

Prophylactic Effect of Vancomycin on Infection after Cranioplasty in Methicillin-Resistant *Staphylococcus Aureus* Carriers with Traumatic Brain Injury

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Objective: Methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant coagulase negative staphylococci (MRCNS) are major causes of neurosurgical infection. Nasal colonization of MRSA is the most important risk factor and MRSA screening can be a screening method to identify MRSA and MRCNS colonization. We retrospectively evaluated prophylactic effect of vancomycin on MRSA or MRCNS surgical site infection (SSI) after cranioplasty following decompressive craniectomy (DC) after traumatic brain injury (TBI) in MRSA carriers.

Methods: The study included 21 patients who were positive in MRSA screening before cranioplasty. These patients underwent DC after TBI and subsequent cranioplasty with autologous bone. The patients were separated into SSI group and no SSI group according to the development of SSI due to MRSA or MRCNS after cranioplasty. Mean follow-up period after cranioplasty was 23.5 ± 22.8 months (range, 3 to 73 months). The rate of MRSA or MRCNS SSI and factors including the prophylactic preoperative antibiotics were compared between groups.

Results: The rate of MRSA or MRCNS SSI was 23.8% (5/21 patients). Mean time from cranioplasty to confirm the SSI was 19.6 ± 10.9 days (6 to 63 days). The rate of MRSA or MRCNS SSI was significantly different from the use of preoperative prophylactic antibiotics ($p=0.047$). MRSA or MRCNS SSI developed in 1 of 13 patients (7.6%) who received vancomycin and in 4 of 8 patients (50%) who received 3rd generation cephalosporin.

Conclusion: Preoperative MRSA screening and administration of vancomycin as a preoperative prophylactic antibiotic should be considered in MRSA carriers who are scheduled to cranioplasty to reduce MRSA or MRCNS SSI.

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KEY WORDS: Vancomycin · Methicillin-resistant *Staphylococcus aureus* · Coagulase · Staphylococcal infections · *Staphylococcus* · Surgical wound infection.

Introduction

Decompressive craniectomy (DC) can be a life-saving

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neurosurgical treatment and is performed in patients with raised intracranial pressure resulting from traumatic brain injury (TBI) and various cerebral lesions.¹⁸⁾ After DC, cranioplasty to replace the bone defect is generally performed for cosmesis, mechanical protection, and potential improvement in intracranial hemodynamics and cerebrospinal fluid dynamics.^{15,25)} Surgical site infection (SSI) is one of the complications associated with cranioplasty and the incidence of SSI after cranioplasty is higher compared with other neurosurgical procedures.^{15,18,19,25)} In addition, it can be a significant cause of morbidity and lead to the long-term use of antibiotics or removal of the graft material and repeated cranioplasty at a later time.^{15,24)} A systematic review of cra-

nioplasty cited a rate of SSI ranging from 0 to 21.4% with an average of 7.9%.²⁴⁾

Recently, methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant coagulase-negative staphylococci (MRCNS) are wide spread and continue to increase in prevalence particularly in health care setting including intensive care unit (ICU) care and surgery.⁸⁾ MRSA and MRCNS are major causes of neurosurgical infection, including SSI after cranioplasty.^{3,15,18,19)} In one study, MRSA was identified in 9 of 11 patients with infection after cranioplasty.¹⁹⁾ In another study, predominant pathogens of infection in patients undergoing cranioplasty was MRSA (42.9%) followed by MRCNS (21.4%).¹⁵⁾ MRSA is often carried asymptotically in moist skin regions including the anterior nares, perineum, axillae, pharynx, umbilicus, and rectum.³⁾ MRSA colonization increases the risk of MRSA infection and particularly, nasal colonization is the most important independent risk factor for the development of a SSI.^{3,10)} Although controversy remains, some authors have recommended universal screening of patients for MRSA on admission to the hospital or ICU or have suggested preoperative MRSA screening and MRSA-specific prophylactic antibiotics before orthopaedic and cardiac surgery.^{4,10,16,23)} In terms of molecular biology, methicillin resistance of staphylococci is created when staphylococci acquires *mecA* gene which encodes the protein penicillin binding protein 2A (PBP2A). PBP2A has a low affinity for beta-lactam antibiotics and it allows a bacterium to be resistant to methicillin.⁸⁾ MRSA screening can also identify *mecA* gene of MRCNS which has structural homology of MRSA. Therefore, MRSA screening can be a screening method to identify MRCNS, although specificity and sensitivity are low compared with MRSA.⁸⁾ In neurosurgery, literatures regarding the value of preoperative MRSA screening and MRSA-specific preoperative prophylactic antibiotics are rare.^{3,11)} Particularly, literatures on these issues focused on the cranioplasty are extremely rare.

We evaluated the prophylactic effect of vancomycin on SSI due to MRSA or MRCNS after cranioplasty following DC in MRSA carriers with TBI and discussed the value of preoperative MRSA screening and the choice of preoperative prophylactic antibiotics in MRSA carriers.

Materials and Methods

Patients

The study included patients who underwent DC for acute brain swelling due to TBI and subsequent cranioplasty with autologous bone between June 2008 and De-

cember 2014 at our institution. Of them, 21 patients were positive in MRSA screening before cranioplasty. MRSA screening by the culture of nasal swab specimen was performed 3 or 4 days before cranioplasty. Those in whom cranioplasty was performed with prosthetic material were excluded.

Cranioplasty

During the study period, there was no specific protocol for the timing of the cranioplasty and choice of preoperative prophylactic antibiotics. All cranioplasty procedures were performed in patients who were neurologically stable, whose brain swelling or intracranial hypertension had resolved, who had no local or systemic infection, and who had no coagulopathy. Preoperative prophylactic antibiotics were used in all cases. The choice of preoperative prophylactic antibiotics was determined by the surgeon's preference. Preoperative prophylactic antibiotics were given intravenously 1 hour before the skin incision when using cephalosporin. When using vancomycin as a preoperative prophylactic antibiotic, it was given 2 hours before the skin incision. The bone flap, which was preserved in a deep freezer at a temperature of -71°C in the hospital bone bank, was retrieved from the freezer, was moved to the operating room, was immersed in povidone-iodine solution for 30 minutes, and then was placed in sterile saline before replacement. The bone flap was fixed to the craniectomy edge using mini-plates. Subgaleal drains were routinely placed. The temporal muscle, galea, and subcutaneous tissues were closed using vicryl in a layer by layer fashion. The scalp was closed with staples.

Postoperative care and SSI

Antibiotics were given at least for 24 hour postoperatively and the duration of postoperative antibiotics was determined by the surgeon's preference. Subgaleal drainage was placed for 2 to 3 days postoperatively. SSI was defined as infection confirmed with culture study resulting in surgical removal of the implanted bone or antibiotics were administered longer than 2 weeks after cranioplasty.^{15,21)}

Analysis of risk factors of SSI and prophylactic effect of antibiotics on SSI

The following data were obtained retrospectively from the patients' electronic medical records: age, gender, previous medical history, duration of admission to the hospital or ICU, in-hospital infection before cranioplasty, number of previous operation, ventriculoperitoneal shunt, interval from DC to cranioplasty, operation time for cranioplasty, duration of postoperative drainage, postoperative hemorrhage, use

and duration of preoperative prophylactic antibiotics. The rate of total SSI and SSI due to MRSA or MRCNS and factors including the preoperative prophylactic antibiotics were compared between patients with MRSA or MRCNS SSI after cranioplasty and without MRSA or MRCNS SSI after cranioplasty.

Statistical analysis

To compare categorical variables, Fisher exact test was used and Student's *t*-test was used for continuous variables. SPSS Statistics (version 20; IBM Corporation, Armonk, NY, USA) was used for statistical analysis and *p*-value of 0.05 or less was considered statistically significant.

Results

During the study period, 21 MRSA-positive patients (MRSA carrier) who were scheduled to cranioplasty after DC due to TBI were identified. The characteristics of the patients are summarized in Table 1. The patients were separated into SSI group and no SSI group according to the development of SSI due to MRSA or MRCNS after cranioplasty. Mean follow-up period after cranioplasty was 23.5±22.8 months (range, 3 to 73). Immediate postoperative complications after cranioplasty were epidural hematoma in 3 patients, and surgery for hematoma evacuation was done.

The rate of SSI due to MRSA or MRCNS in MRSA carri-

TABLE 1. Characteristics of MRSA carriers

	MRSA or MRCNS SSI (n=5)	No MRSA or MRCNS SSI (n=16)	<i>p</i> -value
Age (year)	53.8±20.3 (22–69)	57.8±17.3 (21–86)	0.66
Male:female	3:2	11:5	1.00
Hypertension	1	2	1.00
Diabetes	2	3	0.55
Smoking	3	5	0.32
GCS	7.8±5.2 (4–14)	6.8±3.7 (3–15)	0.66
Duration of hospital admission (day)	129.2±90.3 (46–276)	134.6±90.0 (30–342)	0.92
Duration of ICU admission (day)	23.4±3.9 (20–29)	28.6±16.4 (5–57)	0.25
Infection before cranioplasty	2	7	1.00
Numbers of operation before cranioplasty	3.4±1.9 (1–6)	2.6±1.6 (1–6)	0.39
VPS	0	2	1.00
Interval from DC to cranioplasty (day)	43.6±27.8 (23–60)	45.0±19.6 (14–85)	0.89
Operation time (min)	149.6±57.7 (81–212)	178.4±88.7 (80–350)	0.50
Duration of postoperative drainage (day)	1.8±0.4 (1–2)	2.3±1.2 (1–5)	0.38
Postoperative hematoma	1	2	0.50
Preoperative antibiotics			0.047*
Vancomycin	1	12	
Duration (day)	1	4.0±3.0 (1–7)	0.32
3rd generation cephalosporin	4	4	
Duration (day)	2.7±2.0 (1–5)	5.0±0 (5)	0.11
Follow-up (month)	28.4±34.2 (3–73)	22.0±19.3 (3–60)	0.71

*significantly lower rate of MRSA or MRCNS SSI was found in patients who received vancomycin compared to the patients who received 3rd generation cephalosporin. MRSA: methicillin-resistant *Staphylococcus aureus*, MRCNS: methicillin-resistant coagulase negative staphylococci, SSI: surgical site infection, GCS: Glasgow Coma Scale, ICU: intensive care unit, VPS: ventriculoperitoneal shunt, DC: decompressive craniectomy

TABLE 2. Surgical site infection after cranioplasty in MRSA carriers

Microorganism	Prophylactic antibiotics		Time to infection from cranioplasty (day)
	Antibiotic	Duration (day)	
MRSA	Vancomycin	1	63
MRSA	3rd cephalosporin	4	14
MRSA	3rd cephalosporin	1	8
MRCNS	3rd cephalosporin	5	6
MRCNS	3rd cephalosporin	1	7

MRSA: methicillin-resistant *Staphylococcus aureus*, MRCNS: methicillin-resistant coagulase negative staphylococci, 3rd cephalosporin: third generation cephalosporin

ers was 23.8% (5 of 21 patients). The pathogen was MRSA in 3 patients and MRCNS in 2 patients (Table 2). No SSI due to other pathogen except MRSA and MRCNS was found. Mean time from cranioplasty to confirm the SSI was 19.6 ± 10.9 days (range, 6 to 63). Bone flap was removed in all patients. No statistically significant difference was found in demographic and clinical parameters between two groups except the selected prophylactic antibiotics (Table 1). MRSA or MRCNS SSI developed in 1 of 13 patients (7.6%) who received vancomycin as a preoperative prophylactic antibiotic and in 4 of 8 patients (50%) who received 3rd generation cephalosporin. Significantly lower rate of MRSA or MRCNS SSI was found in patients who received vancomycin compared to the patients who received 3rd generation cephalosporin ($p=0.047$).

Discussion

In the present retrospective analysis, vancomycin is effective in reducing the rate of SSI due to MRSA or MRCNS after cranioplasty following DC after TBI in MRSA carrier. However, issues on the value of routine preoperative MRSA screening, use of preoperative prophylactic antibiotics active against MRSA in MRSA carriers, and preoperative prophylactic antibiotics of choice for MRSA remain controversial.

Controversy remains over the effect of vancomycin on the reduction of the rate of SSI. In the neurosurgical fields, Blomstedt and Kytä⁵ reported bone flap infections after craniotomy was significantly lower in patients with a single prophylactic dose of vancomycin compared to patients to whom no antimicrobial agents were given in a randomized trial. Tacconelli et al.²² suggested that use of vancomycin as preoperative prophylactic agent for cerebrospinal shunt placement reduces the rate of shunt infections compared to cefazolin in a randomized prospective clinical trial. However, preoperative MRSA screening was not performed in these studies. Le et al.¹⁸ reported that perioperative use of vancomycin reduced MRSA SSI after cranioplasty compared the use of cefazolin. However, the choice of preoperative antibiotics was not performed based on MRSA colonization status. Routine use of vancomycin as a preoperative prophylactic antibiotic regardless of MRSA colonization status of patients can cause another controversy, considering the toxicity of vancomycin such as hypotension and so-called “red person syndrome” particularly during the initial infusion and the possibility of postoperative conversion to MRSA carrier in initially MRSA-negative patients.^{2,3,11}

In one review, the rate of MRSA positive in patients who admitted to the hospital was from 1.4 to 16.1%.⁹ However, Abad et al.¹ noted that approximately 20% of the general population is persistently colonized and about 30% is intermittently colonized. This means about 50% of general population can be positive in MRSA screening at a certain time point. In addition, Honda et al.¹⁴ reported 47% of 5,161 patients were positive when MRSA screening was performed in patients who admitted to ICU. And about 2% of patients could be converted from MRSA-negative preoperatively to MRSA-positive postoperatively.² In the present study, MRSA or MRCNS SSI after cranioplasty occurred in approximately a quarter of MRSA carrier. We could not know the exact cause of this relatively high rate of MRSA or MRCNS SSI after cranioplasty. This might come from the high rate of MRSA carrier on admission or from post-DC conversion to MRSA carrier and resultant MRSA or MRCNS SSI. In the present study, we included only MRSA carrier before cranioplasty. Therefore, we did not know the exact incidence of MRSA carrier who admitted to our hospital. It is known that the possibility of MRSA positive on admission in patients with previously unknown carriage of MRSA is high in patients who have any of following risk factors: age >80 years, previous hospitalization within past 12 months, previous antibiotic use within past 6 months, and urinary catheter present on admission.¹³ The patients included in the study had at least 2 or 3 of 4 above mentioned risk factors for the possibility of MRSA positive in patients with previously unknown carriage of MRSA.¹³ The patients had history of recent admission to the ICU before cranioplasty, already used antibiotics in the perioperative period of DC, and most patients had indwelling urinary catheters.¹³ To find the exact cause of the high rate of MRSA or MRCNS SSI after cranioplasty in MRSA carrier in the present study, further study is necessary to elucidate whether this came from high rate on admission or from post-DC conversion to MRSA carrier in preoperative MRSA-negative patients in the future.

There are also conflicting views over the value of preoperative MRSA screening. In a prospective, interventional cohort study in patient who admitted to 8 different surgical specialties including neurosurgery, Harbarth et al.¹² reported 515 (5.1%) of 10,193 patients screened on admission were MRSA-positive and the rate of MRSA SSI did not change significantly after the period of starting MRSA screening on admission. In their study, only 34% of patients with MRSA SSI who could have benefited from antibiotic prophylaxis and 59% had no evidence of MRSA prior to surgery.¹² They suggested postoperative transmission may play an important

role in occurrence of MRSA SSI as well as preoperative carriage of MRSA.¹²⁾ They concluded MRSA screening could be targeted to surgical patients who undergo elective procedures with a high risk of MRSA infection to increase effectiveness.¹²⁾ However, type of the surgery and rate of SSI in an individual surgical department were not described. On the contrary, given the possible consequences associated with MRSA SSIs, many authors recommended MRSA screening and eradication of MRSA carrier status in patients undergoing elective orthopaedic, cardiac, vascular, colorectal, gynecologic, and neurosurgery.^{3,4,6,7,10,11,16,17,20,23)} Tom et al.²³⁾ noted active surveillance can be cost-effective by preventing at least two SSIs per year in cardiac surgery. Chen et al.⁷⁾ concluded preoperative screening and decolonization of MRSA in orthopaedic patients is a cost-effective means to reduce SSIs in the literature review.

The use of preoperative prophylactic antibiotics active against MRSA and antibiotics of choice in MRSA carrier are also debatable. Most authors recommended vancomycin as preoperative prophylactic antibiotics in all MRSA carrier.^{3,4,6,17,23)} Others recommended vancomycin as preoperative prophylactic antibiotics if a previous history of MRSA infection is documented or if placement of artificial prosthesis is scheduled rather than routine use in all MRSA carrier.^{10,20)} In the neurosurgical patients, these issues are also debatable. In a retrospective analysis, Hammond et al.¹¹⁾ reported 15% of the screened who were admitted as transfers from another hospital were MRSA-positive on admission, and concluded cefuroxime plus gentamicin can be used as antibiotic prophylaxis to prevent MRSA wound infection. They recommended vancomycin can be used as preoperative prophylactic antibiotics in case of colonization or infection detected more than 48 hours after admission.¹¹⁾ Akins et al.³⁾ found that MRSA carriers were at a high risk for postoperative neurosurgical wound infections, primarily from gram-positive organisms, and particularly from MRSA itself. This high SSI rate in MRSA carrier can be significantly reduced by the use of MRSA-specific preoperative prophylactic antibiotics such as vancomycin, compared with routinely used preoperative prophylactic antibiotics such as cefazolin, from 32.1 to 7.4%.³⁾ They suggested it is beneficial to screen patients who are scheduled for neurosurgical and spinal procedures for MRSA colonization based on medical history and also direct culture (nasal swab, for example) and advocated that patients with MRSA-positive should receive vancomycin as the preoperative prophylactic antibiotic of choice unless there are clinical contraindications.³⁾ However, in their study, numbers of SSI was too small for a meaningful examination of variables such as procedure type. Of 27

postsurgical infections, only 3 cranioplasty cases were included.³⁾ In the present study, significantly lower rate of SSI due to MRSA or MRCNS was found in patients who received vancomycin as a prophylactic preoperative antibiotic compared to the patients who received 3rd generation cephalosporin. Although, because 1st generation cephalosporin was not used as a preoperative prophylactic antibiotic in MRSA carrier, the comparison of prophylactic effect was impossible between vancomycin and 1st generation cephalosporin or between 1st- and 3rd-generation cephalosporin. However, as previously mentioned, it has been reported that vancomycin is superior to 1st generation cephalosporin in reducing MRSA infection in ventriculoperitoneal shunt and cranioplasty regardless of MRSA colonization status.^{18,22)} The use of vancomycin as a preoperative prophylactic antibiotic did not increase the rate of SSI due to other microorganisms than MRSA and MRCNS in the MRSA carrier in the present study. Therefore, we suggested vancomycin as a preoperative prophylactic antibiotic before cranioplasty following DC after TBI in MRSA carriers.

This is a retrospective analysis. Accordingly, the study has the anticipated deficiencies of a retrospective analysis including loss of patient information. The unknown incidence of MRSA carrier on admission, small numbers of MRSA or MRCNS SSI after cranioplasty, and excluding the patients in whom MRSA colonization status was not identified made a statistically powerful examination of variables such as difference in prophylactic effect of specific antibiotics on SSI impossible. However, in MRSA carriers, vancomycin was effective in reducing the rate of MRSA or MRCNS SSI after cranioplasty following DC and this was helpful in designing further studies to evaluate the value of MRSA screening and the prophylactic effect of vancomycin in MRSA carriers.

Conclusion

In the present study, significantly low rate of MRSA or MRCNS SSI after cranioplasty following DC after TBI was found in MRSA carriers who received vancomycin as a preoperative prophylactic antibiotic. Preoperative MRSA screening and the administration of vancomycin should be considered in MRSA carriers who are scheduled to cranioplasty after DC due to TBI. Further study with large numbers of patients is necessary to evaluate the value of preoperative MRSA screening and the effect of MRSA-specific preoperative prophylactic antibiotics on MRSA or MRCNS SSI after neurosurgical procedures, including cranioplasty.

■ The authors have no financial conflicts of interest.

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