Minocycline-Ethylenediaminetetraacetate Lock Solution for the Prevention of Implantable Port Infections in Children with Cancer

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In this prospective cohort study, minocycline-ethylenediaminetetraacetate (M-EDTA) was used as a lock solution in indwelling ports inserted in 14 children with cancer. No port infections, thrombotic events, or other adverse events were observed, compared with 10 port infections that occurred in 48 control patients whose ports were flushed with heparin. M-EDTA is a promising lock solution in long-term catheters.

Indwelling central venous catheters (CVCs) are essential in the management of patients with cancer. Catheter-related bloodstream infections (CRBSI) and thrombosis of the catheter are the 2 major complications that frequently necessitate the removal of the catheter. Additionally, CVCs have become the major source of nosocomial bloodstream infections. Indwelling implantable ports (referred to here simply as “ports”) are associated with the lowest infection rates [1]. They require minimal maintenance and interfere minimally with the patients’ image and lifestyle. Hence, ports have become the catheter of choice for children.

The current standard of catheter care includes flushing the catheter lumen with heparin. However, heparin has no antimicrobial activity; thus, infections and thrombotic occlusion continue to occur frequently. The use of a flushing solution with intrinsic antimicrobial activity may be beneficial in long-term indwelling catheters, such as ports, because the lumen of these catheters is the major source of the microbes implicated in CRBSI. Minocycline-EDTA (M-EDTA) lock solution was shown to have antithrombotic and broad-spectrum antimicrobial activity against the most common microorganisms associated with CRBSI, resulting in the prevention of recurrent long-term CRBSI [2].

We undertook this prospective cohort study in order to determine the safety and efficacy of an M-EDTA lock solution in the prevention of CRBSI associated with ports in children with cancer. We compared our results with a surveillance study database compiled by our infection control service. Informed consent was obtained by all participants, and the guidelines for human experimentation (of the US Department of Health and Human Services and of the University of Texas, M. D. Anderson Cancer Center) were followed in the conduct of this clinical research.

In order to obtain a control database, between September 1989 and November 1991, we prospectively followed, for a period of 6 months, all new CVC insertions that occurred in the pediatric unit of the University of Texas M. D. Anderson Cancer Center. A total of 48 patients received ports that were flushed with heparin on a monthly basis.

Subsequently, between July 1994 and March 1996, we enrolled 14 children with cancer who had newly inserted ports in a study in which the ports were flushed weekly with an M-EDTA lock solution. The flush solution consisted of 3 mg minocycline (Wyeth-Ayerst) and 30 mg EDTA (Endrate; Abbott Laboratories) per milliliter of water. A volume of 2 mL of M-EDTA was used to fill each port and was locked in place for at least 1 week. All patients were prospectively followed for 6 months, until the port was removed or until the patient died, whichever occurred first. The follow-up examination included recording all signs and symptoms of infection, catheter thrombosis, and adverse events associated with the administration of minocycline and EDTA. Notably, all study participants were evaluated for the development of hypocalcemia, muscle cramps, seizure, and nephrotoxicity (associated with rapid infusion and high concentration of disodium EDTA) and other adverse events associated with the use of minocycline (rash or photosensitivity, tooth discoloration, blurred vision, and vestibular disturbances). Any additional adverse events were recorded and evaluated regarding their possible association to the use of minocycline or EDTA. Except for the use of M-EDTA flush
solution, there was no difference in the port insertion method and maintenance measures between this group and the previous control group studied during 1989–1991.

Neutropenia was defined as an absolute neutrophil count of \( \leq 1000 \). A patient was considered to have probable CRBSI if all of the following conditions were satisfied: (1) isolation of an organism usually associated with CRBSI (coagulase-negative staphylococci, \textit{Staphylococcus aureus}, \textit{Candida albicans}, or \textit{Candida parapsilosis}) from a culture of blood drawn from a peripheral vein; (2) clinical manifestations of infection (temperature \( \geq 38^\circ \text{C} \) or chills); and (3) no apparent source for the bloodstream infection other than the catheter. A definite CRBSI was diagnosed if all the above 3 criteria were met and there was isolation of the same microorganism from the tip of a removed catheter (\( \geq 15 \text{ cfu} \)) or a \( \geq 10 \)-fold colony count of an organism from a quantitative culture of blood drawn through the port compared with a culture of simultaneously collected peripheral blood. Finally, we defined a port site infection as the presence of erythema, tenderness, or swelling at the catheter site with culture-positive material aspirated from the port pocket, evidence of abscess formation, or both.

The demographic characteristics of both patient groups are summarized in table 1. In terms of predisposing factors for infection, the 14 M-EDTA patients had higher rate of hematologic malignancies (\( P = .05 \)), longer duration of neutropenia (\( P = .03 \)), and longer duration of catheterization (\( P = .001 \)), compared with the 48 heparin patients (table 1). Because the duration of neutropenia in the heparin group was calculated only for the 28 patients for whom this information was available, comparison between the 2 groups related to this parameter should be performed with caution. The 14 M-EDTA patients received 14 ports during the 6 months of follow up, totaling 2073 catheter-days (range, 26–195 catheter-days; mean \( \pm SD \), 148 \( \pm 54 \) catheter-days; median, 109 catheter-days). No infections, thromboses, or adverse events were observed. On the other hand, the 48 heparin patients, who were followed for 6 months, received 50 ports totaling 4481 catheter-days (range, 4–183 catheter-days; mean \( \pm SD \), 93 \( \pm 50 \) catheter-days; median, 93 catheter-days). Ten infectious episodes (2.23 infections/1000 catheter-days) occurred in the heparin group, consisting of 2 definite CRBSI, 5 probable CRBSI, and 3 local port infections. In addition 2 thrombotic episodes were observed. Nine catheters in the heparin group were removed as a result of proven or suspected infection, and 1 was removed as a result of thrombosis. Over time, the 14 study patients were significantly less likely to develop catheter infection compared with the 48 control group patients, as assessed via Kaplan-Meier log-rank analysis (\( P = .05 \)), despite the fact that they were predisposed to such infections because more had hematologic malignancy, and they had longer duration of catheterization (figure 1). All of these factors have been shown to place patients with cancer at higher risk for long-term catheter-related infections [1, 3].

Some of the infections in the heparin group were the result of more than one microorganism. The microorganisms causing such infections were as follows: \textit{Staphylococcus epidermidis} (\( n = 10 \)), \textit{S. aureus} (methicillin sensitive; \( n = 2 \)), \( \alpha \)-hemolytic \textit{Streptococcus} (\( n = 2 \)), \textit{Achromobacter species} (\( n = 2 \)), \textit{C. albicans} (\( n = 1 \)), \textit{Enterobacter aerogenes} (\( n = 1 \)), and \textit{Providencia retgeri} (\( n = 1 \)).

Our data indicate that the use of M-EDTA as a lock solution is safe and highly effective in preventing infectious complications associated with ports in children with cancer. Compared with the 48 control heparin patients, the 14 patients that received M-EDTA exhibited no evidence of infection. \textit{S. epidermidis} and \textit{S. aureus} account for \( \sim 75 \% \) of CRBSI. \textit{Candida} species account for another 10%–15% of such infections. Because staphylococci are the most common cause of CRBSI, the combination of vancomycin and heparin has often been used as a flush solution [4–8]. Four prospective randomized studies [4–6, 8] have demonstrated the benefit of heparin-vancomycin lock solution in preventing CRBSI caused by vancomycin-susceptible microorganisms. A smaller prospective randomized, controlled trial in children failed to show any benefit of the vancomycin-heparin lock solution over heparin alone in preventing CRBSI [7]. Although vancomycin is active against \textit{Staphylococcus} species, it is not highly active in eradicating the organisms that are embedded in the biofilm layer of a catheter surface. Additionally, vancomycin use is an in-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>M-EDTA (( n = 14 ))</th>
<th>Heparin (( n = 48 ))</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>.5</td>
</tr>
<tr>
<td>Male</td>
<td>8 (57)</td>
<td>22 (46)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6 (43)</td>
<td>26 (54)</td>
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</tr>
<tr>
<td>Underlying disease</td>
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<td></td>
<td>.05</td>
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<tr>
<td>Hematologic malignancy</td>
<td>9 (64)</td>
<td>17 (35)</td>
<td></td>
</tr>
<tr>
<td>Solid tumor</td>
<td>5 (36)</td>
<td>31 (65)</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>—</td>
<td>10 (21)</td>
<td>.06</td>
</tr>
<tr>
<td>Neutropenia, days( ^a )</td>
<td>11 (79)</td>
<td>25 (52)</td>
<td>—</td>
</tr>
<tr>
<td>Catheter dwell time, mean days ( \pm SD )</td>
<td>148 ( \pm 54 )</td>
<td>93 ( \pm 50 )</td>
<td>.001</td>
</tr>
<tr>
<td>Duration of neutropenia, mean days ( \pm SD )</td>
<td>31 ( \pm 15 )</td>
<td>16 ( \pm 19 )</td>
<td>.03</td>
</tr>
<tr>
<td>Pediatric age, years (up to 14 years)</td>
<td>11 (79)</td>
<td>39 (81)</td>
<td>1.00</td>
</tr>
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\( ^a \) For 20 patients in the heparin group, neutropenia status is unknown.

\textbf{NOTE.} Data are no. (%) of patients, unless noted otherwise.

Table 1. Patient characteristics of 14 children with cancer for whom minocycline-EDTA (M-EDTA) was used as a lock solution in indwelling ports and of a control group for whom heparin was used.
Figure 1. Kaplan-Meier log-rank analysis comparing the infection-free interval of ports flushed with minocycline-EDTA (M-EDTA) versus ports flushed with heparin in children with cancer. The risk of bloodstream infection was significantly lower for ports flushed with M-EDTA ($p = .05$ by the log-rank test).

EDTA is a potent calcium and iron chelator with anticoagulant activity, and antistaphylococcal activity and ant-
*Candida* activity [9, 10]. Minocycline has a broad antistaphylococcal activity and is also highly effective against *S. epidermidis* organisms embedded in the biofilm [11]. In combination, minocycline and EDTA act synergistically against staphylococci, gram-negative bacilli, and *Candida* species [2, 11]. An animal study demonstrated the benefit of M-EDTA over heparin-vancomycin and heparin alone in preventing catheter colonization, catheter-related bacteremia, and phlebitis [12]. Recent laboratory data verify the superiority of M-EDTA as a lock solution in decontaminating silicone catheter segments colonized with *S. aureus* and *C. albicans* [13].

The M-EDTA combination has also been proven clinically to be effective in preventing recurrent CRBSI caused by *S. epidermidis, S. aureus*, and *E. aerogenes* in 3 patients [2]. In addition, a prospective randomized clinical trial in hemodialysis patients demonstrated that M-EDTA was able to reduce 9-fold the risk of catheter colonization and CRBSI and had anticoagulant activity comparable to heparin [14].

Minocycline, although a potent antistaphylococcal antibiotic, is not used as a front-line agent in treating bloodstream infections. Thus, the combination of minocycline and EDTA may be more suitable for use as a prophylactic antibiotic lock solution. Additional data [2, 12] indicate that M-EDTA, when used in the same dose used in the current study, was not detected in the serum, thus rendering the emergence of resistance less likely.

In conclusion, our study shows that M-EDTA as a lock solution was efficacious in preventing port-related infections in children with cancer, without causing any adverse events. Limitations of our study include the small number of patients and the nonrandomized design with a historical control group. Large prospective, randomized, clinical trials are needed to further test the ability of M-EDTA to prevent long-term catheter-related infections.

References