Original Article

In-hospital mortality among patients with invasive non-group A β-hemolytic Streptococcus treated with clindamycin combination therapy: a nationwide cohort study

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Aim: Combination treatment with clindamycin is recommended in patients with invasive group A *Streptococcus* infection; however, whether the same treatment is effective in invasive group B *Streptococcus* and *S. dysgalactiae* subspecies *equisimilis* infections remains unknown. We aimed to investigate whether clindamycin added to standard of care therapy would be effective in patients with invasive non-group A β-hemolytic *Streptococcus* infections.

Methods: This was a nationwide retrospective cohort study using the Japanese Diagnosis Procedure Combination inpatient database focusing on the period between 2010 and 2018. We extracted data on patients diagnosed with sepsis due to non-group A β-hemolytic *Streptococcus*. One-to-four propensity score-matching was undertaken to compare patients who were treated with clindamycin within 2 days of admission (clindamycin group) and those who did not (control group). The primary outcome was in-hospital mortality.

Results: We identified 3754 eligible patients during the study period. The patients were divided into the clindamycin (n = 296) and control groups (n = 3458). After one-to-four propensity score matching, we compared 289 and 1156 patients with and without clindamycin, respectively. In-hospital mortality did not significantly differ between the two groups (9.7% versus 10.3%; risk difference 0.3%; 95% confidence interval, –3.5% to 4.2%).

Conclusions: This nationwide database study showed that combination therapy involving the use of clindamycin was not associated with lower in-hospital mortality in patients with invasive non-group A β-hemolytic *Streptococcus*.

Key words: β-Hemolytic Streptococcus, clindamycin, invasive Streptococcus infection, Streptococcus agalactiae, Streptococcus dysgalactiae subspecies equisimilis

INTRODUCTION

INVASIVE β-hemolytic *Streptococcus* infection is defined as the isolation of β-hemolytic *Streptococcus* from a normally sterile site (i.e., blood, cerebrospinal fluid, joint fluid, or pleural effusion) resulting in a range of severe disease including sepsis syndrome, bacteremia, meningitis, and deep soft tissue infection.[1] Increases in the numbers of patients with invasive β-hemolytic *Streptococcus* infection have been reported in several countries, including Japan.[2–5] Invasive β-hemolytic *Streptococcus* infection is primarily

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caused by *S. pyogenes*, *S. agalactiae*, and *S. dysgalactiae* subspecies *equisimilis* (SDSE).[6] *Streptococcus pyogenes* has Lancefield group A antigens and is called group A *Streptococcus* (GAS). *Streptococcus agalactiae* has Lancefield group B antigens and is called group B *Streptococcus* (GBS). Streptococci that have Lancefield group C and G antigens include the following: SDSE; *S. canis*, *S. dysgalactiae* subsp. *dysgalactiae*, *S. equi* subsp. *equi*, and *S. equi* subsp. *zooepidemicus*.[7]

Treatment with clindamycin in combination with penicillin is recommended for invasive GAS infection.[8] Previous studies suggest that clindamycin has a longer acting post-antibiotic effect than β-lactams such as penicillin, suppresses bacterial toxin synthesis, inhibits the enzyme associated with cell wall synthesis, disrupts lipopolysaccharide-induced cytokine production, is not affected by inoculum size or stage of growth like penicillin, and facilitates GAS phagocytosis in subinhibitory concentrations.[9–13] These purported mechanisms are based on *in vitro* and animal studies; however, the number of clinical investigations published to date are limited. Observational studies have suggested that clindamycin is effective for invasive GAS infections.[14–17]

While combination therapies are recommended in invasive GAS infections, the fundamental treatment for non-group A β-hemolytic *Streptococcus* (NGAS) remains penicillin monotherapy.[8] Although a number of case reports suggest the potential benefits of adding clindamycin for invasive GBS,[18] no large-scale clinical investigations have interrogated the subject of clinical outcomes in patients treated with combination clindamycin therapy in invasive NGAS infections. Given the drug's efficacy in GAS infections, we hypothesized that additional clindamycin therapy would be effective in patients with invasive NGAS infections.

METHODS

Data source

THE PRESENT STUDY is a retrospective cohort study using the Japanese Diagnosis Procedure Combination inpatient database. Approximately 7 million admissions from over 1,200 health-care facilities are reflected in the database annually. Participating health-care facilities account for approximately 90% of all tertiary-care emergency hospitals, 44% of institutions certified by the Japanese Surgical Society, and 80% of institutions certified by the Japanese Association for Infectious Diseases for board specialist training.[19]

The database contains the following information for each patient: date of admission and discharge, sex, age, height, weight, diagnoses, comorbidities at admission, complications after admission, level of consciousness at admission, procedures, medications and devices used and discharge status. Diagnoses are recorded using the International Classification of Diseases, 10th Revision (ICD-10) codes with text data entered in Japanese. Level of consciousness on admission was evaluated using the Japan Coma Scale. Assessments by the Japan Coma Scale and Glasgow Coma Scale have been evaluated and shown to correlate well.[20] A previous study showed that the validity of diagnoses and procedure records in the database was high in general.[21]

Patient selection

We identified data on patients discharged from the hospital between the period of July 2010 to March 2018 with the diagnoses of "sepsis due to *Streptococcus* group B" (ICD-10 code A401) and "other *Streptococcus* sepsis" (A408). The code A408 is classified as "sepsis due to *Streptococcus* group C or G" in Japan. No diagnosis equivalent to invasive NGAS streptococcal infections is available in ICD-10 and therefore we adopted "sepsis due to *Streptococcus* group B" and "sepsis due to *Streptococcus* group C or G" in order to identify invasive streptococcal infections in the database. Because SDSE has been isolated in approximately 80% of patients with group C and G *Streptococcus* sepsis,[4] we defined GBS and SDSE as NGAS. We excluded patients who were under the age of 16 years and who were discharged within 2 days of admission to avoid immortal time bias.

Patient characteristics and outcomes

Patient characteristics included age, sex, diagnoses (cellulitis, ICD-10 code L03x; necrotizing fasciitis, M726; arthritis, M002 and M009; bacteremia, A491 and A499; osteomyelitis, K102, M462, and M86x; empyema, J86x; and endocarditis, I330), procedures performed within 2 days of admission (mechanical ventilation, renal replacement therapy, polymyxin B hemoperfusion, blood transfusion, surgery, and direct measurement of arterial pressure), drugs used within 2 days of admission (vasopressor, i.v. immunoglobulin, penicillin G, combination antibiotics containing penicillin and β-lactamase inhibitor, clindamycin, first-generation cephalosporins, second-generation cephalosporins, third-generation cephalosporins, fourth-generation cephalosporins, carbapenem, glycopeptide, and linezolid), body mass index, level of consciousness at admission (Japan Coma Scale), history of hypertension and diabetes, Charlson comorbidity index (CCI), ambulance use, hospitalization in a teaching hospital, and intensive care unit stay within

2 days of admission. We categorized body mass index into four groups: underweight, <18.5; normal weight, 18.5–24.9; overweight, 25–29.9; and obese, ≥30. Level of consciousness at admission (Japan Coma Scale) was categorized into four groups: 0, alert consciousness; 1–3, awake without any stimuli; 10–30, respond to some stimuli; and 100–300, coma. The CCI is a weighted composite score of comorbidities that is widely used to measure case mixes and disease burdens. We categorized the total score of CCI into four groups as previously reported: 0, 1, 2, and ≥3.[22]

We compared patients who received clindamycin within 2 days of admission (clindamycin group) and those who did not (control group). The primary outcome was in-hospital mortality.

Statistical analysis

Propensity score matching was undertaken to minimize confounding by indication and prevent an unbalanced background between the clindamycin and control groups. We estimated the propensity scores by fitting a logistic regression model for clindamycin treatment within 2 days of admission as a function of the background for the above-mentioned patient characteristics, procedures, and treatments. Using the estimated propensity scores, we used nearest-neighbor one-to-four matching with replacement. The caliper width was set at 20% of the standard deviation of the estimated propensity scores.[23] The balance between the two groups was evaluated by the absolute value of standardized differences. We defined unbalanced background as the value of standardized differences more than 10%.[23]

Continuous variables were reported as median and interquartile range and categorical variables were reported as count and percentage. The outcomes were compared using the χ^2-test. The threshold for significance was a *P*-value of 0.05. All statistical analyses were carried out using Stata/MP 15 (Stata, College Station, TX, USA).

RESULTS

THE PROCESS AND flow of patient selection is shown in Figure 1. We identified 3,754 eligible patients during the study period. The patients were divided into the clindamycin group (n = 296) and control group (n = 3,458). After one-to-four propensity score matching we compared 289 and 1,156 patients with and without clindamycin, respectively. Three patients in the clindamycin group matched the control group at one-to-three. The C-statistic of the logistic regression model was 0.81.

Table 1 shows the baseline characteristics of patients before and after propensity score matching. The patient characteristics were almost balanced between the two groups

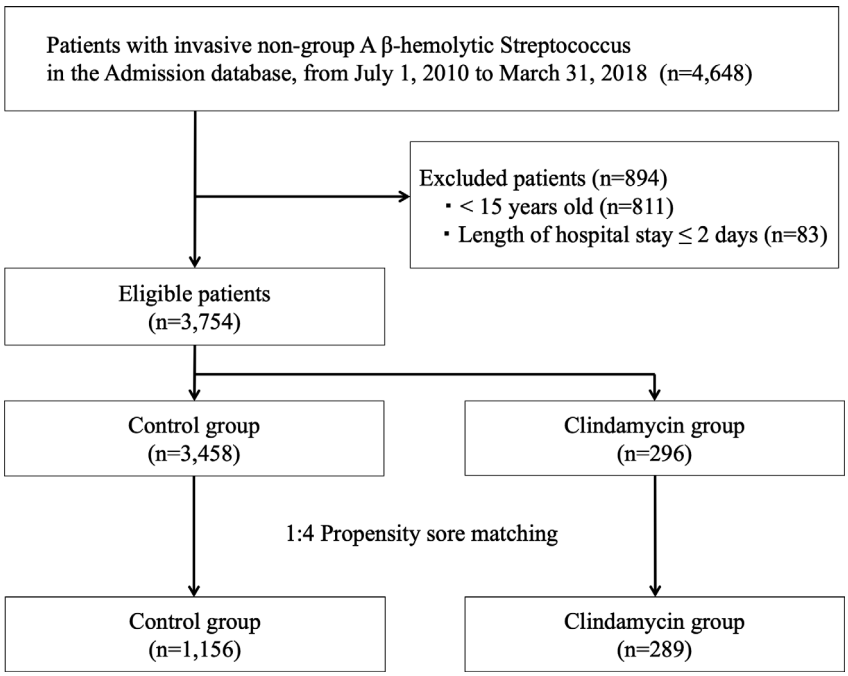

Fig. 1. Flow of patient selection to evaluate in-hospital mortality among patients with invasive non-group A β-hemolytic *Streptococcus* treated with clindamycin combination therapy.

Table 1. Characteristics of patients with invasive non-group A β-hemolytic *Streptococcus*, treated with or without clindamycin combination therapy, before and after propensity score matching

Variable	Before propensity score matching			After propensity score matching		
	Control group (*n* = 3,458)	Clindamycin group (*n* = 296)	ASD (%)	Control group (*n* = 1,156)	Clindamycin group (*n* = 289)	ASD (%)
Age, years; median (IQR)	79 (68–86)	74 (60.5–83)	29.9	73 (61–82)	74 (61–83)	7.3
Male sex	1,686 (48.8)	139 (47.0)	3.6	552 (47.8)	133 (46.0)	3.5
Diagnosis						
Cellulitis	661 (19.1)	132 (44.6)	56.8	507 (43.9)	130 (45.0)	2.3
Necrotizing fasciitis	23 (0.7)	40 (13.5)	51.6	116 (10.0)	34 (11.8)	5.5
Arthritis	67 (1.9)	16 (5.4)	18.5	77 (6.7)	16 (5.5)	4.7
Bacteremia	56 (1.6)	10 (3.4)	11.3	34 (2.9)	10 (3.5)	2.9
Osteomyelitis	26 (0.8)	4 (1.4)	5.9	24 (2.1)	4 (1.4)	5.3
Empyema	9 (0.3)	2 (0.7)	6.1	13 (1.1)	2 (0.7)	4.6
Meningitis	34 (1.0)	2 (0.7)	3.4	8 (0.7)	2 (0.7)	0.0
Endocarditis	121 (3.5)	3 (1.0)	16.8	4 (0.3)	3 (1.0)	8.3
Procedures undertaken within 2 days of admission						
Mechanical ventilation	142 (4.1)	24 (8.1)	16.8	76 (6.6)	21 (7.3)	2.7
Renal replacement therapy	115 (3.3)	19 (6.4)	14.4	48 (4.2)	17 (5.9)	7.9
Polymyxin B hemoperfusion	20 (0.6)	7 (2.4)	14.9	55 (4.8)	7 (2.4)	12.6
Blood transfusion	187 (5.4)	18 (6.1)	2.9	81 (7.0)	18 (6.2)	3.1
Surgery	38 (1.1)	35 (11.8)	44.6	94 (8.1)	28 (9.7)	5.5
Direct measurement of arterial pressure	186 (5.4)	46 (15.5)	33.6	144 (12.5)	42 (14.5)	6.1
Drugs used within 2 days of admission						
Vasopressor	331 (9.6)	75 (25.3)	42.4	285 (24.7)	71 (24.6)	0.2
Intravenous immunoglobulin	142 (4.1)	42 (14.2)	35.5	179 (15.5)	38 (13.1)	6.7
Penicillin G	86 (2.5)	39 (13.2)	40.5	138 (11.9)	33 (11.4)	1.6
Penicillin and β-lactamase inhibitor	876 (25.3)	93 (31.4)	13.5	359 (31.1)	90 (31.1)	0.2
First-generation cephalosporins	393 (11.4)	59 (19.9)	23.7	206 (17.8)	57 (19.7)	4.9
Second-generation cephalosporins	225 (6.5)	12 (4.1)	11.0	50 (4.3)	12 (4.2)	0.9
Third-generation cephalosporins	912 (26.4)	76 (25.7)	1.6	279 (24.1)	75 (26.0)	4.2
Fourth-generation cephalosporins	98 (2.8)	5 (1.7)	7.7	25 (2.2)	5 (1.7)	3.1
Carbapenem	623 (18.0)	85 (28.7)	25.5	334 (28.9)	83 (28.7)	0.4
Glycopeptide	297 (8.6)	39 (13.2)	14.8	127 (11.0)	38 (13.1)	6.6
Linezolid	15 (0.4)	0 (0.0)	9.3	30 (2.6)	0 (0.0)	23.1
Body mass index						
<18.5	553 (16.0)	40 (13.5)	7.0	157 (13.6)	38 (13.1)	1.3
18.5–24.9	1,684 (48.7)	139 (47.0)	3.5	543 (47.0)	135 (46.7)	0.5
25.0–29.9	563 (16.3)	50 (16.9)	1.6	213 (18.4)	50 (17.3)	2.9
≥30.0	241 (7.0)	36 (12.2)	17.7	126 (10.9)	35 (12.1)	3.8
Missing data	417 (12.1)	31 (10.5)	5.0	117 (10.1)	31 (10.7)	2.0
Japan Coma Scale						
Alert	2,302 (66.6)	190 (64.2)	5.0	777 (67.2)	186 (64.4)	6.0
Awake without any stimuli	768 (22.2)	67 (22.6)	1.0	231 (20.0)	65 (22.5)	6.1
Responded to some stimuli	245 (7.1)	25 (8.4)	5.1	102 (8.8)	25 (8.7)	0.6
Coma	143 (4.1)	14 (4.7)	2.9	46 (4.0)	13 (4.5)	2.6
Hypertension	977 (28.3)	69 (23.3)	11.3	266 (23.0)	68 (23.5)	1.2

Table 1. (Continued)

Variable	Before propensity score matching			After propensity score matching		
	Control group (*n* = 3,458)	Clindamycin group (*n* = 296)	ASD (%)	Control group (*n* = 1,156)	Clindamycin group (*n* = 289)	ASD (%)
Diabetes mellitus	788 (22.8)	86 (29.1)	14.3	335 (29.0)	82 (28.4)	1.3
Charlson comorbidity index						
0	1,196 (34.6)	109 (36.8)	4.7	401 (34.7)	106 (36.7)	4.1
1	1,059 (30.6)	90 (30.4)	0.5	336 (29.1)	88 (30.4)	3.0
2	658 (19.0)	58 (19.6)	1.4	273 (23.6)	57 (19.7)	9.4
≥3	545 (15.8)	39 (13.2)	7.3	146 (12.6)	38 (13.1)	1.5
Hospitalization by ambulance	1,614 (46.7)	166 (56.1)	18.9	641 (55.4)	160 (55.4)	0.2
Teaching hospital	2,819 (81.5)	267 (90.2)	25.1	1,045 (90.4)	260 (90.0)	1.5
Intensive care unit admission	201 (5.8)	41 (13.9)	27.2	141 (12.2)	38 (13.1)	2.9

Data are shown as number (%) unless otherwise specified.
ASD, absolute standardized difference; IQR, interquartile range.

after propensity score matching. Patients in the control group were more likely to receive linezolid.

Table 2 shows the outcomes before and after propensity score matching. Before propensity score matching, total in-hospital mortality was 12.4%. In-hospital mortality for the control and clindamycin groups were 12.6% and 9.8%, respectively. After propensity score matching, in-hospital mortality did not significantly differ between the control and clindamycin groups (9.7% versus 10.3%; risk difference, 0.3%; 95% confidence interval, –3.5% to 4.2%).

DISCUSSION

IN THE PRESENT study, we investigated the effectiveness of clindamycin on patients with invasive NGAS using a nationwide inpatient database in Japan. We applied propensity score matching to minimize confounding between the clindamycin and control groups. In-hospital mortality did not significantly differ between the two groups.

Because GAS produce several exotoxins—some of which act as superantigens—previous studies recommended combined treatment with clindamycin and baseline antibiotic therapy for invasive GAS infections with the expectations of suppressing potentially life-threatening bacterial toxin synthesis.[10] In addition to producing pyrogenic toxins, GBS is known to possess virulent factors such as alpha C-proteins, pilins, and polysaccharide capsules.[24–27] In our study we regarded group C and G *Streptococci* as SDSE, because the majority of cases resulting in sepsis due to group C and G *Streptococci* were attributed to SDSE.[4] Furthermore, genome sequence analysis indicates that SDSE closely resembles GAS with a 72% genomic similarity.[7] *Streptococcus dysgalactiae* subspecies *equisimilis* also shares a number of genes that encode virulence factors in GAS, including the antiphagocytic M protein, streptolysin O, streptolysin S, and streptokinase.[7] Additionally, NGAS is known to induce *Streptococcus* toxic shock syndrome in a manner similar to GAS, which supports the theory that certain exotoxins produced by NGAS could act as a superantigen reminiscent of

Table 2. Outcomes before and after propensity score matching among patients with invasive non-group A β-hemolytic *Streptococcus* treated with or without clindamycin combination therapy

Outcomes	In-hospital mortality, *n* (%)			*P*-value
	Overall	Control group	Clindamycin group	
Before propensity score matching	465/3,754 (12.4)	436/3,458 (12.6)	29/296 (9.8)	0.16
After propensity score matching	141/1,445 (9.8)	112/1,156 (9.7)	29/289 (10.3)	0.86

GAS exotoxins.[18] For these reasons, we hypothesized that clindamycin could also be effective for invasive NGAS infection. To our knowledge, the effect of clindamycin on invasive NGAS infections has never been dissected at the large-scale level. This is the first nationwide study investigating the effects of clindamycin on invasive NGAS infection.

Additional clindamycin treatment was not associated with lower in-hospital mortality in the present study and there are three possible reasons for this outcome. The first conceivable reason is antibiotic resistance. Group B *Streptococcus* resistance to clindamycin has been reported as in Japan as 5.3% in 2015.[28] With regard to SDSE, resistance to clindamycin was 14.1–16.2% in Japan[29,30] and 17.4% in Korea.[29] The increasing rate of resistance might have inadvertently influenced the results. Second, in the present study there was an underlying prevalence of broad-spectrum antibiotics such as carbapenem, third- and fourth-cephalosporins, and β-lactamase inhibitor antibiotics being adopted for treatment. The use of such potent antibiotics could have overshadowed the additional benefits of combined clindamycin. The third possible reason for the achieved outcome stems from the inherent limitation of clindamycin for treatment of β-hemolytic *Streptococcus* infections. Although the scientific evidence in support of clindamycin combination therapy in GAS patients is documented to some degree, the same cannot be said for NGAS. Perhaps as a result of a mechanism still unknown, clindamycin could simply be ineffective on NGAS.

There are several limitations associated with this study that should be acknowledged. First, the extracted data do not reflect all cases involving invasive NGAS because the data extraction was based on the ICD-10 codes. Invasive NGAS infections are not specifically included in the ICD-10 codes and therefore the system inherently fails to place a distinction on sepsis and invasive forms of NGAS. This could inadvertently result in a skewed patient population. However, a previous observational study undertaken in Japan showed that mortality among the adult population (≥15 years old) was 16.7% in invasive GAS, 10.8% in invasive GBS, and 12.7% in invasive SDSE infections.[6] The overall mortality in the present study (12.4%) is consistent with the population data reported previously. The second limitation is the absence of key clinical factors from the database. Although we used propensity score matching to adjust for various confounders, there are several factors that the database does not include, such as vital signs at admission, laboratory data, and degree of surgical intervention. Finally, we did not have a standardized protocol for the administration of clindamycin. The effects of dose or duration of clindamycin are ultimately unknown. Furthermore, we defined the exposure time window for clindamycin treatment to be within 2 days of admission. This decision was grounded upon the recommendations of a previous review suggesting early intervention yields positive outcomes.[8] The justification for the adopted criteria is relatively poor due to a lack of published scientific reports on the subject.

This nationwide cohort study showed that combination therapy with clindamycin was not associated with lower in-hospital mortality in patients with invasive NGAS infection. Additional prospective studies are warranted to examine the efficacy of clindamycin in greater detail.

DISCLOSURE

APPROVAL OF THE research protocol: The present study was approved by the Institutional Review Board at the University of Tokyo (approval number: 3501-1).

Informed consent: Due to the anonymous nature of the data, the requirement for patient informed consent was waived.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

Conflict of interest: None.

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