A comparative multicentre study on the incidence of catheter-associated urinary tract infection between nitrofurazone-coated and silicone catheters

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Abstract

The efficacy of nitrofurazone-coated urinary catheter in inhibitory activity of catheter-associated urinary tract infection (CAUTI) was evaluated. The incidence rate and onset of CAUTI after catheterisation of standard silicone urinary catheters and nitrofurazone-coated catheters was compared. There was no statistical significance between the two groups in the incidence rate of CAUTI. However, in patients who had indwelling urinary catheters for 5–7 days, the incidence rate of CAUTI was significantly lower in the experimental group. Logistic regression analysis showed that the two variables, including age and period of insertion, affected the incidence rate of CAUTI significantly. Nitrofurazone-coated catheters can be useful for inhibition of CAUTI in patients who have indwelling urinary catheter for 5–7 days and in old-age patients.

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1. Introduction

Urinary tract infection is the most prevalent cause of nosocomial infections, with an incidence of about 40% of all nosocomial infections cases [1]. Among these 40%, 80% involve catheter-associated urinary tract infection (CAUTI) [2,3]. Although most CAUTI is asymptomatic, it was reported that a close relationship is present between symptomatic expressions and increased rate of mortality in diabetic, immune-compromised, debilitated patients [4]. The major route of infection in CAUTI is ascending, through the urethral opening at the time of insertion of a catheter, mucosal layer between the catheter and urethra, and catheter lumen [2]. The most effective way of preventing CAUTI is to keep the system of urine drainage closed between the catheter from the bladder to the collection bag [2,4,5]. CAUTI is shown within several days in 100% of cases when the system of urine drainage could not be maintained as closed [6]. However, maintaining the system of urine drainage closed is actually difficult, and even if the system was maintained as closed, CAUTI was reported to occur in 50% when the system is in operation for more than 5 days [7]. Various methods such as daily antimicrobial application on the urethra and perineum where a catheter is inserted [8], instillation of antimicrobial agents in the collection bag [9], bladder irritation with antimicrobial solutions [10], and the use of silver oxide-coated catheter [11], were attempted in clinical settings to prevent CAUTI. No significant effect could however be seen compared with the closed drainage system. Thus, the present study was conducted to determine the CAUTI inhibition effect by a recently developed nitrofurazone-coated catheter for the purpose of preventing
CAUTI, and its safety through a comparative study with the existing silicone catheter in patients who had indwelling catheters.

2. Materials and methods

The study included 177 male and female patients (>18 years of age) who were catheterised for more than 24 h at five university hospitals. The control group included 85 patients who were inserted with Silicone Foley Catheter (Se- woon Medical Company, Seoul Korea), and the study group included 92 patients who were inserted with Release Nitro- furazone Foley Catheter (Rochester Medical Corporation, MN, USA). The outside circumference of these two catheters was 16 Fr., and the patients were divided randomly into the control and experimental groups according to each hospital. Patients whose clinical results could be affected by conditions such as silicone sensitivity, nitrofurazone or nitrofurantoin sensitivity, pregnancy, lactating, hospitalisation for more than 7 days, and having urinary diseases were excluded. Furthermore, patients who were selected initially meeting the criteria of selection, were excluded later when they had a positive urine culture result before catheter insertion or when the catheter was removed within 24 h of insertion.

The release Nitrofurazone Foley Catheter used in the experimental group was made with pure silicone containing no latex and polyvinyl chloride, with nitrofurazone coating its surface. The catheter used in the control group was a silicone catheter made with pure silicone without any other treatment.

The patients registered for the study were examined by reviewing the results of vital signs, the use of drugs, urinalysis and urine culture for the selection process. Until the removal of catheter, vital signs and the use of drugs were monitored, urinalysis and urine culture were performed, abnormal reactions from catheter were examined, and complete blood counts and blood chemistry tests were done when necessary. When the catheter was maintained for more than 8 days, the patient was followed up for only 7 days. Urethral catheterisation was performed aseptically, and the closed drainage system was maintained by connecting the catheter threading through the urethra into the urine bag. During the screening process before urinary catheterisation, urine sample was collected aseptically by collecting 20 ml of mid-stream urine during the natural urination process. A 20 ml urine sample was also collected immediately after inserting a catheter. After catheterisation, urine sample was obtained from a sterile mid-catheter aspirate with a syringe. The expression of CAUTI was defined as urine culture containing $>10^5$ CFU/ml. When removing a catheter, the catheter tip including 1 cm distal to the catheter balloon was cut using a pair of sterile scissors. For scanning electron microscopy (SEM) the catheter tips were fixed in 5% glutaraldehyde in cacodylate buffer (0.1 mol/l, pH 7.2) for 24 h at 4 °C and post-fixed in 1% osmium tetroxide. Each sample was observed under SEM for biofilm pattern on catheter surface. The methods of statistical analysis used were Student’s t-test, chi-square test, multivariate analysis, and logistic regression analysis.

3. Results

Among a total of 177 patients, there were 85 (45 men and 40 women) in the control group where silicone catheter was used. In the experimental group where nitrofurazone-coated catheter was used there were 92 patients (69 men and 23 women). The average age of the patients in these groups was 54.1 and 55.3 years in the control and the experimental group, respectively. The average period of catheterisation was 3.9 days in the control group and 4.4 days in the experimental group, showing no significant difference. The most prevalent accompanied disease was cancer, followed by diabetes in both groups, with no significant difference in the incidence of these diseases between the two groups (Table 1).

The incidence rate of CAUTI (more than $10^5$ CFU/ml bacteria in urine culture analysis) was seen in 33 out of 177 patients (18.6%). Although it was lower in the experimental group—14 patients (15.2%) compared with the control group—19 patients (22.4%), this difference was not statistically significant ($P = 0.223$). The CAUTI incidence rate was further analysed according to the duration of catheterisation by dividing the patients into catheterisation group 1–4 days, and catheterisation group 5–7 days. It was shown that the 1–4 days group had CAUTI in 3 of 46 control patients (6.5%) and 2 of 34 experimental patients (5.9%), showing a significantly lower rate in the experimental group but this was not statistically significant ($P = 0.642$). The incidence rate of CAUTI in the 5–7 days group was 16 of 39 control patients (18.8%) and 12 of 58 experimental patients (13.0%), showing a significantly lower rate in the experimental group ($P = 0.030$) (Table 2).

The time (period) when CAUTI occurred was examined in order to determine the effects of nitrofurazone-coated catheter.
catheter compared to patients who were inserted with silicone catheters. CAUTI was more prevalent after urinary catheterisation when the duration of insertion was longer, but was lower in the experimental group compared with the control group (not statistically significant; \( P = 0.088 \)). Although the incidence rate of CAUTI was lower in the 1–4 days group, as the period of catheterisation was longer in the experimental group compared with the control group, this difference was not statistically significant (\( P = 0.224 \)). The incidence rate of CAUTI in the 5–7 days group was however significantly lower in the experimental group compared with the control group even when the period of catheterisation was longer (\( P = 0.026 \)) (Fig. 1).

The other variables such sex, age, current disease, treatment history and use of drugs showed no significant differences (using multivariate analysis) in the incidence rate of CAUTI between control and experimental groups. When logistic regression analysis was performed by controlling the overall demographic variables, the two variables of age and period of insertion, affected the incidence rate of CAUTI significantly. The odds ratio increased as the age increased and the period of catheterisation being longer.

A total of 40 causative microorganism strains were identified in CAUTI. Mixed infection involving more than two organisms was observed in five patients. Eighteen strains (45.0%) were Gram-positive bacteria with *Enterococcus* species being the most prevalent; 22 strains (55.0%) were Gram-negative bacteria with *Pseudomonas* species being the most prevalent (Table 3).

**Table 3**

<table>
<thead>
<tr>
<th>Organisms causing CAUTI</th>
<th>Silicone catheter</th>
<th>Nitrofurazone-coated catheter</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive bacteria</td>
<td></td>
<td></td>
<td>18 (45.0)</td>
</tr>
<tr>
<td><em>Enterococcus</em> species</td>
<td>7</td>
<td>2</td>
<td>9 (22.5)</td>
</tr>
<tr>
<td><em>E. faecalis</em></td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><em>E. gallinarum</em></td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Coagulase-negative</td>
<td>5</td>
<td>1</td>
<td>6 (15.0)</td>
</tr>
<tr>
<td><em>Staphylococcus</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-negative bacteria</td>
<td></td>
<td></td>
<td>22 (55.0)</td>
</tr>
<tr>
<td><em>Pseudomonas</em> species</td>
<td>9</td>
<td>3</td>
<td>12 (30.0)</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><em>P. fluorescens</em></td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><em>Stenotrophomonas</em></td>
<td>0</td>
<td>4</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td><em>multophilia</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others*</td>
<td>3</td>
<td>6</td>
<td>6 (15.0)</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>16</td>
<td>40 (100)</td>
</tr>
</tbody>
</table>

SEM showed no bacterial infection or biofilm on relatively clean catheter surface in both groups undergoing catheterisation for 1–4 days. However, bacterial colonies together with biofilm formation were seen in those who were catheterised for 5–7 days in both control and experimental groups (Fig. 2A). Although bacteria were observed on catheter surface in the experimental group, the surface was relatively clean with inhibited biofilm formation (Fig. 2B).

Although burning sensation was reported in one patient (1.2%) in the control group and in six patients (6.5%) in the experimental group, this difference was not statistically significant (\( P = 0.118 \)). No problem was observed in the retention of catheter due to this complication.

**4. Discussion**

Urinary catheterisation is a common practice in the process of treating various diseases and is required in about 15% of hospitalised patients [12]. However, bacteriuria is seen about 30% of hospitalised patients requiring urinary catheterisation [13–15]. The risk of CAUTI is related to the method of catheter insertion, insertion period, post-catheterisation management and patient health status.

CAUTI results from ascending bacterial colonisation within biofilm on the inner or outer surface of the catheter [16]. Two types of bacteria, planktonic and sessile may exist in the infected bladder, and elicit the inflammatory response that results in acute and chronic cystitis with pyuria [17]. Sessile biofilm-bacteria appear to be resistant to antibiotics [18]. The biofilm also acts as a mechanical barrier, protecting the entrapped bacteria from natural host defense mechanisms and antibiotic activity [19,20].
Fig. 2. Scanning electron micrographs of the catheter surface from patients catheterised for 7 days with a silicone urinary catheter (A) and a nitrofurazone-coated catheter (B). In (A), thick biofilms of bacteria cover the entire surface of the catheter with many rod-shaped bacterial cells. In (B), there are relatively clean exposed regions of catheter surface despite few biofilm with some rod-shaped bacterial cells.

Administration of systemic antibiotics may kill planktonic bacteria within the urine and reduce the initial rate of catheter-associated bacteriuria. It does not, however, eradicate sessile biofilm-bacteria except when a very high dose of antibiotic could kill the biofilm-bacteria on a catheter [21]. The use of catheters coated with drugs showing antibiotic action against bacteria on catheter surface would aid in decreasing the occurrence of CAUTI.

Nitrofurazone is a nitrofuran derivative, similar to nitrofurantoin, and have been used for more than 40 years in the treatment of urinary tract infection. It is a broad-spectrum antibiotic, active against most Gram-positive and -negative bacteria, excepting *Pseudomonas* species. The present study compared the effects of nitrofurazone-coated catheter on inhibiting CAUTI and also its safety compared with existing silicone catheters. The nitrofurazone-coated catheter is coated with nitrofurazone silicone matrix in the lumen and outer surface at 10.2–2.0 μg/mm². This catheter is known to release more than 50 mg/l nitrofurazone for 44 days in vitro and to have an inhibitory effect against most bacteria related with CAUTI. The drug can be released at the catheter surface into the urethra for more than 30 days after insertion [22].

Johnson et al. [23] reported that silver hydrogel-catheter inhibited the growth of Gram-positive bacteria including *Staphylococcus* species for less than 1 day in vitro, whereas nitrofurazone-coated catheter persistently inhibited the growth of the major causative organisms of CAUTI including *E. coli*, *Klebsiella pneumoniae*, *Citrobacter freundii*, *Staphylococcus* species, and *Enterococcus faecium* for 2–5 days. In the present study, the most prevalent causative organisms of CAUTI were *Enterococcus* and *Pseudomonas* species. We could not determine information on presence and rate of resistant bacteria since we did not perform susceptibility studies on the organisms isolated.

The incidence rate of CAUTI is closely related with the period catheter retention but fortunately, most urinary catheters are retained only for short periods of time [24]. According to a large clinical study on urinary catheters, catheter was removed within 7 days in most patients requiring catheter insertion and only 5% of these patients required retention for more than 7 days [25]. The incidence rate of CAUTI is very low within the 5 days of catheter insertion provided that the catheter was inserted aseptically and a closed drainage system was maintained [24]. In the present study, the CAUTI incidence rate in the 1–4 days catheterisation group was 6.3% (in five of 80 patients), which was significantly lower than 18.6%, the rate seen in all patients. No incidence of CAUTI, especially, was seen in patients who maintained the catheters for more than 1 day but less than 2 days. Therefore, considering that most urinary catheters are used within 7 days, the retention of catheters for a short period of time (especially in inhibiting CAUTI between 5–7 days of insertion) would be important in actual clinical settings. According to the results of the present study, the incidence rate of CAUTI was lower in the nitrofurazone-coated catheter (experimental) group compared to that in the control group, although the difference was not statistically significant. However, when the catheters were maintained for more than 5 days but less than 7 days the rate was statistically significantly lower in the experimental group compared with that in the control group. Furthermore, the incidence rate of CAUTI in the 5–7 days catheterisation group was lower in the experimental group compared with the control group even when the insertion period was longer. This result is clinically important since the effect of inhibiting CAUTI was proven during the clinically important period of CAUTI expression between 5–7 days of catheterisation. Recently, Maki and Tambyah [26] reported the same results that novel urinary catheters impregnated with nitrofurazone or minocycline and rifampin significantly reduced the risk of CAUTI for short-term catheterisations not exceeding 2–3 weeks. We need to
Further confirm the effectiveness of nitrofurazone-coated catheter during insertion periods longer than 7 days. Local side effects of nitrofurazone coating were rare (1.2%) and generally related with skin response [27]. There was no significant difference related to side effects between the two groups in this study.

We conclude that nitrofurazone coating could inhibit the expression of CAUTI by inhibiting the formation of biofilm that could occur in the presence of indwelling urinary catheter. The incidence rate of CAUTI was especially lower in those patients requiring the retention of urinary catheter for 5–7 days and in older patients by the use of nitrofurazone-coated catheter compared with existing silicone catheters. Release Nitrofurazone Foley Catheter may be used effectively in clinical settings with no specific side effects and lower the incidence rate of CAUTI.

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References