparin	10/ 10/10	63 ± 8	17/13	TCC	NR	SC: 20 JU: 10	NR
9	Hendrickx 2001	Belgium	Citrate	Heparin	10/9	74.6/71.6	4/6 4/5	TCC	1370	JU: 1370	6
10	Dogra 2002	Australia	Gentamicin + citrate	Heparin	42/37	55.7 ± 2.5/ 59.3 ± 2.1	24/18 26/11	TCC	216	NR	24
11	McIntyre 2004	UK	Gentamicin + heparin	Heparin	25/ 25	63.6 ± 2.8/ 57.8 ± 3.2	18/7 14/11	TCC	NR	NR	12
12	Bleyer 2005	USA	Minocycline EDTA	Heparin	30/27	58.7 ± 13.5/ 50.1 ± 19.6	13/14 11/19	NTCC/ TCC	NR	NR	14
13	Kim 2006	Korea	Cefazolin + gentamicin + heparin	Heparin	60/60	53.6 ± 15.2/ 56.1 ± 15.6	27/33 32/28	NTCC	NR	NR	NR
14	Solomon 2010	UK	Taurolidine–citrate	Heparin	53/ 54	59.8 ± 14.7/ 56.7 ± 17.4	27/26 13/41	TCC	107	SC: 2 JU: 113	19
15	Moran 2012	USA	Gentamicin + citrate	Heparin	155/ 148	63.4 ± 15.6/ 62.8 ± 16.8	67/81 76/79	TCC	303	SC: 13 JU: 117 FV: 3	56
16	Worth 2014	Australia	Ethanol	Heparin	42/ 43	47.0/48.1	14/28 19/24	TCC	NR	NR	15
17	AlHwiesh 2008	Saudi Arabia	Vancomycin + gentamicin	Heparin	36/33	47.4 ± 11.5/ 45.5 ± 7.4	14/22 12/21	TCC	69	JU: 60 FV: 9	18
18	Pervez 2002	USA	Gentamicin + citrate/ heparin + sterile bag	Heparin	14/ 22/19	53.7 ± 4.0/ 47.6 ± 3.3/ 47.6 ± 3.2	4/10 12/10 11/8	TCC	55	NR	16
19	Maki 2011	USA	Citrate	Heparin	201/ 206	62.2 ± 15.4/ 61.7 ± 15.2	103/98 100/106	TCC	407	JU: 407	6
20	Boersma 2015	New Zealand	Citrate	Heparin	108/ 99	55.2/54.1	48/60 31/68	TCC	207	SC: 13 JU: 195	48
21	Bonkain 2013	Belgium	Taurolidine–citrate	Saline	33/33	67/61	16/17 12/21	TCC	66	NR	NR
22	Broom 2012	Australia	Ethanol	Heparin	25/24	52 ± 18/64 ± 16	12/13 13/11	TCC	NR	NR	NR
23	Davanipur 2011	Iran	Cloxacillin + heparin	Heparin	50/50	50.1/52.3	22/28 24/26	TCC	NR	NR	6

Table 1 (*Continued*)

No.	Study ID	Country	Treatment group (T)	Control group (C)	T/C	Age (T/C) (years)	Female/ male (T/C)	Type of CVC	Number of catheters	Catheter insertion site	Duration of trial (months)
24	Barcellos 2017	Brazil	Citrate	Heparin	231/ 233	58.61/57.44	121/110 116/117	NTCC	464	SC: 109 JU: 298 FV: 36	24
25	Filiopoulos 2011	Greece	Gentamicin + heparin/ citrate	Heparin	60/ 59/ 58	72/70/75	31/29 26/33 28/30	TCC	NR	SC: 38 JU: 179	12
26	Bosma 2009	New Zealand	Citrate	Heparin	6/5	64.7/ 61.7	3/3 3/3	TCC	11	NR	3
27	MacRae 2008	Canada	Citrate	Heparin	32/ 29	63 ± 16/69 ± 15	11/21 15/14	TCC	61	NR	8
28	Kanaa 2015	UK	Cathasept	Heparin	58/ 59	60/61	15/44 20/38	TCC	141	NR	26
29	Weijmer 2005	Netherlands	Citrate	Heparin	148/ 143	61.6 ± 14.8/ 61.3 ± 16.0	87/61 87/56	NTCC/ TCC	NR	SC: 4 JU: 243 FV: 44	17
30	Moghaddas 2015	Iran	Co-trimoxazole	Heparin	46/41	63.6 ± 10.63/ 60.7 ± 14.40	26/20 18/23	TCC	87	NR	14
31	Oguzhan 2012	Turkey	Saline + heparin	Heparin	26/30	60.2 ± 15.1/ 58.0 ± 14.3	13/13 19/11	TCC	NR	SC: 3 JU: 53	12
32	Silva 2013	Brazil	Cefazolin + gentamicin + heparin	Heparin	107/ 126	56.4 ± 14.4/ 56.6 ± 14.6	51/56 57/69	TCC	325	SC: JU: 196 FV: 35	24
33	Sofroniadou 2017	Greece	Ethanol	Heparin	52/51	69/72	20/32 18/33	TCC	NR	SC: 37 JU: 57 FV: 9	57
34	Sofroniadou 2012	Greece	Vancomycin + heparin/ linezolid + heparin	Heparin	52/ 49/51	67.5/72/72	28/24 30/19 33/18	NTCC	152	SC: 87 JU: 87 FV: 9	48
35	Souweine 2015	France	Ethanol	Saline	730/ 730	65/66	286/444 284/446	NTCC	2173	SC: 23 JU: 663 FV: 1486	30
36	Vercaigne 2016	Canada	Ethanol + citrate	Heparin	20/19	63.0/62.3	8/12 10/9	TCC	NR	NR	NR
37	Zhang 2009	China	Gentamicin + heparin	Heparin	71/69	52.0 ± 16.3/ 52.1 ± 16.7	20/51 19/50	TCC	NR	JU: 140	NR
38	Fluck 2018	Netherlands	Minocycline EDTA	Heparin	140/ 130	65.5/67.0	62/78 59/71	TCC	NR	NR	NR
39	Winnicki 2018	Australia	Taurolidine	Citrate	52/57	56.2 ± 15.3/ 58.4 ± 15.5	22/30 30/27	TCC	NR	SC: 19 JU: 87	NR
40	Goossens 2013	Belgium	Saline	Heparin	404/ 398	56.7/54.6	261/143 263/135	TIVAD	NR	CV: 695 JV: 101	NR
41	Dal Molin 2015	Italy	Saline	Heparin	203/ 212	62.93/62.56	102/101 120/98	TIVAD	415	SC: 67/73 JU: 101/ 113	NR
42	Schallom 2012	USA	Saline	Heparin	150/ 145	58.3 ± 17.5/ 59.1 ± 15.2	83/67 68/77	TCC	326	SC: 107 JU: 197 FV: 22	13
43	Handrup 2013	Germany	Taurolidine	Heparin	64/ 65	6/5	19/45 22/43	TCC	NR	NR	NR
44	Bisseling 2010	Netherlands	Taurolidine	Heparin	16/14	55.3/48.6	10/6 12/2	TCC	NR	NR	23

Table 1 (*Continued*)

No.	Study ID	Country	Treatment group (T)	Control group (C)	T/C	Age (T/C) (years)	Female/ male (T/C)	Type of CVC	Number of catheters	Catheter insertion site	Duration of trial (months)
45	Klek 2015	Poland	Taurolidine/ Taurolidine–citrate	Saline	10/ 10/10	52.3	13/17	TCC	NR	NR	NR
46	Salonen 2018	USA	Ethanol	Saline	18/20	49 ± 16/52 ± 16	12/6 14/6	TCC	38	NR	22
47	Tribler 2017	Denmark	Taurolidine–citrate	Heparin	20/21	58.2 ± 12.4/ 54.8 ± 14.4	10/10 11/10	TCC	41	SC: 23 JU: 24 FV: 2	8
48	Wouters 2018	Israel	Taurolidine	Saline	52/50	59/55	29/23 33/17	TCC	112	NR	NR
49	Birch 2010	New Zealand	Heparin	Saline	102/ 108	28.7 ± 3.6/ 29.0 ± 4.2	48/53 55/53	TCC	210	NR	43
50	Beigi 2014	Iran	Heparin	Saline	47/49	62.3 ± 11.7/ 63.8 ± 10.8	24/23 20/29	TCC	96	NR	12
51	Majewska 2011	Iran	Cefotaxime	Heparin	15/15	52 ± 10.3/56 ± 9.6	9/6 8/7	TCC	30	NR	NR
52	Abdel 2018	Egypt	Citrate	Heparin	105/ 105	NR	NR	NTCC	310	NR	NR

CVC, central venous catheter; EDTA, ethylenediaminetetraacetic acid; JU, internal jugular catheter; SC, subclavian catheter; FV, femoral vein; CV, cephalic vein; TCC, tunneled catheter; NTCC, non-tunneled catheter; TIVAD, implanted venous access device; NR, not reported.

gentamicin + heparin, ethanol, and citrate (Supplementary material Appendix p. 11). According to the SUCRA for CRT, cefotaxime + heparin (96.1%) ranked as the most effective lock solution, followed by saline (72.1%). Citrate (5.4%) ranked as the worst (Supplementary material Appendix p. 22).

Secondary outcome—Exit-site infection

Figure 2c shows the network plot of the treatment comparisons for exit-site infections. Data on exit-site infection were available from 22 RCTs (2518 patients). Compared with EDTA, vancomycin + heparin, taurolidine, saline, polygeline, linezolid + heparin, heparin, gentamicin + heparin, gentamicin + citrate, ethanol, co-trimoxazole, citrate, and cefotaxime + heparin were associated with a significantly increased risk of exit-site infection. Vancomycin + heparin, taurolidine–citrate, saline, and heparin were associated with a greater effect on the prevention of exit-site infections. Ethanol was associated with a greater effect on the prevention of exit-site infections than taurolidine–citrate (Supplementary material Appendix p. 13). According to the SUCRA for exit-site infection, EDTA (99.3%) had the highest probability of effectiveness on exit-site infection, followed by vancomycin + heparin (84.9%). Gentamicin + citrate (7.2%) ranked as the worst (Supplementary material Appendix pp. 23–24).

Evaluation of statistical inconsistency

The loop-specific approach did not suggest any inconsistency between closed loops (Supplementary material Appendix pp. 15–20). After design by treatment test, the *p*-value of three outcomes was greater than 0.05. Similarly, side-splitting did not suggest the presence of statistical inconsistency for any outcomes (Supplementary material Appendix pp. 17–19).

Sensitivity analyses

The results of the sensitivity analyses are presented in the Supplementary material (Appendix pp. 27–28). Excluding studies with a sample size of 100 or less and studies with a high risk bias did not significantly change the results and overall conclusions.

Small-study effects

Overall, no strong evidence of small-study effects was found across outcomes, except that one study of EDTA was more likely to find large CRBSI and one trial of ethanol and one trial of cefotaxime + heparin found larger efficacy estimates for CRT (Supplementary material Appendix pp. 29–30).

Discussion

This network meta-analysis of different CLSs for the prevention of CRBSI included data from 52 clinical trials including 9099 patients with CVCs who were randomized to 20 treatment protocols (single and combinations). With regard to the quality of the evidence, the risk of bias was typically low or unclear (45 out of 52 trials; 86.5%). This appears to be the first study that has included all CLSs (single and combinations) for patients with CVCs in the same analysis using the network meta-analysis method. Based on the rank probability, it was found that EDTA appears to be the most effective for CRBSI and exit-site infections, while cefotaxime + heparin appears to be the most effective for CRT. However, cefotaxime + heparin appeared to have moderate treatment effects for CRBSI and exit-site infection (SUCRA of 55.9% and 49%, respectively). In the pairwise meta-analyses for CRBSI and CRT, some CLSs, such as EDTA, cloxacillin + heparin, citrate, taurolidine, heparin, and

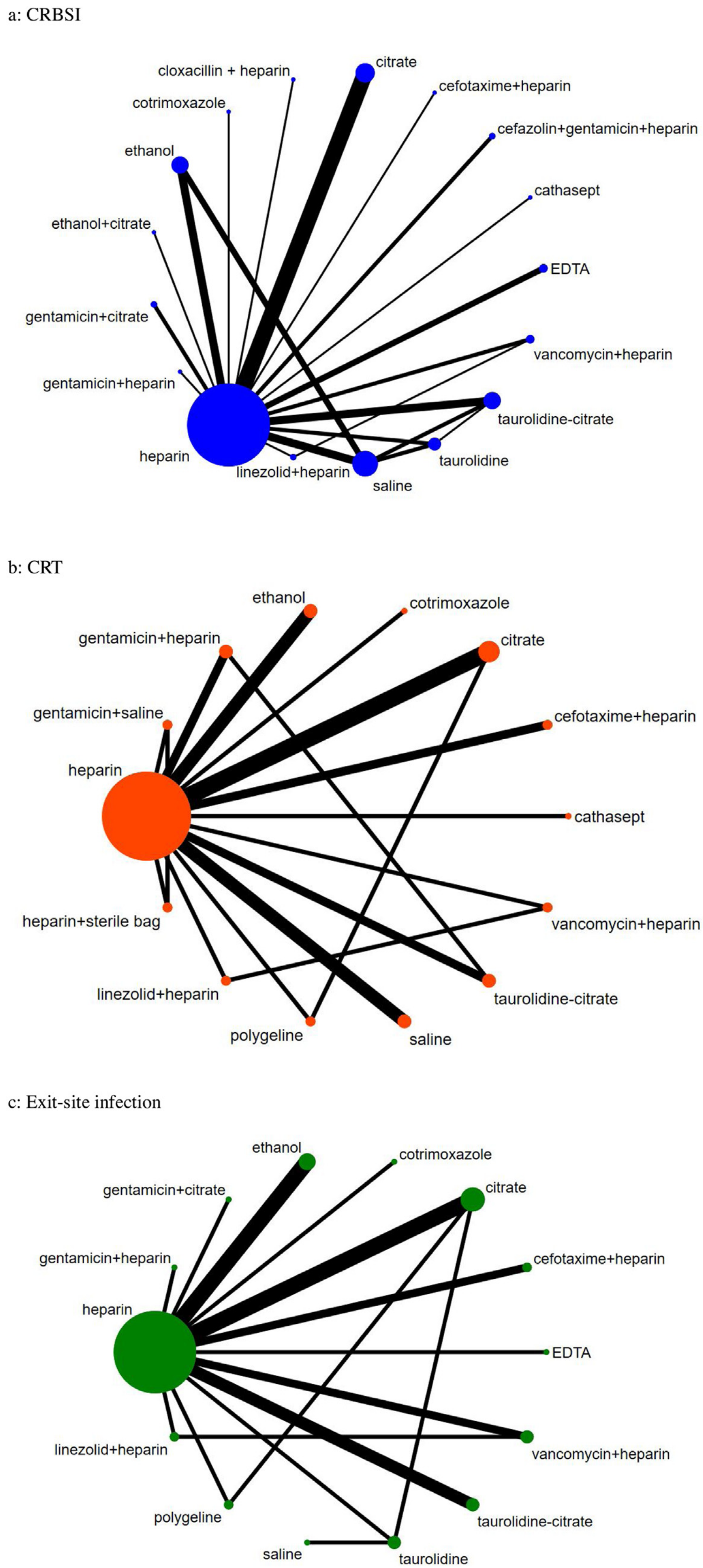
a: CRBSI
cloxacillin + heparin
citrate
cefotaxime+heparin
cotrimoxazole
cefazolin+gentamicin+heparin
ethanol
cathasept
ethanol+citrate
EDTA
gentamicin+citrate
vancomycin+heparin
gentamicin+heparin
taurolidine-citrate
heparin
taurolidine
linezolid+heparin
saline
b: CRT
ethanol
cotrimoxazole
gentamicin+heparin
citrate
gentamicin+saline
cefotaxime+heparin
heparin
cathasept
heparin+sterile bag
vancomycin+heparin
linezolid+heparin
taurolidine-citrate
polygeline
saline
c: Exit-site infection
ethanol
cotrimoxazole
gentamicin+citrate
citrate
gentamicin+heparin
cefotaxime+heparin
heparin
EDTA
linezolid+heparin
vancomycin+heparin
polygeline
taurolidine-citrate
saline
taurolidine

Figure 2. xxx.

Table 2
League table comparing lock solutions with respect to the CRBSI.[a]

heparin	0.17 (0.02,1.86)	0.34 (0.08,1.52)	0.25 (0.03,2.07)	0.12 (0.03,0.46)	0.04 (0.00,3.14)	0.32 (0.01,16.55)	0.02 (0.00,0.31)	0.71 (0.01,36.56)	0.19 (0.04,0.82)	0.11 (0.00,4.14)	0.01 (0.00,0.44)	1.06 (0.29,3.78)	1.00 (0.03,37.84)	0.27 (0.01,5.11)	0.10 (0.00,3.85)	0.17 (0.01,2.69)
5.97 (0.54,66.20)	vancomycin+heparin	2.03 (0.12,34.51)	1.46 (0.06,36.56)	0.71 (0.04,11.15)	0.26 (0.00,35.25)	1.88 (0.02,13.76)	0.13 (0.00,4.67)	4.22 (0.04,42.96)	1.12 (0.07,18.81)	0.65 (0.01,51.04)	0.03 (0.00,4.78)	6.30 (0.41,95.95)	5.97 (0.08,46.10)	1.59 (0.09,28.67)	0.58 (0.01,47.11)	1.03 (0.03,39.63)
2.94 (0.66,13.11)	0.49 (0.03,8.37)	taurolidine-citrate	0.72 (0.07,7.32)	0.35 (0.06,2.17)	0.13 (0.00,11.75)	0.93 (0.01,36.90)	0.07 (0.00,1.33)	2.08 (0.03,14.31)	0.55 (0.07,4.38)	0.32 (0.01,16.37)	0.02 (0.00,1.64)	3.10 (0.50,19.09)	2.94 (0.06,14.48)	0.79 (0.03,21.48)	0.29 (0.01,15.17)	0.51 (0.02,11.58)
4.08 (0.48,34.47)	0.68 (0.03,17.04)	1.39 (0.14,14.06)	taurolidine	0.48 (0.06,4.21)	0.18 (0.00,20.58)	1.29 (0.01,11.60)	0.09 (0.00,2.66)	2.88 (0.03,25.84)	0.76 (0.06,9.69)	0.45 (0.01,30.18)	0.02 (0.00,2.89)	4.30 (0.37,49.90)	4.08 (0.06,27.65)	1.09 (0.03,41.59)	0.40 (0.01,27.90)	0.70 (0.02,22.81)
8.44 (2.19,32.46)	1.41 (0.09,22.26)	2.87 (0.46,17.85)	2.07 (0.24,18.05)	saline	0.37 (0.00,30.44)	2.66 (0.04,14.47)	0.19 (0.01,3.58)	5.97 (0.09,38.73)	1.58 (0.25,9.94)	0.92 (0.02,44.52)	0.04 (0.00,4.49)	**8.90 (1.43,55.58)**	8.44 (0.18,40.52)	2.25 (0.09,57.84)	0.82 (0.02,41.28)	1.45 (0.07,31.01)
22.66 (0.32,16.02)	3.80 (0.03,8.07)	7.71 (0.09,18.35)	5.56 (0.05,36.38)	2.69 (0.03,19.67)	linezolid+heparin	7.15 (0.02,24.29)	0.51 (0.00,75.54)	16.04 (0.05,53.23)	4.25 (0.08,23.44)	2.48 (0.01,67.78)	0.12 (0.00,54.86)	23.91 (0.28,48.26)	22.66 (0.08,61.35)	6.05 (0.03,10.50)	2.21 (0.01,61.20)	3.90 (0.02,62.22)
3.17 (0.06,16.27)	0.53 (0.01,4.62)	1.08 (0.02,74.28)	0.78 (0.01,69.93)	0.38 (0.01,24.63)	0.14 (0.00,47.13)	gentamicin+heparin	0.07 (0.00,8.16)	2.24 (0.01,600.19)	0.59 (0.01,40.67)	0.35 (0.00,74.87)	0.02 (0.00,6.24)	3.34 (0.05,14.44)	3.17 (0.01,32.95)	0.85 (0.01,11.26)	0.31 (0.00,68.65)	0.55 (0.00,67.67)
2.92 (1.32,6.42)	7.47 (0.21,26.68)	15.17 (0.75,37.19)	10.95 (0.38,31.01)	5.29 (0.28,9.97)	1.97 (0.01,22.64)	14.07 (0.12,61.48)	gentamicin+citrate	31.57 (0.28,59.87)	8.36 (0.42,16.08)	4.88 (0.06,42.67)	0.23 (0.00,39.55)	**7.07 (2.57,16.91)**	44.61 (0.51,91.14)	11.92 (0.23,61.48)	4.34 (0.05,39.36)	7.67 (0.17,34.14)
1.41 (0.03,73.01)	0.24 (0.00,24.04)	0.48 (0.01,32.65)	0.35 (0.00,30.76)	0.17 (0.00,10.82)	0.06 (0.00,20.79)	0.45 (0.00,11.30)	0.03 (0.00,3.59)	ethanol+citrate	0.26 (0.00,17.87)	0.15 (0.00,33.01)	0.01 (0.00,2.75)	1.49 (0.02,94.23)	1.41 (0.01,30.52)	0.38 (0.00,52.09)	0.14 (0.00,30.27)	0.24 (0.00,29.79)
5.33 (1.22,23.32)	0.89 (0.05,15.01)	1.81 (0.23,14.40)	1.31 (0.10,16.60)	0.63 (0.10,3.97)	0.24 (0.00,12.87)	1.68 (0.02,11.14)	0.12 (0.01,2.40)	3.77 (0.06,25.59)	ethanol	0.58 (0.01,29.48)	0.03 (0.00,2.95)	5.63 (0.80,39.43)	5.33 (0.11,26.18)	1.42 (0.05,38.64)	0.52 (0.01,27.32)	0.92 (0.04,20.78)
9.15 (0.24,36.67)	1.53 (0.02,19.78)	3.11 (0.06,18.40)	2.24 (0.03,15.01)	1.08 (0.02,52.32)	0.40 (0.00,10.56)	2.89 (0.01,23.31)	0.21 (0.00,18.02)	6.47 (0.03,13.45)	1.71 (0.03,8.68)	cotrimoxazole	0.05 (0.00,14.57)	9.65 (0.20,45.74)	9.15 (0.05,15.58)	2.44 (0.02,26.04)	0.89 (0.01,15.86)	1.57 (0.02,15.09)
2.07 (1.19,5.49)	32.83 (0.21,51.79)	6.66 (0.61,17.15)	4.09 (0.35,16.29)	23.23 (0.22,42.67)	8.65 (0.02,41.71)	6.83 (0.16,23.52)	4.39 (0.03,36.50)	8.69 (0.36,19.75)	6.75 (0.34,39.18)	21.43 (0.07,66.91)	cloxacillin+heparin	**2.82 (2.02,21.50)**	16.00 (0.63,61.30)	2.36 (0.25,16.31)	19.09 (0.06,61.91)	33.70 (0.18,62.17)
0.95 (0.26,3.40)	0.16 (0.01,2.42)	0.32 (0.05,1.98)	0.23 (0.02,2.70)	0.11 (0.02,0.70)	0.04 (0.00,3.58)	0.30 (0.00,19.17)	0.02 (0.00,0.39)	0.67 (0.01,42.37)	0.18 (0.03,1.24)	0.10 (0.00,4.88)	0.00 (0.00,0.49)	citrate	0.95 (0.02,44.58)	0.25 (0.01,6.31)	0.09 (0.00,4.53)	0.16 (0.01,3.38)
1.00 (0.03,37.84)	0.17 (0.00,13.08)	0.34 (0.01,17.29)	0.25 (0.00,16.60)	0.12 (0.00,5.71)	0.04 (0.00,11.97)	0.32 (0.00,68.07)	0.02 (0.00,1.97)	0.71 (0.00,15.97)	0.19 (0.00,9.46)	0.11 (0.00,18.66)	0.01 (0.00,1.59)	1.06 (0.02,49.64)	cefotaxime+heparin	0.27 (0.00,28.83)	0.10 (0.00,17.13)	0.17 (0.00,16.39)
3.74 (0.20,17.66)	0.63 (0.03,11.27)	1.27 (0.05,34.81)	0.92 (0.02,35.09)	0.44 (0.02,11.39)	0.17 (0.00,29.56)	1.18 (0.01,16.92)	0.08 (0.00,4.32)	2.65 (0.02,36.42)	0.70 (0.03,19.03)	0.41 (0.00,44.23)	0.02 (0.00,3.97)	3.95 (0.16,9.49)	3.74 (0.03,40.96)	cefazolin+gentamicin+heparin	0.36 (0.00,40.73)	0.64 (0.01,36.40)
10.27 (0.26,46.08)	1.72 (0.02,13.33)	3.49 (0.07,14.96)	2.52 (0.04,17.03)	1.22 (0.02,61.13)	0.45 (0.00,12.45)	3.24 (0.01,20.19)	0.23 (0.00,20.94)	7.26 (0.03,15.43)	1.92 (0.04,10.22)	1.12 (0.01,19.65)	0.05 (0.00,16.81)	10.83 (0.22,31.40)	10.27 (0.06,18.54)	2.74 (0.02,30.38)	cathasept	1.77 (0.02,17.31)
5.82 (0.37,19.04)	0.97 (0.03,37.61)	1.98 (0.09,15.32)	1.43 (0.04,46.46)	0.69 (0.03,14.74)	0.26 (0.00,41.04)	1.83 (0.01,22.82)	0.13 (0.00,5.80)	4.12 (0.03,50.63)	1.09 (0.05,24.71)	0.64 (0.01,60.69)	0.03 (0.00,5.54)	6.14 (0.30,27.30)	5.82 (0.06,54.32)	1.55 (0.03,87.88)	0.57 (0.01,55.94)	EDTA

CRBSI, catheter-related bloodstream infection; AN, vancomycin; TAUR, taurolidine; LZD, linezolid; GEN, gentamicin; SXT, co-trimoxazole; CLOX, cloxacillin; CTX, cefotaxime; CFZ, cefazolin; EDTA, ethylenediaminetetraacetic acid.

[a] *Note*: Effect sizes represent standardized mean differences and 95% confidence intervals. Comparisons should be read from left to right. Values lower than 1 favor the treatment in the corresponding row, while values higher than 1 favor the treatment in the corresponding column. Significant results (95% CI for standardized mean difference does not include 1) are in bold.

gentamicin + citrate, had a relatively lower risk of CRBSI than the other CLSs, and cefotaxime + heparin had a relatively lower risk of CRT, which is similar to the results of the present network meta-analyses.

Interestingly, evidence of CLS efficacy in pairwise analyses but not in the network meta-analysis was also found. For example, the pairwise meta-analysis showed that heparin is superior to EDTA regarding exit-site infection; however, the outcome is the opposite when considering the network meta-analysis. As the direct evidence is based on data from only one RCT (Jansen and Naci, 2013), further investigations are necessary in the future. To make the results as relevant and robust as possible in order to inform clinical practice, sensitivity analyses were conducted and it was found that the results did not change substantially. Assessment of inconsistency using the node-splitting model showed little inconsistency between direct and indirect results.

This appears to be the first network meta-analysis for the comparison of various CLSs for the prevention of CRBSI. Although some pairwise meta-analyses (Zacharioudakis et al., 2014; Liu et al., 2013; Labriola et al., 2007; Zhao et al., 2018; Bleyer et al., 2005; Snaterse et al., 2010) have shown that the application of CLSs significantly reduces the risk of CRBSI by 50–90%, it is unclear from these meta-analyses whether a particular antimicrobial CLS or certain combinations of antimicrobial CLSs were responsible for the treatment effects observed. Besides, no evidence has focused on the CRT caused by CLSs. Therefore, this research provides a more complete understanding of these previous efforts, giving a more comprehensive picture of the available evidence of the comparative effectiveness of CLSs in the prevention of CRBSI.

The network meta-analysis showed that EDTA seemed to be the most effective for CRBSI and exit-site infection. This is a CLS consisting of minocycline and EDTA. Minocycline has been indicated to be more active than linezolid and vancomycin in penetrating and eradicating Gram-positive organisms (Yahav et al., 2008; Domalaon et al., 2017). In addition, EDTA can complement the antimicrobial activity of minocycline in eradicating organisms in biofilms (Raad et al., 2007; Raad et al., 2003). A remaining concern of CLSs is the potential for the emergence of antibiotic resistance. In a single randomized trial, EDTA significantly reduced CRBSI from 4.3 to 1.1/1000 days in 204 hemodialysis patients (Sherertz et al., 2006). The effect was significant for gram-negative, but not for gram-positive organisms. Meanwhile, in an in vitro analysis, gentamicin, oxacillin, and vancomycin lock solutions, even at very high pharmacological concentrations (10 000, 5000, and 5000 μg/ml, respectively), failed to sterilize the biofilms of many coagulase-negative *Staphylococcus* strains (Campos et al., 2011a). However, the CLS with ethanol that reduced the incidence of CRBSI has also been shown to sterilize biofilms of gram-positive and gram-negative bacteria and fungal pathogens in vitro. Therefore, ethanol at low concentrations for a short time has higher efficacy than conventional antibiotics at high concentrations for a long period to treat CRBSI (Qu et al., 2009; Chandra et al., 2018).

Although previous studies have demonstrated that EDTA can prevent thrombogenesis and thrombotic occlusions (Fluck, 2018; Reardon et al., 1991; Campos et al., 2011b), the present network meta-analysis showed that cefotaxime + heparin seemed to be the most effective for CRT. Because there is no RCT to compare the effect of EDTA in preventing CRT. Moreover, a major concern related to CLSs is the increasing need for thrombolytic interventions to maintain catheter patency (Sofroniadou et al., 2017; Raad et al., 2016). So, there should be more research on CRT in the future.

Exit-site infections are an additional cause of morbidity in patients with CVCs, which can lead to subsequent bloodstream infections, even after catheter removal (Zacharioudakis et al., 2014). One pairwise meta-analysis demonstrated that CLSs have a significant effect in reducing the risk of CRT beyond the prevention of CRBSI. A possible explanation is that some CLSs leak from the catheter lumen into the circulation. In this case, the concentration may be maintained in the blood and subcutaneous tissue at the catheter exit site, minimizing the risk of exit-site infection. Besides, this meta-analysis assessed not only hematology patients, but also cancer patients and patients receiving home parenteral nutrition. The meta-analysis by Salanti et al. (2014) showed that there was no statistically significant difference between citrate and heparin in the prevention of exit-site infection. An RCT (Abdel et al., 2018) showed that citrate-based locking solutions have a favorable effect in the prevention of catheter-related infections due to their additional antiseptic properties as compared to heparin. Recently, Mai et al. (2019) performed an updated meta-analysis to assess the comparative efficacy of citrate and heparin in reducing exit-site infections, and they included 16 studies with 224 196 catheter-days. It was shown that citrate lock with non-tunneled catheters was more effective in preventing exit-site infection than heparin (risk ratio (RR) 0.48, 95% CI 0.31–0.75), while the risk of exit-site infection was similar for citrate and heparin with tunneled catheters (RR 0.97, 95% CI 0.62–1.51).

A limitation of this study is that seven of the studies included (Raad et al., 2016; Moghaddas et al., 2015; Dümichen et al., 2012; Boersma et al., 2015; Souweine et al., 2015; Goossens et al., 2013; Wouters et al., 2018) were deemed to have a high overall risk of bias (13.5%). In three of these (Raad et al., 2016; Dümichen et al., 2012; Souweine et al., 2015), this was due to the high risk of bias resulting from the failure to blind participants or outcome assessment, and in another three (Boersma et al., 2015; Goossens et al., 2013; Wouters et al., 2018), it was due to the attrition rate, which was greater than 5% of the total sample size. In the remaining study, the risk was high because the random method used the first letter of the name (Moghaddas et al., 2015). Another limitation is that most comparisons were performed based on only two or three small RCTs, and most results had wide credibility intervals, so the potential for bias should be confirmed. Additionally, the results are based on direct and indirect comparisons between CLSs. Some results may change with an increased number of head-to-head trials in the future.

Conclusions

Overall, most CLSs when combined with other lock solutions showed superiority over the other single CLSs in terms of CRBSI, CRT, and exit-site infections. This network meta-analysis showed that EDTA seemed to be the most effective for the prevention of CRBSI and exit-site infection, and cefotaxime + heparin seemed to be the most effective for CRT. The study findings also highlight important research priorities in the specialty of CLSs for CRBSI, such as the need to conduct further RCTs for some novel CLSs.

Author contributions

FPD and JHT conceived and designed this network meta-analysis. FPD, RJW, HC, and JJR were involved in the acquisition and analysis of the data. FPD and QW interpreted the results. FPD and HJL drafted this protocol. All authors have read and provided feedback and consented to the content of the article as submitted.

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Ethical approval

As the present meta-analysis was performed based on previously published studies, no ethical approval was required.

Conflict of interest

All authors: No potential competing interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.08.017.

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