Research on the effects of pharmacist intervention for the drug therapy in dentistry

Kensuke Yoshida

第 1 報

Clinico-statistical Survey of Oral Antimicrobial Prophylaxis and Surgical Site Infection Regarding Ordinary Tooth Extraction and Mandibular Wisdom Tooth Extraction in the Dental Outpatient Clinic

Kensuke Yoshida, Yasumitsu Kodama, Takahiro Nagai, Andrea Rei Estacio Salazar, Syouta Kaneko, Chie Saito, Akira Toyama, Ritsuo Takagi

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第 2 報

Comparison between the Prophylactic Effects of Amoxicillin 24 and 48 hours pre-operatively on Surgical Site Infections in Japanese Patients with Impacted Mandibular Third Molars: A Prospective Cohort Study

Kensuke Yoshida, Yasumitsu Kodama, Atsushi Nishikawa , Andrea Rei Estacio Salazar, Akira Toyama, Ritsuo Takagi

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Original Article

Clinico-statistical survey of oral antimicrobial prophylaxis and surgical site infection regarding ordinary tooth extraction and mandibular wisdom tooth extraction in the dental outpatient clinic☆

Kensuke Yoshida [a, b, *], Yasumitsu Kodama [a], Takahiro Nagai [a], Andrea Rei Estacio Salazar [a], Syouta Kaneko [b], Chie Saito [b], Akira Toyama [b], Ritsuo Takagi [a]

[a] Division of Oral and Maxillofacial Surgery, Faculty of Dentistry & Graduate School of Medical and Dental Sciences, Niigata University, 1-754, Asahimachi-dori, Chuo-ku, Niigata, 951-8520, Japan
[b] Division of Hospital Pharmacy, Niigata University Medical and Dental Hospital, 1-754, Asahimachi-dori, Chuo-ku, Niigata, 951-8520, Japan

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ABSTRACT

Introduction: We investigated the use of oral antibiotics (OA) and surgical site infection (SSI) related to extractions of ordinary teeth and mandibular wisdom teeth in a dental outpatient clinic from January 2015 to December 2019.
Methods: The following information were surveyed: (1) presence/absence of OA, (2) timing, (3) type, (4) administration period, and (5) SSI rates.
Results: The use of OA during ordinary tooth extraction decreased from 68.3% to 41.3%, but SSI rate did not change during this period of time. Total SSI rate was 0.8% (122/14,832) on average.
For mandibular wisdom tooth extraction, preoperative administration of third-generation cephalosporins decreased from 70.4% to 0.3% while that of penicillin (AMPC) increased from 0% to 98%. SSI rate was not changed after these improvements. Total SSI rate was 3.5% (180/5106) on average. The duration of OA was slightly decreased to two days in 2018 and 2019, and it was found that there was no significant difference in SSI rates between 2- and 3-day durations. Preoperative administration had 0.37 odds ratio (OR) (95% confidence interval (95%CI): 0.22–0.63) of SSI compared with postoperative administration. AMPC had 0.76 OR (95% CI: 0.55–1.04) of SSI compared with Third-generation cephalosporins and others. Timing of OA was $P < 0.01$.
Conclusions: SSI rates did not change over time, administration period of OA decreased and the use of AMPC increased. Therefore, it seems necessary to continue to investigate the effects of SSI risk factors proactively in the future and to make efforts in the advocacy of appropriate antimicrobial use.

1. Introduction

Antimicrobial resistance (AMR) is a major international challenge [1]. In Japan, an AMR Action Plan was suggested by the Ministry of Health, Labor and Welfare in 2016. The content is a specific guideline to reduce the use of cephalosporins, fluoroquinolones, and macrolide oral antibiotics to 50% by 2020 [2].

Each healthcare facility needs to understand the use of antimicrobial agents and their compatibility with the causative microorganism, as well as the promotion of the proper use of antimicrobial agents in cooperation with different departments in the healthcare facility. Antimicrobial use in Japanese dental wards includes administration for dental infections (therapeutic antimicrobial administration) and administration for prevention of surgical site infection (SSI) (antimicrobial prophylaxis), in which each follows its guidelines [3,4]. An Infection Control Team (ICT) is responsible for understanding the use of antimicrobial agents in dental wards as same as medical wards. In 2016 pharmacists have been stationed in our dental ward, and the dentists and pharmacists work together to promote proper use of antibacterial agents following Antimicrobial

☆ Authorship: All authors meet the ICMJE authorship criteria.
* Corresponding author. Division of Oral and Maxillofacial Surgery, Faculty of Dentistry & Graduate School of Medical and Dental Sciences, Niigata University, 1-754, Asahimachi-dori, Chuo-ku, Niigata, 951-8520, Japan.
E-mail address: kensukeyoshida-nii@umin.ac.jp (K. Yoshida).

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Stewardship Program(ASP) [5–9]. On the other hand, the dental ICT is responsible for understanding the use of antimicrobial agents in the dental outpatient clinic. However, since there are many departments and dentists in the dental outpatient clinic, the implementation of the appropriate use of antimicrobial agents on all of the departments has not yet commenced.

There is much issue for improvement in the use of oral antimicrobial agents with a particular focus on SSI [10]. In this study, we focused on the SSI rates after ordinary tooth extraction and mandibular wisdom tooth extraction in our dental outpatient clinic, and we retrospectively investigated the use of oral antibiotics from a pharmacist's perspective.

2. Materials and methods

2.1. Subjects

The subjects were patients who underwent ordinary tooth extraction and mandibular wisdom tooth extraction in our dental outpatient clinic from January 2015 to December 2019 (5-year duration). Patients were excluded from the study if they had a medical history known as an SSI risk factor, such as diabetes, steroid or immunosuppressant use, BMI of ≥25, or endocarditis. The maximum number of days for oral antibiotic administration was set at 5 days. An administration period longer than 5 days was regarded as therapeutic use and patients with such use were, therefore, excluded as the subjects.

A retrospective survey of the electronic medical records was conducted with the cooperation of the Medical Information Department of our hospital. The following information were surveyed: (1) the presence or absence of oral antibiotics, (2) the timing of oral antibiotic administration, (3) the type of oral antibiotics, (4) the administration period, and (5) the SSI rate.

2.2. Definition of terms

In this study, the "administration of oral antibiotics on the day of the tooth extraction" is considered as "postoperative administration" in the prescription system of our dental outpatient clinic. Japanese Practical guidelines for the prevention of postoperative infection [3] recommend that "oral antibiotic administration is unnecessary" for ordinary extraction (ordinary extraction not including mandibular wisdom tooth extraction) except for patients who are at risk of acquiring SSI, and "single administration of amoxicillin 1 h before mandibular wisdom tooth extraction" or "administration of amoxicillin from 1 h before surgery up to 48 h after surgery(250 mg to 1 g/dose)." Therefore, oral antibiotics on the day of tooth extraction were described as the improper use of oral antibiotics that deviates from the guidelines. The term "preoperative oral antibiotics" was also used to describe this practice if the antibiotic was prescribed 30 days before the scheduled day of treatment, excluding the day of tooth extraction. Also, the term SSI is interchangeable with "post-extraction infection," "post-extraction alveolar osteomyelitis," and "infected fistula" in the electronic medical records after tooth extraction.

2.3. Statistical analysis

For comparison between two groups, Fisher's exact test was used, and a significance level of $p < 0.05$ was set. We estimated the odds ratio (OR) and 95% confidence interval (95%CI) between the two groups using a logistic regression analysis of independent factors for SSI after impacted mandibular third molar surgery. We adjusted for timing and types of oral antibiotics. JMP v14.2 (14.0) was used for statistical analysis.

2.4. Ethics

This study was performed with the approval of our Research Ethics Committee (approval number 2017–0130). Also, all authors in this paper have no conflict of interest with any of the companies involved.

3. Results

3.1. About ordinary tooth extraction (Table 1–1)

3.1.1. Presence or absence of oral antibiotics

In the span of five years from 2015 to 2019, the candidate cases were 14,832 in total (Table 1). Of these patients, 56.0% (8306) received oral antibiotics, all of which were administered postoperatively.

3.1.2. Changes in types of oral antibiotics (Table 1–2)

Oral antibiotics that were selected for tooth extraction were amoxicillin (AMPC), cefaclor (CCL), cefcapene pivoxil (CFPN-PI), cefdinir (CFDN), cefditoren pivoxil (CDTR-PI), cefteram pivoxil (CFTM-PI), faropenem (FRPM), azithromycin (AZM), clarithromycin (CAM), levofloxacin (LVFX), and sitafloxacin (STFX). The use of third-generation cephalosporins as the oral antibiotics of choice changed from 86.2% in 2015 to 17.9% in 2019, while the use of penicillin (AMPC) changed from 9.6% to 78.8%.

3.1.3. Changes in the administration period of oral antibiotics

In this study, the median duration of oral antibiotic administration was 3 days. The span of oral antibiotic use had a minimum of 1 day and a maximum of 5 days. The administration period of AMPC, third-generation cephalosporins, and others was no change.

Table 1
The presence or absence of oral antibiotics about ordinary tooth extraction

Table 1–1

	All	2015	2016	2017	2018	2019
All tooth extraction	14,832	2894	3143	3062	3127	2606
Presence of oral antibiotics	8306	1978	2132	1766	1354	1076
Rate (%)	56.0	68.3	67.8	57.7	43.3	41.3

Table 1–2 Changes in types of oral antibiotics about ordinary tooth extraction

	All	2015	2016	2017	2018	2019
Penicillin (%)	3246 (39.1)	190 (9.6)	479 (22.5)	860 (48.7)	869 (64.2)	848 (78.8)
Third-generation cephalosporins (%)[a]	4756 (57.3)	1706 (86.2)	1571 (73.7)	839 (47.5)	447 (33.0)	193 (17.9)
Others (%)[b]	304 (3.6)	82 (4.2)	82 (3.9)	67 (3.8)	38 (2.8)	35 (3.3)

[a] Cefcapene pivoxil, cefdinir, cefditoren pivoxil, and cefteram pivoxil.
[b] Cefaclor, faropenem, azithromycin, clarithromycin, levofloxacin, and sitafloxacin.

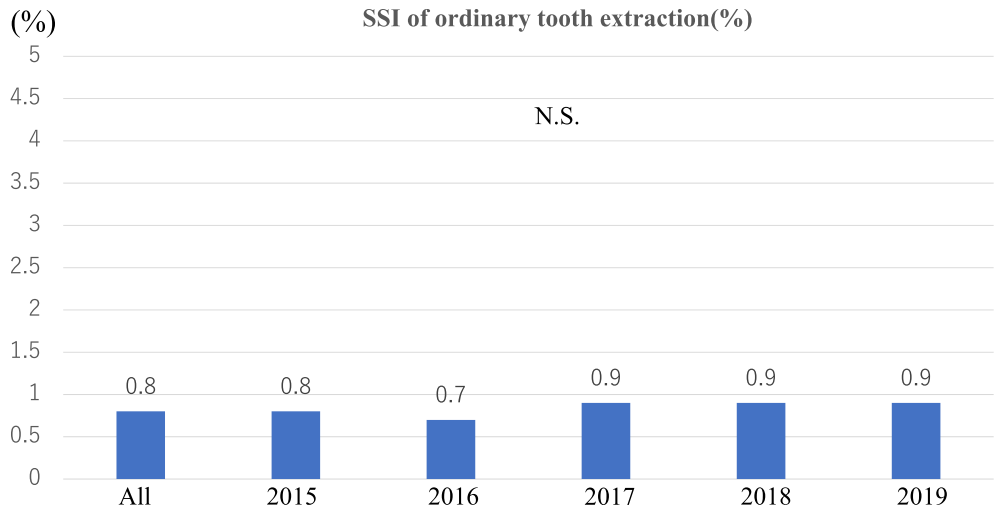

Fig. 1. Changes in SSI of ordinary tooth extraction rates comparisons.

Table 2
Relationship between oral antibiotics and SSI about ordinary tooth extraction.

Oral antibiotics	All	SSI				P value
		occurrence		non occurrence		
		N	%	N	%	
Presence	8306	63	0.76	8243	99.2	0.33[a]
Absence	6526	59	0.90	6467	99.1	

[a] Fisher's exact test.

3.1.4. Changes in SSI rates (Fig. 1)

The overall SSI rate was 0.8% (122/14,832). There was no significant difference in the SSI rates.

3.1.5. Relationship between oral antibiotics and SSI (Table 2)

Out of the 8306 patients who received oral antibiotics, 0.76% (63 cases) had SSI, and 6526 patients who did not receive oral antibiotics had an SSI occurrence of 0.90% (59 cases). The SSI occurrence was not significantly different when compared with the presence or absence of oral antibiotic administration.

3.2. About mandibular wisdom tooth extraction

3.2.1. Timing of oral antibiotics (Table 3–1, Table 3–3)

From 2015 to 2019, the total number of cases was 5106. Preoperative administration of oral antibiotics was approximately 25.2% (1284 cases) and postoperative administration was 74.9% (3822 cases).

3.2.2. Changes in types of oral antibiotics (Table 3–2, Table 3–4)

Oral antimicrobials that were selected for mandibular wisdom tooth extraction were AMPC, CCL, CFPN-PI, CFDN, CDTR-PI, CFTM-PI, FRPM, AZM, CAM, LVFX, and STFX. The use of third-generation cephalosporins changed from 70.4% in 2015 to 0.3% in 2019 while the use of AMPC increased from 0% to 98.0%.

3.2.3. Changes in the administration period of oral antibiotics

The median duration of oral antibiotics was 3 days for all antibiotics from 2015 to 2017. In 2018 and 2019, it was 3 days for third-generation cephalosporins and other non-AMPC antibiotics and 2 days for AMPC.

3.2.4. Changes in SSI rates (Fig. 2)

The overall SSI rate was 3.4% (180/5106). There was no significant difference in SSI rates from one year to the next.

3.2.5. Relationship between timing of oral antibiotics and SSI (Table 4)

The rates of SSI occurrence were 1.4% (18/1284) after preoperative administration and 4.2% (162/3822) after postoperative administration. The rate of SSI occurrence was significantly lower ($P < 0.05$) in the former than the latter.

3.2.6. Relationship between administration period of oral antibiotics and SSI (Table 5)

SSI occurred in 3.9% (79/2025) of the patients who received oral antibiotics for 2 days and 3.3% (101/3081) of those who received antibiotics for 3 days. There was no significant difference in the SSI rate by administration period of oral antibiotics.

3.3. Relationship between type of oral antibiotics and SSI (Table 6)

The rate of SSI occurrence was approximately 2.7% (85/3115) even after AMPC administration and 4.8% (95/1991) after the administration of third-generation cephalosporins and other types of antibiotics. The rate of SSI occurrence was significantly lower ($P < 0.01$) by AMPC.

3.3.1. Logistic regression analysis of independent factors for SSI after impacted mandibular wisdom tooth extraction (Table 7)

Preoperative administration had 0.37 OR (95% CI: 0.22–0.63) of SSI compared with postoperative administration. AMPC had 0.76 OR (95% CI: 0.55–1.04) of SSI compared with Third-generation cephalosporins and others. Timing of oral antibiotics was $P < 0.01$.

Table 3
Timing of oral antibiotics with preoperative administration about mandibular wisdom tooth extraction

Table 3–1						
	All	2015	2016	2017	2018	2019
Mandibular wisdom tooth extraction	5106	1054	1081	946	808	1217
Preoperative administration	1284	27	79	143	287	748
Rate (%)	25.2	2.6	7.3	15.1	35.5	61.5
Table 3–2 Changes in types of oral antibiotic with preoperative administration about mandibular wisdom tooth extraction						
	All(N = 1284)	2015(N = 27)	2016(N = 79)	2017(N = 143)	2018(N = 287)	2019(N = 748)
Penicillin (%)	1172(91.3)	0 (0)	44 (55.7)	131 (91.6)	264 (92.0)	733(98.0)
Third-generation cephalosporins (%)[a]	54(4.2)	19 (70.4)	24 (30.4)	2 (1.4)	7 (2.4)	2(0.3)
Others (%)[b]	58(4.5)	8 (29.6)	11 (13.9)	10 (7.0)	16 (5.6)	13(1.7)
Table 3–3 Timing of oral antibiotics with postoperative administration about mandibular wisdom tooth extraction						
	All	2015	2016	2017	2018	2019
Mandibular wisdom tooth extraction	5106	1054	1081	946	808	1217
Postoperative administration	3822	1027	1002	803	521	469
Rate (%)	74.9	97.4	92.7	84.9	64.5	38.5
Table 3–4 Changes in types of oral antibiotic with postoperative administration about mandibular wisdom tooth extraction						
	All(N = 3822)	2015(N = 1027)	2016(N = 1002)	2017(N = 803)	2018(N = 521)	2019(N = 469)
Penicillin (%)	1943(50.8)	127 (12.4)	386 (38.5)	565 (70.4)	455 (87.3)	410(87.4)
Third-generation cephalosporins (%)[a]	1837(48.1)	884 (86.1)	609 (60.8)	227 (28.3)	61 (11.7)	56(11.9)
Others (%)[b]	42(1.1)	16 (1.6)	7 (0.7)	11 (1.4)	5 (1.0)	3(0.6)

[a] Cefcapene pivoxil, cefdinir, cefditoren pivoxil, and cefteram pivoxil.
[b] Cefaclor, faropenem, azithromycin, clarithromycin, levofloxacin, and sitafloxacin.

Table 4
Relationship between timing of oral antibiotics and SSI about mandibular wisdom tooth extraction.

Oral antibiotics	All	SSI				P value
		occurrence		non occurrence		
		N	%	N	%	
Preoperative	1284	18	1.4	1266	98.6	0.001[a]
Postoperative	3822	162	4.2	3660	95.8	

[a] Fisher's exact test.

Table 5
Relationship between administration period of oral antibiotics and SSI about mandibular wisdom tooth extraction.

Oral antibiotics	All	SSI				P value
		occurrence		non occurrence		
		N	%	N	%	
2 days	2025	79	3.9	1946	96.1	0.23[a]
3 days	3081	101	3.3	2980	96.7	

[a] Fisher's exact test.

4. Discussion

Antimicrobial resistance (AMR) is a major international challenge [1]. In Japan, an AMR Action Plan was suggested by the Ministry of Health, Labor, and Welfare in 2016 [2]. Proper use of antimicrobials is needed in the dental field as well as in other healthcare fields. However, the proper use of antimicrobial agents has not advanced sufficiently in the dental field [11]. In particular, it has been pointed out that there is much issue for improvement in the administration of oral antibiotics [12].

In our dental outpatient clinic, the ASP by the dental ICT has been implemented, which has resulted in a reduction of

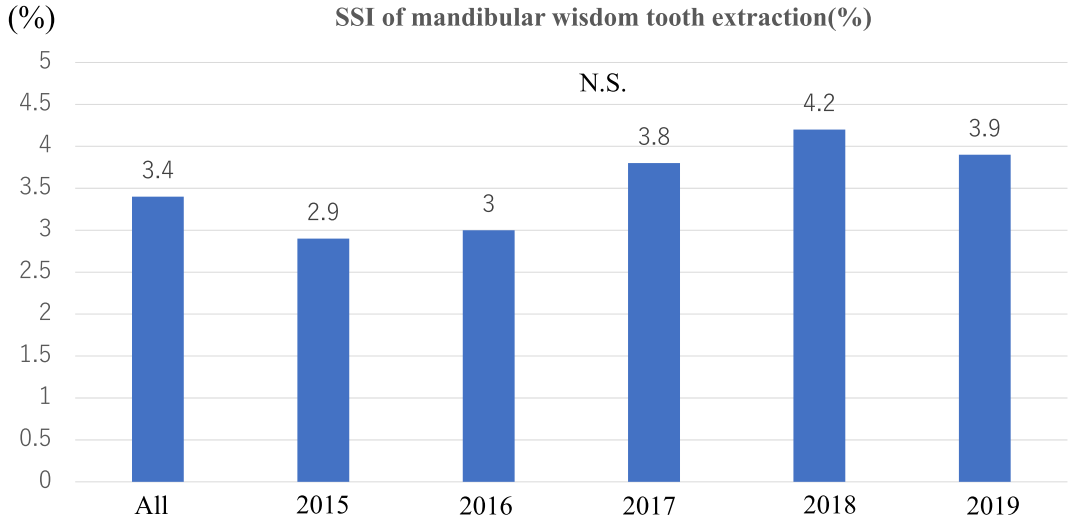

Fig. 2. Changes in SSI of mandibular wisdom tooth extraction rates comparisons.

Table 6
Relationship between type of oral antibiotics and SSI about mandibular wisdom tooth extraction.

Oral antibiotics	All	SSI				P value
		occurrence		non occurrence		
		N	%	N	%	
Penicillin	3115	85	2.7	3030	97.3	0.001[a]
Third-generation cephalosporins and others	1991	95	4.8	1896	95.2	

[a] Fisher's exact test.

Table 7
2–8. Logistic regression analysis of independent factors for SSI after impacted mandibular wisdom tooth extraction.

	Category	OR(CI)	P value
Timing(Ref: postoperative)	Preoperative	0.37(0.22–0.63)	0.0001
Type(Ref:Third-generation cephalosporins and others)	AMPC	0.76(0.55–1.04)	0.09

OR: odds ratio, CI: 95% confidence interval.

antibacterial administration as well as a reduction in medical expenses [13]. Dental ICT is organized by dentists, nurses, dental hygienists, and dental technicians. Dental ICT holds a monthly infection control study subcommittee to update and examine infection control information specialized for dental outpatients, including information on proper use of oral antibiotics. We are updating and studying infection control information specialized for dental outpatients. Dental ICT carries out a dental outpatients infection audit from January to March every year, and uses e-learning to confirm knowledge. In addition, questions regarding the proper use of oral antibiotics are provided, and the results of e-learning and new findings are feedback to all staff through an infection control staff meeting held once every four months. In addition, a pharmacist has been stationed in our dental ward of the main department of oral surgery since November 2016. As a result, the opportunity to advise on the selection and administration period of antibiotics is not limited to inpatients but also provided to dental outpatients. This situation has influenced the attending dentists choice of antibiotic prescription. There are only a few types of research on the appropriate antibiotic administration for the prevention of SSI in dental outpatient clinic. Therefore, in this study, we decided to investigate the changes in oral antibiotic use and the rates of SSI in ordinary tooth extraction and mandibular wisdom tooth extraction in the dental outpatient clinic.

Initially, oral antibiotics were used in 68.3% of ordinary tooth extraction cases in the dental outpatient clinic supervised by the dental ICT before ASP and the start of the pharmacist's residency (2015). At that time, third-generation cephalosporins were used in 86.2% of the antibiotic-treated cases (Table 1). These rates were consistent with some reports in the past [11,12], suggesting that the social and historical background [14], particularly in Japan, had a great influence on the type of antibiotic prescription.

A systematic review of the practical guidelines for the prevention of postoperative infection stated that the incidence of SSI did not differ between cases with oral antibiotics and those without them during ordinary tooth extraction [15]. In our hospital, efforts made to share this information through the help of the dental ICT reduced oral antibiotic use to 41.3% in 2019 (Table 1). Although there are still many inappropriate administrations of antibiotics that are inconsistent with the guidelines, there are also ordinary extractions that antibiotics administrations can serve as anti-inflammatory measures and counter the unexpected findings of infection risk during the operation. It is also considered that the decrease rate does not progress because there are many complicated cases in university hospitals. However, at the moment, it is considered important to maintain this situation for a while, as appropriate use is progressing smoothly at this moment. In addition, the proportion of third-generation cephalosporin use decreased from 86.2% in 2015 to 17.9% in 2019. Although oral antibiotics on the day of ordinary tooth extraction were said to be an inappropriate use of antibiotics that did not consider the Practical guidelines for the prevention of postoperative infection, there was still a decrease in the use of third-generation cephalosporins following the AMR action plan. Under these conditions, the occurrence of SSI was approximately 0.8% (122/14,832). Past reports showing SSI rates after ordinary tooth extraction ranged from 0.66 to 2.1% [10,16], which were in line with our survey results.

The rates of SSI occurrence did not differ significantly between cases with oral antibiotics use and those without (Table 2). It was presumed that some of these cases might have been administered at the discretion of dentists with consideration of the local condition and the degree of surgical invasion. However, concrete details are unknown. This lack of concrete details is a limitation in the retrospective survey using an electronic medical record system.

Postoperative administration of oral antibiotics has decreased over the long term for mandibular wisdom tooth extraction (Table 3). A very notable finding in this study is that the use of preoperatively administered third-generation cephalosporins decreased from 70.4% to 0.3% while AMPC use increased from 0% to 98%. The total SSI rate was 3.5% (180/5106) for pre- and post-operative administrations combined. The rates of SSI were reported to be 0.2–27% in the mandibular wisdom tooth extraction [17–21], and our survey results showed similar rates.

Another notable finding in this research is the relationship between the timing of oral antibiotics and SSI about mandibular wisdom tooth extraction, wherein preoperative administration has significantly reduced the rates of SSI ($P < 0.05$) (Table 4). Other reports similarly suggested that a decrease in the rates of SSI is achieved by increasing the blood and tissue levels of the antibiotics before surgery [22,23]. After we followed the recommendation in the guideline, preoperative antibiotic treatment increased to 61.5% in 2019, suggesting that a more thorough implementation of preoperative antibiotic treatment could further reduce the incidence of SSI.

The administration period of oral antibiotics was reduced to 2 days in 2018 and 2019. There was no significant difference in the rates of SSI between 2 days and 3 days (Table 5). Murakami et al. reported that there was no difference in SSI between AMPC for 1 day and 2 days [24]. It is desirable to further shorten the administration period to reduce the occurrence of side effects and medical costs, as recommended by this study guideline.

The rate of SSI occurrence was significantly lower ($P < 0.01$) by AMPC (Table 6). Yamagami et al. reported that CFPN-PI had significantly higher rates of SSI occurrence compared with AMPC for lower impacted mandibular wisdom tooth extraction [25]. Since third-generation cephalosporin oral antibiotics with low bioavailability have poor tissue transfer and may promote the risk of resistant bacteria. In addition, the use of preoperatively administered AMPC has increased in recent years. It will be necessary to select oral antibiotics according to the guideline. But, as a result of logistic regression analysis, AMPC was not superior to CFPN-PI and may have been strongly affected by preoperative administration.

In our hospital, the appropriate use of oral antibiotics in line with the guidelines has progressed over the years. However, the conditions in our study did not fully comply with the guidelines in terms of use, timing, type, and administration period according to the surgical procedure. On the other hand, SSI rates did not change over the years, while the administration period of oral antibiotics decreased and the use of AMPC antibiotics increased. The results were presumed to have been affected by the ASP and pharmacist with both starting their activities around the same time in 2016.

Various factors are involved in the prevalence of SSI, such as oral environment, patient background, type of surgical procedure, operation time, and infection control in the facility, including the perioperative management system. More accurate studies require the exclusion of the aforementioned SSI risk factors from all cases, critical observation of SSI cases, and the need for prospective studies in the future.

Based on our results, it seems necessary to continue to investigate the effects of SSI risk factors proactively in the future and to make efforts in the advocacy of the appropriate use of antimicrobial agents.

Authors' contribution

Contributors Yoshida was responsible for the organization and coordination of the trial. Kodama was responsible for the data analysis. Nagai, Andrea, Kaneko, and Saito was the investigator. Toyama and Takagi developed the trial design. All authors contributed to the writing of the final manuscript.

Declaration of competing interest

All authors declare no competing interests.

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Comparison between the prophylactic effects of amoxicillin 24 and 48 hours pre-operatively on surgical site infections in Japanese patients with impacted mandibular third molars: A prospective cohort study

Kensuke Yoshida [a, b, *], Yasumitsu Kodama [a], Atsushi Nishikawa [a], Andrea Rei Estacio Salazar [a], Akira Toyama [b], Ritsuo Takagi [a]

[a] Division of Oral and Maxillofacial Surgery, Faculty of Dentistry & Graduate School of Medical and Dental Sciences, Niigata University, Japan
[b] Division of Hospital Pharmacy, Niigata University Medical and Dental Hospital, 1-754, Asahimachi-dori, Chuo-ku, Niigata (city), 951-8520, Japan

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ABSTRACT

Introduction: According to the guidelines, the dosage for mandibular wisdom tooth extraction (MWTE) varies within the administration period. There is a 24-fold difference between the minimum and maximum doses. If an appropriate antimicrobial can be administered without increasing incidence of surgical site infection (SSI), it may lead to a global action plan on antimicrobial resistance (AMR). Therefore, we prospectively surveyed incidence of SSI post-operatively and use of oral antibiotics (OA) for MWTE.

Methods: Subjects were patients who underwent MWTE in our dental outpatient clinic from May 2019 to April 2020. Two groups were formed depending on type of administration period they received: 24 h and 48 h after surgery. The following information was collected: (1) patient factors (age, gender, body mass index, presence/absence of preoperative medication, diagnosis, impacted wisdom tooth status; (2) surgical factors (operative time, presence/absence of closure, presence/absence of hemostat, doctor career, type and frequency of painkiller); (3) relationship between administration period of OA and SSI occurrence; and (4) details of SSI.

Results: Three hundred forty subjects were analyzed, all of which used amoxicillin. There were 106 cases in 24 h group and 234 cases in 48 h group. The total incidence of SSI was 1.1% (4/340 cases), with 0.9% (1/106 cases) in 24 h group and 1.3% (3/234 cases) in 48 h group; there was no difference between the two groups.

Conclusion: Our study suggests that amoxicillin (250 mg/dose every 8 h x 3 doses beginning 1 h before surgery) might be sufficient in preventing SSI in Japanese dental patients without SSI risk factors.

1. Introduction

A global action plan on antimicrobial resistance (AMR) is a major international challenge [1]. In Japan, to prevent AMR an action plan was suggested by the Ministry of Health, Labor and Welfare in 2016 [2]. The action plan contains the proper use of oral antibiotics (OA). It includes a specific guideline to reduce the use of cephalosporins, fluoroquinolones, and macrolide OA to 50% by 2020 [2]. Each healthcare facility needs to understand the use of antimicrobial agents and their compatibility with the causative microorganism. Furthermore, cooperation between the different departments in an institution should be upheld in order to promote the proper use of antimicrobial agents. Appropriate use of antimicrobials is needed in all healthcare fields. However, it's use has not advanced in the field of dentistry.

Therefore, a study conducted in our institution investigated the use of OA and SSI related to mandibular wisdom tooth extraction (MWTE) in the dental outpatient clinic [3]. This study was a retrospective study. The study did not include factors such as: the patient background, type of surgical procedure, operation time, infection control in the facility, and the perioperative management

* Corresponding author. Division of Oral and Maxillofacial Surgery, Faculty of Dentistry & Graduate School of Medical and Dental Sciences, Niigata University, Japan.
E-mail address: kensukeyoshida-nii@umin.ac.jp (K. Yoshida).

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system. A prospective study may produce a more accurate result in addition to the exclusion of the aforementioned SSI risk factors and the critical observation of SSI cases. Also, SSI is greatly affected by environmental factors. Reports conducted outside Japan focus on different environmental factor [4–9]. The study conducted at the university hospital dentistry department is unified with the environmental factors. Previous reports have shown that antibiotics may or may not reduce the incidence of SSI [4–11]. In addition, the type, dose, administration period, and timing of antimicrobials is not standardized. Thus, antimicrobial use is not unified. The guidelines recommended not to administer prophylactic antibiotics after MWTE [12,13]. However, the Japanese dental wards still administer OA for dental infections (therapeutic antimicrobial administration) and prevention (antimicrobial prophylaxis) of surgical site infections (SSI), each of which adheres to published guidelines [14,15]. Therapeutic antimicrobial administration is recommended as de-escalation therapy [14], and for bacterium identification. Thus, allowing switching to narrow spectrum antibiotics based on the results of antibiotic sensitivity testing. In contrast, the Japanese Practical guidelines for the prevention of postoperative infection recommend antimicrobial prophylaxis [15]. According to the Japanese Practical guidelines for the prevention of postoperative infection, uncomplicated tooth extractions without SSI risk factors do not require OA. The type, dose, and duration of OA for MWTE have been established. Two studies reported that amoxicillin (AMPC)/clavulanic acid (CVA) or AMPC reduced the incidence of SSI [4,5]. This guideline recommends that “single administration of AMPC 1 h before MWTE” or “administration of AMPC 1 h before surgery up to 48 h after surgery. A notable finding in this guideline is that there is a fourfold difference in the amount of AMPC administered per orally for single dose. In addition, within the administration period, there is a 24-fold difference between the minimum and maximum doses, and the dose is left at the discretion of the attending physician. If we can use the appropriate antimicrobials without increasing SSI, the dose of OA can be reduced and the administration period can be shortened. As a result, we can contribute to the reduction of AMR. Therefore, we prospectively surveyed the incidence of SSI and the use of OA (type, dose, and administration period) for MWTE in a dental outpatient clinic [16–19].

2. Materials and methods

2.1. Subjects

This study was a prospective cohort study. The subjects were patients who underwent MWTE in our dental outpatient clinic from May 2019 to April 2020 (1-year duration). The details of OA were left to the discretion of the attending physician in charge according to guidelines of antimicrobial administration, but the administration period was divided into to 2 groups: 1 h before surgery to 24 h post-operatively and 1 h before surgery to 48 h post-operatively. The following information was collected: (1) patient factors (age, gender, body mass index [BMI], the presence/absence of preoperative medications, diagnosis, and impacted wisdom tooth status [Winter classification, Apex position, and Pell-Gregory classification]); (2) surgical factors (operative time, the presence/absence of closure, the presence/absence of hemostat, doctor career, and the type of painkiller); (3) relationship between administration period of OA and SSI occurrence; and (4) details of SSI. Patients were excluded from the study if they had a medical history of a known SSI risk factor, such as: BMI $\geq$25 kg/m^2, diabetes, forgot to take OA as prescribed, penicillin allergy, operative time (greater than 60 min), steroid or immunosuppressant use, and endocarditis. Potential effect modifier was SSI risk factor, such as: BMI $\geq$25 kg/m^2, diabetes, forgot to take OA as prescribed, penicillin allergy, operative time (greater than 60 min), steroid or immunosuppressant use, and endocarditis. All patients who underwent MWTE in our dental outpatient clinic during the investigation period were surveyed as a countermeasure against selection bias. Investigators were not involved in MWTE as a countermeasure against medical surveillance bias.

In a prospective randomized, double-blind, controlled trial following MWTE with AMPC versus placebo, the incidence of SSI was reported to be 0% (0/83) in the AMPC group and 12.5% (5/40) in the placebo group [5].

Because the difference in the incidence of the SSI was 0.125, the sample size of the non-inferiority trial was based on this result. Therefore, the non-inferiority was 0.05, the effectivity rate in both groups was 0.99, the α was 0.025, the 1-β was 0.9, the allocation was 24 h: 48 h = 1:4, and the required number of cases was 310. This paper was conducted in accordance with the strengthening the reporting of observational studies in epidemiology (STROBE) statement [20].

2.2. Definitions of terms

2.2.1. Japanese Practical guidelines for the prevention of postoperative infection [4]

For the MWTE the guidelines recommend: 1) AMPC or CVA/AMPC; 2) AMPC (250 mg-1 g/dose), CVA/AMPC (375 mg-1.5 g/dose); 3) OA administration of a single dose up to 48 h with the first dose 1 h before surgery; and 4) clindamycin for penicillin allergy.

2.2.2. Type of oral antibiotics

AMPC or CVA/AMPC are recommended; however, CVA/AMPC was not covered by dental insurance in Japan when this study commenced, and penicillin allergy was excluded, so the entry was only AMPC.

2.2.3. Dose of oral antibiotics

Range from: minimum of 250 mg/dose to a maximum of 1 g/dose. The minimum single dose of 250 mg/dose was established in consideration with the fact that Japanese has smaller physical size compared to other countries [21].

2.2.4. Use of antibiotics

The administration period ranged from a single dose of OA to administration of OA up to 48 h (3 times a day after each meal). In this study, the dose used was 250 mg and the patients were then divided into 2 groups (1 h before surgery to 24 h after surgery [24 h group] and 1 h before surgery to 48 h after surgery [48 h group]). Total number of AMPC dosage taken by the patients were: 750 mg for the 24 h group, and 1500 mg for the 48 h group. The dentist confirmed that the patients took the exact dosage through a face-to-face interview. The choice of the administration period was left at the discretion of the dentist in charge. The recommended starting time for OA administration according to the Japanese Practical guidelines for the prevention of postoperative infections was 1 h before surgery, so this starting time was adopted in the current study.

2.2.5. Type of painkiller administration

The dentist in charge considered the patient's background and degree of surgical invasion.

2.2.6. Doctor career

Based on the requirements of the Japanese Society of Oral and Maxillofacial Surgeons for specialist application, doctors were

classified into two groups (clinical experience >6 years and residents <5 years after obtaining a license to practice dentistry).

2.2.7. SSI

The body temperature of >37.8 °C with an unknown cause. Patients treated due to abscess within 90 days post-operatively, or those who received additional antibiotics, in reference to the guideline [22]. We defined inflammation by the presence or absence of antibiotics. Our SSI judgment was equivalent to Clavien-Dindo classification grade II or higher [23].

2.2.7.1. Criteria for Clavien–Dindo classification. Grade I: pain and mild swelling, follow-up continued without a prescription for antibiotics.

Grade II: antibiotic treatment prescribed following persistent swelling, marked pain, and drainage from the extraction socket was observed.

Grade IIIa: surgical intervention required under local anesthesia to place a drain, when antibiotic treatment has not improved the abscess formation either on the skin or the extraction socket.

Grade IIIb: surgical intervention under general anesthesia required following no improvement in abscess formation either on the skin or the extraction socket with antibiotics or placement of a drain.

Grade IV: indicates life-threatening complications.

Grade V: represents the patient's death.

The follow-up time was 90 days after MWTE. All patients returned to the referring dental clinic. The follow-up time after surgical removal of mandibular third molar was monitored by the referring dental clinic. If there were no symptoms during that period, it was judged that there was no SSI.

2.2.8. Conditions of impacted mandibular third molar

The position of the impacted mandibular third molars in the occlusal plane were classified into five types according to the Winter's classification [24]. It is as follows (Fig. 2–1):

1 Vertical
2 Mesio-angular
3 Horizontal
4 Disto-angular
5 Inverted

The relationship between the position of the mandibular canal and the root apex of the impacted third molar were classified into five [25], as follows (Fig. 2–2):

Ap 0: The root and mandibular canal do not touch and do not intersect.

Ap 1: The root is in contact with the upper edge of the mandibular canal.

Ap 2-s: The root extends beyond the upper edge of the lower canal to the upper half of the lower canal.

Ap 2-d: Root is above the upper half of the mandibular canal and not below the lower edge of the mandibular canal.

Ap 3: The root extends beyond the lower edge of the mandibular canal.

Surgical removal of the mandibular third molar was classified in terms of the relationship of the position of the anterior edge of the mandibular branch with the crown of the third molar (Class category) and the relationship between the depth of the existing tooth with the depth of the impacted third molar tooth crown (Position category) in reference to the Pell-Gregory classification [26] (Fig. 2–3).

2.2.8.1. Class category. CLASS I: Sufficient amount of space between the ramus and the distal aspect of the second molar for accommodation of the mesio-distal diameter of the crown of the third molar.

CLASS II: The space between the ramus and the distal aspect of the second molar less than the mesio-distal diameter of the crown of the third molar.

CLASS III: All or most of the third molar within the ramus.

2.2.8.2. Position category. POSITION A: The highest portion of the tooth on the level of or above the occlusal line.

POSITION B: The highest portion of the tooth below the occlusal line, but above the cervical line of the second molar.

POSITION C: The highest portion of the tooth on a level with or below the cervical line of the second molar.

2.3. Statistical analysis

We compared the duration of OA (24 h/48 h), with the incidence of the SSI as the primary endpoint. For comparison between two groups, Fisher's exact test was used to compare qualitative data, and the Mann-Whitney *U* test was used to compare quantitative data, and a significance level of $p < 0.05$ was set. JMP v14.2 (14.0) was used for statistical analysis.

2.4. Ethics

This study was conducted with the approval of our Research Ethics Committee (approval number, 2018-0148). Also, all authors declare no conflicts of interest.

3. Results

3.1. Background of patients

A total of 46 cases were excluded in this study, thus a total of 340 subjects were analyzed. 106 cases were in the 24 h group and 234 were in the 48 h group (Fig. 1). There was no difference between the two groups concerning age, gender, BMI, pre-operative medication, diagnosis, and condition of the impacted tooth (Winter's classification, Apex position, and Pell-Gregory classification; Table 1); however, there was a difference between the groups in the Class category of the Pell-Gregory classification ($P < 0.05$; Table 2).

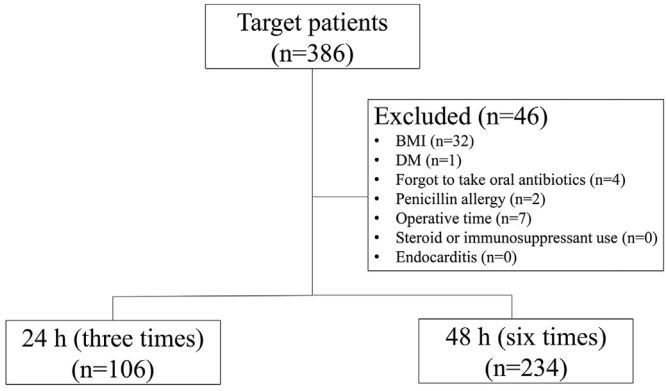

Fig. 1. Mandibular wisdom tooth extraction flow diagram.

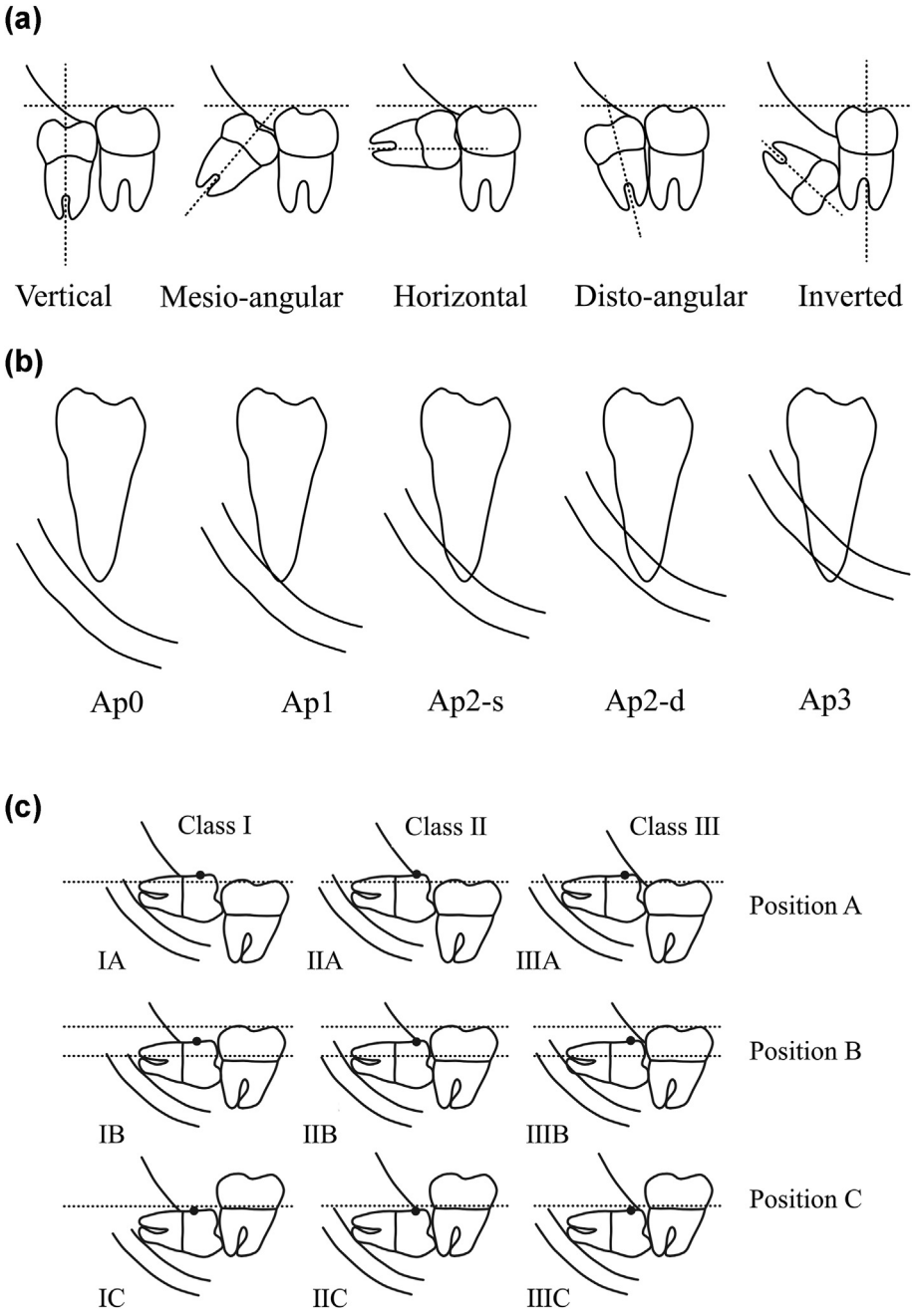

Fig. 2. 1. Winter's classification. 2. Apex classification. 3. Pell-Gregory classification.

3.2. Background of operative factors and painkillers

The average operative time was 21.8 min in the 24 h group and 25.4 min in the 48 h group; the operative time was prolonged in the 48 h group ($P < 0.05$). There was no difference between the two groups concerning the presence or absence of closure, presence or absence of hemostat, doctor's career, or the type of painkillers (Table 3).

3.3. Relationship between period of oral antibiotic administration and SSI occurrence

The overall SSI incidence was 1.1% (4/340 cases); 0.9% (1/106 cases) in the 24 h group, and 1.3% (3/234 cases) in the 48 h group. There was no significant difference between the two groups (Table 4).

3.4. Details of SSI

SSI occurred in 4 cases, with the following details: the median age was 30.5 years (minimum-maximum, 19–38 years); 2 males and 2 females; average BMI of 21.4 kg/m^2 (20.7–22.2 kg/m^2); preoperative medication (0 cases); and the diagnosis was pericoronitis (3 cases) and impacted third molar (1 case). The conditions of the impacted teeth were mesio-angular (2 cases), horizontal (2 cases), Ap 0 (1 case), Ap 1 (2 cases), Ap 2-d (1 case), IC (1 case), IIB (2 cases), IIIB (1 case), smoking (0 cases), and alcohol (0 cases). For the period of administration, 1 case was in the 24 h group and 3 cases

Table 1
Background of patients.

	24 h(n = 106)	48 h(n = 234)	*p*
Age[a]	25(22–34.3)	26(21–35)	0.81[b]
Gender (male: female)	27:79	82:152	0.10[c]
BMI[a]	20.3(18.9–22)	20.8(19.1–22.4)	0.25[b]
Preoperative medication (presence:absence)	11:95	24:210	1.00[c]
Diagnostic			
Dental caries	2	12	0.35[c]
Pericoronitis	27	74	
Impacted wisdom tooth	77	148	
Condition of impacted tooth			
Winter classification			
Vertical	13	33	0.20[c]
Mesio-angular	34	61	
Horizontal	51	132	
Disto-angular	8	8	
Invert	0	0	
Apex position			
Ap0	26	52	0.67[c]
Ap1	50	105	
Ap2-s	9	14	
Ap2-d	20	59	
Ap3	1	4	
Pell-Gregory classification			
I A	39	104	0.87[c]
I B	20	25	
I C	2	1	
II A	24	39	
II B	15	31	
II C	1	1	
IIIA	2	7	
IIIB	3	22	
IIIC	0	4	

[a] Median (interquartile range).
[b] Mann-Whitney *U* test.
[c] Fisher's exact test.

Table 2
Details of Pell-Gregory classification.

	24 h (n = 106)	48 h (n = 234)	*p*
Class category			
I	61	130	0.02[a]
II	40	71	
III	5	33	
Position category			
A	65	150	0.87[a]
B	38	78	
C	3	6	

[a] :Fisher's exact test.

Table 3
Background of operative factor and painkiller.

	24 h (n = 106)	48 h (n = 234)	*p*
Operative time (min)[a]	21.8(11.1)	25.4(13.5)	0.046[b]
Closure (presence: absence)	100:6	229:5	0.10[a]
Hemostat (presence: absence)	20:86	51:183	0.57[a]
Doctor career			
Resident	21	60	0.27[a]
Over 6 years	85	174	
Type of painkiller			
Loxoprofen	100(94.3%)	226(96.6%)	0.54[a]
Acetaminophen	5(4.7%)	6(2.6%)	
Celecoxib	0(0%)	1(0.4%)	
Nothing	1(0.9%)	1(0.4%)	

a:Mean (standard deviation(SD)).
[b]Fisher's exact test.
[c]:Mann-Whitney *U* test.

were in the 48 h group. The average operative time was 37.5 min (range, 15–50 min), closure of surgical site (4 cases), use of hemostat (3 cases), doctor's career (all with clinical experience > 6 y), type of painkiller (all loxoprofen), and 5 doses or more. Extraction time (4 cases) until the onset of SSI was around 27.6 days (range, 22–60 days), hospitalization (0 cases), benzethonium chloride used as mouthwash after SSI (3 cases), and AMPC (2 cases) or azithromycin (2 cases) for SSI. Healing was confirmed in all cases without the condition becoming severe (Table 5).

Table 4
Relationship between administration period of oral antibiotics and SSI occurrence.

		SSI				*P*
Administration period	All	occurrence		non occurrence		
		N	%	N	%	
24 h	106	1	0.9	105	99.1	1.00
48 h	234	3	1.3	231	98.7	

a) Fisher's exact test.

4. Discussion

According to Japanese Practical guidelines for the prevention of postoperative infection established in 2016, ordinary tooth extraction does not generally require OA in cases other than patients with SSI risk factors, such as diabetes and a BMI ≥25 kg/m^2. Therefore, it is important to accurately understand the SSI risk factors to promote the proper use of antimicrobials in uncomplicated tooth extractions. With respect to OA administration for MWTE, various reports have been made on the type of OA, timing, dose, and administration period [6–8]; however, there is still no consensus on the proper use of antimicrobials [9–11]. Specifically,

Table 5
Details of SSI.

No	Age	Sex	BMI	Preoperative medication	Diagnostic	Winter	Apex	Pell-Gregory	Smoke	Alcohol	Administration period(hr)
1	19	female	21.8	No	Perico	Mesio-angular	Ap1	II B	No	No	48
2	29	male	21.0	No	Perico	Horizontal	Ap2-d	IIIB	No	Yes	48
3	38	female	20.7	No	Perico	Mesio-angular	Ap1	II B	No	Yes	48
4	32	male	22.2	No	IWT	Horizontal	Ap0	I C	No	Yes	24

No	Ope(min)	Closure	Hemostat	Doctor career	Painkiller	Removal	SSI(day)	Hosipitalization	Mouthwash	Antibiotics prescribed at SSI
1	25	Yes	Yes	Over 6 years	Loxoprofen	Yes	22	No	BC	AZM
2	50	Yes	No	Over 6 years	Loxoprofen	Yes	23	No	BC	AZM
3	15	Yes	Yes	Over 6 years	Loxoprofen	Yes	60	No	BC	AMPC
4	50	Yes	Yes	Over 6 years	Loxoprofen	Yes	32	No	Nothing	AMPC

IWT: Impacted wisdom tooth.
AZM: Azithromycin, AMPC: Amoxicillin.
BC: Benzethonium Chloride.

there are no reports about prospective studies on the proper use of antimicrobials targeted in the Japanese population. While the Japanese guidelines were prepared with reference to past reports [1,2,5,19,27]. It has been reported that Japanese people are small in physical size compared to other races [21], so when applying overseas guidelines, it is necessary to consider the populations physical size. In addition, other factors such as culture, eating habits, and insurance system differences between Japan and overseas countries should also be considered. For this reason, at first, we investigated the duration of OA use [3]. The study consisted of three groups (24 h, 48 h, and 72 h). Results show that there was no difference among the three groups in SSI. However, our previous study was a retrospective study, therefore we could not include accurate patient background. According to the guidelines, the maximum of duration of OA administration was 48 h, so it was arbitrarily defined as 24 h or 48 h. However, a clear recommendation for appropriate type, dose and timing of OA in Japan is yet to be established. Therefore, in this study we focused on the duration of administration of OA and the SSI incidence in MWTE. In addition, we report the first prospective study in Japan created within the framework of the current guideline.

A sufficient sample size of 386 patients was used in this study. There was no statistical difference between the 24 h and 48 h groups with respect to the patient factors (Table 1). The quality of evidence was improved as a prospective study. Surgical factors (the presence/absence of closure, the presence/absence of hemostat, doctor career, and the type of painkiller) were not statistically different between the 24 h and 48 h groups (Table 3). In the selection of painkillers, loxoprofen was most often used in both groups, and was prescribed within the expected range. The likelihood of using loxoprofen was similar to another report [28], and it was speculated that loxoprofen was the first choice for prescription analgesics after MWTE in a dental outpatient clinic.

In contrast, the operative time was prolonged in the 48 h group ($P < 0.05$). We considered several factors for this reason. It is generally known that the longer the operative time, the higher the risk of SSI [29,30]. Therefore, there is an undeniable tendency that the administration period of OA will increase when a long operative time is estimated before surgery. Since these factors may increase SSI susceptibility. The extension of the operative time is influenced by preoperative image evaluation, the range at which the patient can effectively open his/her mouth and the degree of eruption of the existing teeth. Similarly, prolonging the operative time depends on the doctor's career and skills, but in this study, the bias in clinical experience was denied (Table 3). There was no relationship between the nine pathologic conditions of the Pell-Gregory classification and the administration period of antibiotics (Table 1). However, class category, which reflects the need for bone removal around the impacted wisdom tooth, was significantly related to the administration period of antibiotics. More Class III patients who needed more complex surgery with a large amount of bone removal in the 48-hour group than in the 24-hour group (Table 2). Consequently, this leads to the prolonged operative time in the 48-hour group (Table 3).

The incidence of SSI for MWTE has been reported to be 1.2%–27% [7,10,19]. The overall SSI incidence was 1.1% (4/340 cases) in this study, which was similar to a previous study. Also, the administration period of OA was not related to the incidence of SSI between both groups. Furthermore, we did not find a difference between the groups with respect to the details of SSI. Nevertheless, it was thought that the influence of patient and surgical factors was low. Also, SSI cannot be controlled by OA alone, and are affected by environmental factors, such as the surgical field disinfection method, the method of surgical scrubbing, the operating room ventilation, and the peri-operative management system [31]. This study was conducted by dentists who used the same operating room and were provided the same education and training with the same peri-operative management system, so it was estimated that there was no influence from the environmental factors. Based on our results, it suggests that the 24 h administration of AMPC as the first choice sufficiently prevent SSI in Japanese patients undergoing surgical removal of impacted mandibular third molar without SSI risk factors. On the other hand, reports show that the use of AMPC does not reduce incidence of SSI [7,32]. However, Japanese guideline recommended the use of pre-operative antibiotics. Thus, this study was conducted to reduce the amount of antibiotics use that is still within the range recommended by the guideline.

This study has several limitations. First, the prospective cohort study may introduce unavoidable bias. The second limitation of our study is the uneven number of cases in each group. We also considered the study conducted in the oral surgery department of the university hospital as a limitation of a non-randomized controlled trial. Therefore, randomized controlled trials are needed. Lastly, we thought that operative time, doctor career, and conditions of impacted teeth could be included in the confounding factors. However, we did not perform multivariate analysis because there were not enough events for multivariate analysis.

Notwithstanding, a long OA administration period may lead to the development of AMR and other side effects, such as various allergies [33–36]; thus, administration for a shorter period is desirable. It is speculated that the results of this study would be useful in many respects because shortening the administration of OA also affects medical cost reduction and compliance. In the future, a prospective study using a single dose of antibiotics preoperatively is warranted to determine the proper use of antimicrobials.

5. Conclusion

We suggest that AMPC (250 mg/dose every 8 h x 3 doses beginning 1 h before surgery) might be sufficient to prevent SSI in Japanese dental patients without SSI risk factors.

Authors' contributions

All authors meet the ICMJE authorship criteria.

Contributors

Yoshida was responsible for the organization and coordination of the trial. Kodama was responsible for the data analysis. Yoshida, Nishikawa, and Andrea were the investigators. Toyama and Takagi developed the trial design. All authors contributed to the writing of the final manuscript.

Declaration of competing interest

None
All authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2021.01.018.

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