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Original article

Evaluation of antimicrobial prophylaxis against postoperative infection after spine surgery: Limit of the first generation cephem

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ABSTRACT

In our department, first-generation cephem (CEZ) are generally administered for 2 days as antimicrobial prophylaxis (AMP) for spinal surgery. However, the incidence of surgical site infection (SSI) has recently increased, particularly cases involving coagulase-negative Staphylococci (CNS) as an etiologic agent.

The objective was to elucidate the problems with the current AMP and the risk factors of SSI through a retrospective investigation of affected cases.

The subjects were patients who underwent spine surgery at our department between August 2007 and June 2013. The subjects were divided into those who developed SSI (S group) and who did not develop SSI (non-SSI (N) group), patients who developed CNS infection in the S group was subdivided as C group, and the risk factors were investigated. The significance of each factor was analyzed using cross tabulation, and multivariate logistic regression analyses were performed with 22 of the investigation factors as explanatory variables.

The incidence of SSI was 2.55%, and the etiologic agent was CNS in 17 patients. Upon comparison between the S and N groups, the presence of 3 or more underlying diseases and blood loss were extracted as significant risk factors. Upon comparison between the C and N groups, emergency surgery and intra- and postoperative steroid administration were extracted as significant risk factors, in addition to the presence of 3 or more underlying diseases and blood loss.

The effect of the current AMP using first generation cephem is limited, and reconsideration of the protocol may be necessary.

1. Introduction

Regarding antimicrobial Prophylaxis (AMP) for spinal surgery, the Centers for Disease Control and Prevention (CDC) published guidelines for the prevention of Surgical Site Infection (SSI) in 1999 [13], and guidelines for the prevention of postoperative bone and joint infections were prepared in Japan in 2006. With reference to these guidelines, the Toho University spine group prepared an AMP protocol comprised of Cefazolin (CEZ) administration for 2 days including the day of operation and has applied it since 2007.

Our countermeasures against SSI for spinal surgery were: shortening of preoperative hospital stay, abolition of shaving, cleaning of the surgical field with povidone iodine before surgery, initial administration of 1 g of CEZ at the time of introduction of anesthesia, additional administration every 2–3 h during surgery, cleaning of the surgical field with saline every hour during surgery, disinfection of the hands and changing gloves every 3 h during a long surgery, and additional CEZ administration every 6–8 h after surgery for a maximum of 2 days including the day of operation.

However, the incidence of SSI after the introduction of these countermeasures in 2007 was 2.55%, which is not low. The time between surgery and on set SSI was 2–143 days, average of 13.5 days. The most frequent etiologic agent was *Staphylococcus epidermidis*, and coagulase-negative Staphylococci (CNS) including *S. epidermidis* accounted for more than half of the cases 58.6%.

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The objective of this study was to retrospectively investigate SSI cases following spinal surgery at our hospital and to assess the current AMP and its problems and limitations.

2. Patient and methods

Of 1180 patients who underwent spinal surgery performed by the Toho University spine group between August 2007 and June 2013, 1137 patients, excluding those with spinal infection and those underwent percutaneous surgery, were selected as the subjects. There were 638 male and 499 female patients, and the mean age was 61.3 (7–91) years old.

SSI was determined according to the Center for Disease Control and Prevention (CDC) definition [13]. The subjects were divided into those who developed SSI (S group) and who did not develop SSI (non-SSI (N) group) SSI, and patients who developed CNS infection in the S group were further divided into the CNS infection group (C group).

Risk factors of SSI were analyzed by comparison between the S and N groups and between the C and N groups.

The investigation factors were: advanced age, gender, presence or absence of DM and collagen disease, multiple spine surgeries, history of cigarette smoking, excess alcohol consumption, BMI, malnutrition, 3 or more underlying diseases, trauma, bladder and rectal disturbance, serious paralysis (Frankel > C), duration of preoperative hospital stay (>7 or ≤7 days), emergency surgery, operative time (min), blood loss (ml), multilevel spinal surgery, anterior surgery, presence or absence of instrumentation, drainage volume (ml), use of steroid, blood transfusion, and admission to ICU(Table 1). BMI (22>; 0, ≥22–25>; 1, ≥25–30>; 2, ≥30; 3), operative time (120 min>; 0, ≥120–300>; 1, ≥300; 2), blood loss (100 ml>; 0, ≥100–300>; 1, ≥300–1000>; 2, ≥1000; 3), and drainage volume (100 ml>; 0, ≥100–300>; 1, ≥300–1000>; 2, ≥1000; 3) were converted to data staged at each cut-point. The significance of each factor was analyzed employing cross tabulation, and multivariate logistic regression analyses were performed. In the analysis, firstly, forced input analysis with all items was performed, followed by extraction of significant risk factors using the stepwise method. Specifically, the forward selection method and backward elimination method were applied, and the p-value, odds ratio, and its 95% confidence interval of each factor were determined. For statistical analysis software, IBM SPSS Statistics, Version 19 (IBM Co. Ltd., USA) was used.

This study was approved by the ethics committee of Toho University School of Medicine (approval number: 27077).

3. Results

On comparison between the S and N groups, significant differences were noted on cross tabulation for the presence of 3 or more underlying diseases ($p = 0.001$), operative time ($p < 0.001$), blood loss ($p < 0.001$), number of surgically treated intervertebral segments ($p = 0.012$), anterior surgery ($p = 0.031$), instrumentation ($p = 0.004$), drainage volume ($p = 0.001$), use of steroid ($p = 0.033$), blood transfusion ($p = 0.021$), and admission to ICU ($p < 0.001$) (Table 2). In the analysis using forced input of all variables, the presence of 3 or more underlying diseases (OR: 3.93; CI: 1.65–9.37; $p = 0.002$) and blood loss (OR: 1.90; CI: 1.00–3.60; $p = 0.050$) were extracted. In the analysis using the forward selection method, significant differences were noted for the presence of 3 or more underlying diseases (OR: 4.12; CI: 1.88–9.04; $p < 0.001$) and blood loss (OR: 2.42; CI: 1.59–3.68; $p < 0.001$), and a tendency toward significance was noted for the anterior surgery ($p = 0.080$). When the analysis was conducted using the backward elimination method, significant differences were noted for the presence of 3 or more underlying diseases (OR: 3.94; CI: 1.80–8.61; $p = 0.001$) and blood loss (OR: 2.40; CI: 1.58–3.65; $p < 0.001$), and a trend toward significance was noted for the use of steroid ($p = 0.075$) (Table 3). In comparison between the C and N groups, significant differences were noted on cross tabulation for the presence of 3 or more underlying diseases ($p = 0.012$), emergency surgery ($p = 0.017$), operative time ($p < 0.001$), blood loss ($p < 0.001$), number of surgically-treated intervertebral segments ($p = 0.048$), instrumentation ($p = 0.041$), drainage volume ($p = 0.019$), and use of steroid ($p = 0.010$) (Table 4). In the analysis using forced input of all variables, advanced age (OR: 4.95; CI: 1.14–21.56; $p = 0.033$) and

Table 1
Patient characteristics.

	N-group	S-group	C-group
Number	1108	29	17
Advanced age (range)	61.3 (7–91)	61.5 (15–81)	64.1 (15–81)
Gender (male/female)	622/486	16/13	9/8
DM (%)	182 (16.4)	2 (6.9)	1 (5.9)
Collagen disease (%)	72 (6.5)	3 (10.3)	2 (11.8)
Multiple spinal surgeries (%)	149 (13.5)	7 (24.1)	5 (29.4)
History of cigarette smoking (%)	320 (31.2)	8 (27.6)	5 (29.4)
Excessive alcohol consumption (%)	48 (4.7)	2 (6.9)	1 (5.9)
BMI (range)	24 (13.7–43.7)	24.8 (18.2–34)	26.1 (19.1–34)
Malnutrition (%)	103 (9.3)	2 (6.9)	2 (11.8)
3 or more underlying diseases (%)	225 (20.4)	14 (48.3)	8 (47.1)
Trauma (%)	21 (1.9)	1 (3.4)	1 (5.9)
Bladder and rectal disturbance (%)	29 (2.6)	0	0
Serious paralysis (%)	72 (6.5)	2 (6.9)	2 (11.8)
Duration of preoperative hospital stay (range)	4.2 (0–196)	5.7 (0–49)	7.4 (0–49)
Emergency surgery (%)	96 (8.7)	4 (13.8)	4 (23.5)
Operative time (range)	167 (20–663)	284 (80–586)	290 (102–586)
Blood loss (range)	298 (0–8160)	1130 (0–6710)	1163 (0–6710)
Multilevel spinal surgery (range)	2.2 (1–14)	4.2 (1–13)	3.7 (1–13)
Anterior surgery (%)	56 (5.1)	2 (6.9)	0
Instrument (%)	483 (43.6)	21 (72.4)	12 (70.6)
Drainage volume (range)	321 (0–2946)	571 (0–1630)	499 (35–1440)
Use of steroid (%)	346 (31.4)	14 (48.3)	10 (58.8)
Blood transfusion (%)	329 (29.8)	15 (51.7)	8 (47.1)
Admission to ICU (%)	40 (3.6)	5 (17.2)	2 (11.7)

Table 2
Cross tabulation, S group vs. N group.

Investigation factors	p-Value
Advanced age	0.259
Gender	0.921
DM	0.115
Collagen disease	0.481
Multiple spinal surgeries	0.151
History of cigarette smoking	0.835
Excessive alcohol consumption	0.548
BMI	0.793
Malnutrition	0.582
3 or more underlying diseases	0.001
Trauma	0.394
Bladder and rectal disturbance	0.386
Serious paralysis	0.899
Duration of preoperative hospital stay	0.699
Emergency surgery	0.229
Operative time	<0.001
Blood loss	<0.001
Multilevel spinal surgery	0.012
Anterior surgery	0.031
Instrument	0.004
Drainage volume	0.001
Use of steroid	0.033
Blood transfusion	0.021
Admission to ICU	<0.001

Table 4
Cross tabulation, C group vs. N group.

Investigation factors	p-Value
Advanced age	0.077
Gender	0.794
DM	0.187
Collagen disease	0.441
Multiple spinal surgeries	0.087
History of cigarette smoking	0.997
Excessive alcohol consumption	0.79
BMI	0.382
Malnutrition	0.81
3 or more underlying diseases	0.012
Trauma	0.145
Bladder and rectal disturbance	0.507
Serious paralysis	0.363
Duration of preoperative hospital stay	0.27
Emergency surgery	0.017
Operative time	<0.001
Blood loss	<0.001
Multilevel spinal surgery	0.048
Anterior surgery	0.602
Instrument	0.041
Drainage volume	0.019
Use of steroid	0.01
Blood transfusion	0.168
Admission to ICU	0.093

blood loss (OR: 2.88; CI: 1.17–7.05; $p = 0.021$) were extracted, and tendencies toward significance were noted for the presence of 3 or more underlying diseases ($p = 0.056$), emergency surgery ($p = 0.074$), and use of steroid ($p = 0.062$). In the analyses using the forward selection and backward elimination methods, significant differences were noted for the presence of 3 or more underlying diseases (OR: 3.06; CI: 1.13–8.28; $p = 0.028$), emergency surgery (OR: 3.81; CI: 1.144–12.66; $p = 0.029$), blood loss (OR: 2.99; CI: 1.71–5.23; $p < 0.001$), and use of steroid (OR: 3.33; CI: 1.22–9.10; $p = 0.019$) (Table 5). Based on the above findings, the presence of 3 or more underlying diseases and blood loss were extracted as risk factors of SSI, and emergency surgery and use of steroid were also included among the risk factors when the etiologic agent was CNS.

4. Discussion

The CDC reported that the incidence of SSI following spinal surgery is 0.72–4.1% for all spine surgeries and 3.2–4.1% for spinal fusion [13]. In Japan, the incidence was 3.73% for spinal instrumentation surgery performed at 2241 Japanese Orthopaedic Association-certified training facilities [16] and 1.1% in a survey of 31,380 patients reported by the Japanese Society for Spinal surgery and Related Research [9]. Smith et al. recently reported that the incidence was 2.1% in a survey of 108,419 patients [21]. The incidence of SSI at our department since 2007 was 2.55% (29/1137 patients), and it may have been due to recent aging of the patients, advances in spinal instrumentation surgery, and the accompanying expansion of the indication for spinal fusion. Therefore, we considered that extraction of problems with the current AMP is necessary and countermeasures must be developed against these limitations.

The characteristic among the SSI cases of our department is the etiologic agent. In general, Methicillin-sensitive Staphylococcus Aureus (MSSA) is the frequent etiologic agent, but it was not detected amongst our population. *S. epidermidis* was detected in 10 patients, being the most frequent, and CNS including *Staphylococcus capitis* was the etiologic agent in 17 patients, accounting for more than half of the cases(Fig. 1). Moreover, the CNS was CEZ-resistant MRCNS in 15 (88.2%) of the 17 patients on bacterial culture drug-sensitivity tests, suggesting that the AMP protocol of our department is effective against MSSA but ineffective against CNS. CNS, represented by *S. epidermidis*, are low-virulent indigenous

Table 3
Multivariate logistic regression analysis of S group vs. N group.

Investigation factors	p-Value	Odds ratio	95% confidence interval of odds ratio	
			Lower limit	Upper limit
Forced input of all variables				
3 or more underlying diseases	0.002	3.93	1.65	9.37
Blood loss	0.05	1.9	1	3.6
Forward selection method				
3 or more underlying diseases	<0.001	4.12	1.88	9.04
Blood loss	<0.001	2.42	1.59	3.68
Anterior surgery	0.06	4.38	0.93	24
Backward elimination method				
3 or more underlying diseases	0.001	3.94	1.8	8.61
Blood loss	<0.001	2.4	1.58	3.65
Use of steroid	0.075	2.01	0.93	4.33

Table 5
Multivariate logistic regression analysis of C group vs. N group.

Investigation factors	p-Value	Odds ratio	95% Confidence interval of odds ratio	
			Lower limit	Upper limit
Forced input of all variables				
Advanced age	0.033	4.95	1.14	21.56
3 or more underlying diseases	0.056	3.07	0.97	9.74
Emergency surgery	0.074	4.73	0.86	26.09
Blood loss	0.021	2.88	1.17	7.05
Use of steroid	0.062	2.92	0.95	8.98
Forward selection method/backward elimination method				
3 or more underlying diseases	0.028	3.06	1.13	8.28
Emergency surgery	0.029	3.81	1.14	12.66
Blood loss	<0.001	2.99	1.71	5.23
Use of steroid	0.019	3.33	1.22	9.1

bacteria that are able to become an etiologic agent in compromised hosts. The detection frequency of methicillin-resistant CNS is generally reported to be about 60–80% [18]. It remains controversial whether CNS detected in surgical wounds should be regarded as contamination with indigenous bacteria or an etiologic agent of infection, but vancomycin (VCM) administration (88.2%; 15/17 cases) and wound cleansing/debridement (47.1%; 8/17 cases) were effective for all patients. None of the patients required implant removal, and inflammatory reactions were improved, suggesting that CNS should be regarded as pathogen.

In general, the risk factors of SSI include advanced age, DM, collagen disease, MOB, history of cigarette smoking, excess alcohol consumption, distribution of body mass, malnutrition, and compromised host on patient's side, and surgical stress (operative time, blood loss, and range of surgery), concomitant use of instruments, and the type of antimicrobial prophylaxis on the medical care side [3,4,6,17,19,20]. Our study clarified the involvement of compromised hosts, because the presence of 3 or more underlying diseases was extracted as a factor on the patient's side, and the involvement of surgical stress because blood loss, emergency surgery, and use of steroid before and after surgery were extracted as factors on the medical care side.

For countermeasures, a new AMP targeting MRCNS should be prepared for the cases that are at high risk of SSI [1,18]. Specifically, changes in antimicrobial prophylaxis and additional administrations are necessary, and VCM should be considered as the antimicrobial agent. However, the CDC recommends that VCM should not be used routinely, as a prophylactic antimicrobial agent [2]. There have also been reports that prophylactic VCM use in the wound bed in spinal surgery could increase the incidence of gram-negative or polymicrobial spinal infection [7], that VCM could be effective as an AMP protocol for MRSA carriers [12], and that there are no established criteria for prophylactic administration of VCM [24]. Thus, no consensus has been reached regarding the use of VCM. Regarding the method of VCM administration, it is necessary to compare the efficacy of intravenous administration vs. intrawound VCM powder, which has been frequently reported [25]. For intravenous VCM administration, the CDC guidelines recommend the dose and duration of administration immediately before surgery and up to two additional doses in case of surgeries that last longer than 6 h

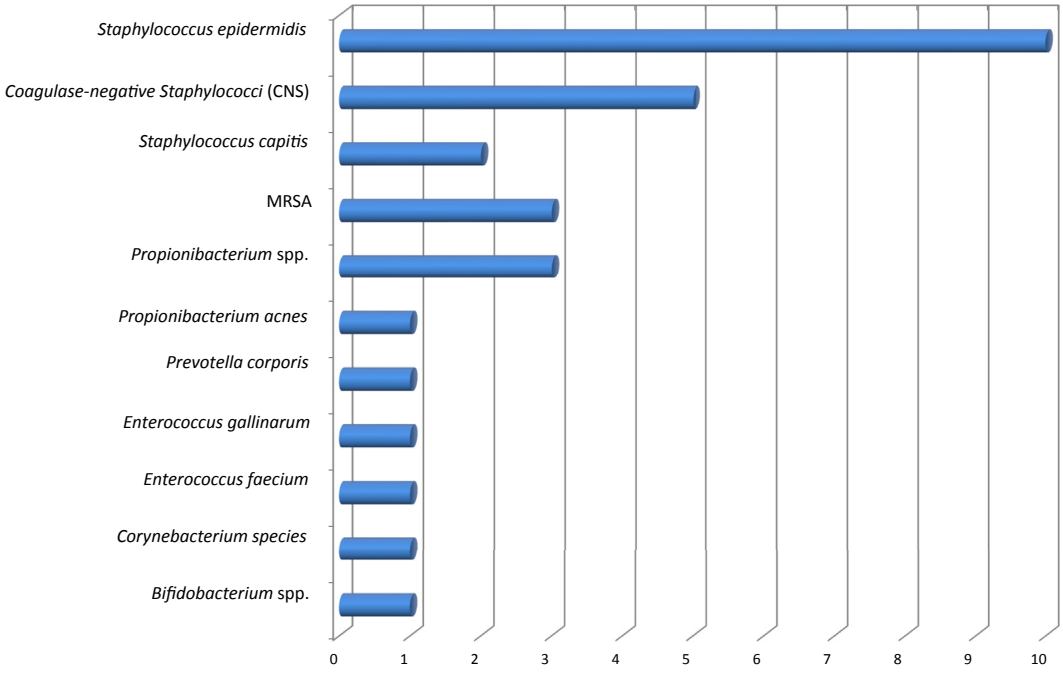

Fig. 1. Etiologic agents of SSI in our department.

[2]; however, no consistent viewpoint has been presented in the protocols of the reported cases. The use of intrawound VCM powder remains controversial; some studies have reported its effectiveness [5,8,11,22] but many others have reported that it was ineffective [10,14,15,23]. Furthermore, the intrawound VCM powder dose was not consistent between reports.

Thus, the Toho University spine group is currently investigating the appropriate criteria for the application of an AMP protocol using VCM. We are planning to score the risk factors for SSI based on the results of this study, to establish a protocol for the use of VCM in limited cases with scores above a specific level, and to confirm whether or not the prospective use reduces the incidence of SSI.

In conclusion, SSI was investigated in 1137 patients who underwent spinal surgery at our department. The incidence of SSI after treatment with the current AMP was 2.55%. Risk factors for SSI were the presence of 3 or more underlying diseases and blood loss, and in cases in which the etiologic agent was CNS, emergency surgery and use of steroid were also risk factors. The etiologic agent was MRCNS in many cases, and CNS control by the current AMP remains limited. It may be necessary to establish a new AMP protocol focusing on VCM for patients at high-risk of SSI.

Conflict of interest statement

None declared.

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None.

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