Impact of needle-free connectors compared with 3-way stopcocks on catheter-related bloodstream infection rates: A meta-analysis

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**Key Words:**
- Mechanical valve
- Needleless connector
- Split septum
- Negative-, positive-, and neutral-displacement needleless connectors
- Open system connectors

**Background:** Needle-free connectors (NFCs) were introduced to eliminate the use of needles in intravascular catheters, and their newest generations were designed to improve patient safety and reduce catheter-related bloodstream infection (CRBSI) risks. The aim of this meta-analysis was to compare NFCs with 3-way stopcocks (3WSCs) and their effects on CRBSI rates.

**Methods:** A meta-analysis was conducted using a research protocol consistent with the PRISMA statement for reporting meta-analyses. The Cochrane Database of Systematic Reviews and MEDLINE were searched for relevant randomized studies published from January 2000 to September 2018.

**Results:** We identified and selected for the meta-analysis 8 studies comparing CRBSI rates (according to the Centers for Disease Control and Prevention’s National Healthcare Safety Network definition) associated with NFCs utilizing negative-displacement, neutral-displacement, or positive-displacement devices with rates for 3WSCs. Relative risk was 0.53 with a 95% CI of 0.28 to 1.00, and the relative difference was −0.018 with a 95% CI of −0.039 to 0.004.

**Conclusions:** CRBSI risk was statistically higher for 3WSCs compared to NFCs.

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resulting in fewer CRBSI outbreaks being associated with these NFCs.\textsuperscript{4,5} Eventually, the Food and Drug Administration required US manufacturers of positive-displacement NFCs to provide evidence showing that their devices were associated with lower or equal risks of CRBSI in comparison with negative-displacement NFCs.

To date, newly designed features of NFCs include a solid, flat, smooth access surface for effective disinfection; a visible fluid path to enable clinicians to assess the efficacy of their flush technique; 1-part activation of the fluid path for effective flush; and an open fluid pathway to provide a high flow rate and avoid hemolysis, among other desired safety features (eg, tight septum seal, minimal internal complexity, ability to flush with saline alone).\textsuperscript{5} The objective of this meta-analysis was to compare CRBSI risks between patients using OSs and CSs.

Needle-free connectors

NFCs provide needle-free access at the hub end of the catheter for IV medication administration, fluid infusion, or withdrawal of blood samples or to connect administration sets to the intravascular catheters. Needle-free connectors include split-septum connectors and luer-activated mechanical valves. The standard split-septum connectors or negative-reflux caps do not have internal mechanisms and are pre-pierced to allow access by a blunt cannula to open the fluid pathway for IV fluid infusion or medication administration.

Based on their internal membrane function, mechanical valves are classified as negative-, neutral-, or positive-displacement types. Mechanical valves have an internal membrane or valve and require a mating luer connector when flushing or administering IV fluids or medications. The syringe tip or the tip of the IV tubing is directly inserted into the cap without the need for a blunt needle.\textsuperscript{7} The design of positive-pressure valves is aimed at preventing retrograde blood flow inside the catheter after the luer is disconnected to prevent thrombotic occlusions and also to avoid catheter hub and endoluminal microbial contamination, assuming that aseptic techniques are followed.\textsuperscript{5}

Types of IV needle-free connectors

- **Negative-displacement** NFCs allow blood reflux into a vascular access device lumen upon disconnection due to movement of valve mechanism or removal of the syringe or set. With negative-displacement mechanical valves, the luer caps must be clamped prior to removing the syringe or tubing set to prevent blood from backing up into the catheter.

- **Positive-displacement** NFCs allow a small amount of fluid to be held in the device; upon set or syringe disconnection, this fluid is pushed through the catheter lumen to clear any blood that refluxed into the lumen. The positive-displacement valves, also called positive-pressure valves, have a fluid reservoir that creates a positive-displacement movement or pressure and should not be clamped when disconnecting the syringe or IV administration sets.

- **Neutral-displacement** NFCs contain an internal mechanism designed to prevent blood reflux into the catheter lumen upon connection or disconnection. For neutral-displacement valves, there is no displacement of fluid into the catheter when connecting or disconnecting the syringe or tubing, and their use requires no change in clamping practices.

- **3-way stopcocks** consist of a valve or turning plug that controls the flow of fluid from a container through a tube. A 3WSC can be used on IV tubing to turn off one solution and turn on another. It is open to the air, without a membrane, when the cover is not in place and for that reason is considered to be an open IV system.

**METHODS**

**Data sources**

We developed a research protocol and data collection tools consistent with PRISMA recommendations.\textsuperscript{6} We searched the MEDLINE database for relevant studies published from January 2000 to September 2018, as well as ClinicalTrials.gov, Embase, and the Cochrane Database of Systematic Reviews.

**Study selection and data extraction**

Study inclusion criteria were randomized controlled trials or observational studies that reported CRBSI rates in patients with positive-, negative-, or neutral-displacement devices compared to 3WSC connectors. For the search, we used the following medical subject headings and key words: catheter-related bloodstream infection, bloodstream infections, central venous catheter-associated infections, mechanical valve, needle-free connector, needle free connector, needle less connector, needless connector, split septum, negative-displacement needle less connector, neutral-displacement needle less connector, open system connectors, three ways stop cock.

An Internet search was conducted independently by 2 investigators. All abstracts identified were read independently by 2 investigators (1 with a PhD, 1 with an MD). Disagreement was resolved by discussions with a third investigator. Data extracted from these studies on standardized forms included study design; setting; patient population; facility location; and number of CRBSIs (numerator) and number of central line (CL) days (denominator) during the study for needle-free device periods compared to 3WSC device periods. We recorded CRBSI incidence density (infections per 1000 CL days) at each site.

**Meta-analysis**

An overall estimate of relative risk (RR) was calculated treating the study as a random effect. A closed system was defined as the treatment (ie, probability in the numerator); consequently, a RR of 1 indicates similar risk, and a RR of <1 indicates that the closed system has less risk than the open system. The overall RR estimate is complicated by the open system positives reported by Khalidi in 2009.\textsuperscript{10} A 0 in a numerator or denominator of a fraction is mathematically intractable. Generally, 0 events are handled by:

- Dropping any 0 event studies from the overall estimate
- Adding a small number, such as 1/2, to the 0 event or to all of the events

Neither approach is completely satisfying. Dropping a study or studies introduces a potential bias to the overall estimate,\textsuperscript{11} and the outcome of adding a small number is sensitive to the number chosen and method used (ie, different conclusions can be reached depending on the number or method used). For the analysis reported here, the 0-event study was excluded from the estimate of overall RR. To mitigate any bias introduced by this exclusion, the RR analysis was supplemented with an estimate of the overall relative difference (RD), as suggested by Keus et al.\textsuperscript{12} The overall RD estimate is robust to 0 events.

**RESULTS**

We selected 8 randomized, prospective in vivo studies that compared CRBSI rates associated with the use of OSs versus CSs. Table 1 summarizes the counts and rates for the 8 articles selected for the
meta-analysis, and Table 2 shows the RR and RD estimates and 95% CIs for the individual studies and overall. The RR null value is 1; the RD null value is 0. The CI for the overall RR estimate is strictly lower than 1, implying that the risk is lower with the CSs. However, the CI for the overall RD estimate includes 0, implying that a conclusion of “no difference” cannot be ruled out. Details are given in Table 2 and depicted in Figure 1.

DISCUSSION

In this meta-analysis, we identified 8 relevant randomized studies published from January 2000 to December 2018 in which CRBSI rates for NFCs with negative-displacement devices, neutral-displacement devices, or positive-displacement devices were compared with cases with 3WSCs. In a pre-post study conducted by Royer et al,20 a swabable positive-displacement device (MaxPlus clear needleless connector; Becton Dickinson, Franklin Lakes, NJ) was compared to another non-swabable positive-displacement device (MaxPlus). For the swabable positive-displacement device, the CRBSI rate was 0.84 per 1000 CL days; for the non-swabable positive-displacement device, the CRBSI rate was 1.73 per 1000 CL days.

In a pre-post study conducted by Wheeler et al,21 a negative-displacement device was compared with another negative-displacement device. The authors observed an unexpected increase in the rate of CRBSI at their institution during August 2009. They discovered that the Spiros closed male connector (ICU Medical; San Clemente, CA) had been introduced in these 2 units around the same time that the cluster of infections occurred. Based on this information, use of this device was discontinued, and the CRBSI rate and distribution of causative microorganisms returned to their previous baseline values.

In a meta-analysis conducted by Tabak et al,22 positive-displacement devices were compared with negative- or neutral-displacement devices. Studies reporting the CRBSIs in patients using the positive-displacement NFC (study NFC) compared with negative- or neutral-displacement NFCs were analyzed. In the comparator period, total CL days were 111,255, and the CRBSI rate was 1.5 events per 1000 CL days. In the study NFC period, total CL days were 95,383, and the CRBSI rate was 0.5 events per 1000 CL days. The pooled CRBSI RR associated with NFC period (7.52, 6.62, and 6.30 per 1000 patient days, respectively) was 0.86 per 1000 CL days; for the non-swabable positive-displacement device, the CRBSI rate was 1.73 per 1000 CL days.

In a pre-post study conducted by Wallace et al,23 the use of a non-swabable positive-displacement NFC (MaxPlus) resulted in a CRBSI rate of 2.9/1000 in 2010. After implementation of the swabable positive-displacement NFC, the CRBSI rate dropped and remained statistically stable: 0.8 per 1000 CL days (95% CI, 0.1–3.0) in 2011, 0 (95% CI, 0.0–1.8) in 2012, and 0.91 (95% CI, 0.1–3.3) in 2013.

In a pre-post study conducted by Casey et al,24 a positive-displacement device was compared with a neutral-displacement device. There were 557 needle-free IV access devices connected to 167 catheters (86 in the neutral- and 81 in the positive-displacement group) from 157 patients that were studied (2 catheters were studied in 10 patients).

Table 1
Summary of article metrics

<table>
<thead>
<tr>
<th>Source</th>
<th>Catheter days</th>
<th>Positives</th>
<th>Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yebenes et al (2004)14</td>
<td>1,404</td>
<td>7</td>
<td>5.0</td>
</tr>
<tr>
<td>Esteve et al (2007)15</td>
<td>10,462</td>
<td>43</td>
<td>4.1</td>
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<tr>
<td>Casey et al (2007)16</td>
<td>200</td>
<td>20</td>
<td>100.0</td>
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<tr>
<td>Yebenes et al (2008)17</td>
<td>241</td>
<td>8</td>
<td>33.2</td>
</tr>
<tr>
<td>Khalidi et al (2009)10</td>
<td>768</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>Catheter days</th>
<th>Positives</th>
<th>Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casey et al (2003)13</td>
<td>274</td>
<td>18</td>
<td>65.7</td>
</tr>
<tr>
<td>Yebenes et al (2004)14</td>
<td>1,362</td>
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<td>0.7</td>
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<td>10,195</td>
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<td>4.6</td>
</tr>
<tr>
<td>Casey et al (2007)16</td>
<td>193</td>
<td>1</td>
<td>5.2</td>
</tr>
<tr>
<td>Yebenes et al (2008)17</td>
<td>221</td>
<td>1</td>
<td>4.5</td>
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<tr>
<td>Khalidi et al (2009)10</td>
<td>864</td>
<td>2</td>
<td>2.3</td>
</tr>
<tr>
<td>Gonzalez Lopez et al (2013)18</td>
<td>2,257</td>
<td>13</td>
<td>5.8</td>
</tr>
<tr>
<td>Rosenthal et al (2015)19</td>
<td>3,619</td>
<td>8</td>
<td>2.2</td>
</tr>
</tbody>
</table>

*Rates are per 1000 catheter days.

There was no difference in the rates of CRBSI among the first neutral- and positive-displacement device periods and the second neutral-displacement device period (7.52, 6.62, and 6.30 per 1000 patient days, respectively) (first neutral-displacement device vs positive-displacement device, \(P = 0.60\); first neutral-displacement device vs second neutral-displacement device, \(P = 0.56\); positive-displacement device vs second neutral-displacement device, \(P = 0.85\)). There was also no difference in the rates of non-mucosal barrier injury, laboratory-confirmed CRBSIs among the 3 periods (4.30, 3.42, and 2.00 per

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Table 2
Relative risk and relative difference estimates for the individual studies and overall

<table>
<thead>
<tr>
<th>Source</th>
<th>Relative risk (95% CI)</th>
<th>Relative difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casey et al (2003)13</td>
<td>0.37 (0.22, 0.61)</td>
<td>-0.14 (-0.166, -0.062)</td>
</tr>
<tr>
<td>Yebenes et al (2004)14</td>
<td>0.15 (0.02, 1.20)</td>
<td>-0.004 (-0.008, 0.000)</td>
</tr>
<tr>
<td>Esteve et al (2007)15</td>
<td>1.12 (0.74, 1.69)</td>
<td>0.000 (-0.001, 0.002)</td>
</tr>
<tr>
<td>Casey et al (2007)16</td>
<td>0.05 (0.01, 0.38)</td>
<td>-0.095 (-0.138, -0.052)</td>
</tr>
<tr>
<td>Yebenes et al (2008)17</td>
<td>0.14 (0.02, 1.08)</td>
<td>-0.029 (-0.053, -0.004)</td>
</tr>
<tr>
<td>Khalidi et al (2009)10</td>
<td>NA</td>
<td>0.002 (-0.002, 0.006)</td>
</tr>
<tr>
<td>Gonzalez Lopez et al (2013)18</td>
<td>0.86 (0.41, 1.83)</td>
<td>-0.001 (-0.006, 0.004)</td>
</tr>
<tr>
<td>Rosenthal et al (2015)19</td>
<td>0.35 (0.16, 0.76)</td>
<td>-0.004 (-0.007, -0.001)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.40 (0.20, 0.80)</td>
<td>-0.025 (-0.052, 0.003)</td>
</tr>
</tbody>
</table>

NA, not available.
1000 patient days, respectively) (first neutral-displacement device vs positive-displacement device, $P = .49$; first neutral-displacement device vs second neutral-displacement device, $P = .11$; positive-displacement device vs second neutral-displacement device, $P = .19$). Fewer sepsa and internal fluid pathways were contaminated in the positive-displacement device group compared to the neutral-displacement device group. Most microorganisms isolated were skin or environmental bacteria.

**Limitations**

This meta-analysis had several limitations. Bias may have been introduced in the selection and location of studies, resulting in publication bias, English language bias, and citation bias. Also, studies from limited-resource countries are more likely to be published in journals indexed in a literature database, thus introducing database bias. Finally, this meta-analysis did not include sensitivity or subgroup analyses or meta-regression to examine the possible introduction of biases in the study selection process.\(^{25}\)

**CONCLUSIONS**

The results of this meta-analysis showed that CRBSI risk was statistically higher for 3WSCs compared to NFCs.

**Acknowledgments**

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**References**