Original Article

Amoxicillin Versus Amoxicillin-Clavulanate for Prophylaxis of Infection in Dog and Cat Bite/Scratch: A Randomized Comparative Study

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Objective: To compare the infection rates in patients receiving amoxicillin versus amoxicillin-clavulanate as a prophylactic antibiotic in dog and cat bite or scratch wounds.

Materials and Methods: The present report was a single-blind, true experimental study conducted in patients at the risk of rabies exposure category III and presented within 24 hours after dog or cat bites or scratches at the emergency department in Banbung Hospital between February 2018 and May 2018. All patients were randomized to the block size of four and randomized into amoxicillin or amoxicillin-clavulanate group for five days. The outcome of wound infection was evaluated on the third day and the seventh day after receiving the antibiotics.

Results: The overall infection rate was 3%. No statistically significant difference in infection rate between amoxicillin and amoxicillin-clavulanate groups was found (1.7% versus 4.2%, p=0.447). The patients in the amoxicillin-clavulanate group had more adverse drug reactions (17.5% versus 10.3%, p=0.113) than patients who received amoxicillin.

Conclusion: Amoxicillin can be used as a prophylactic antibiotic in dog and cat bite or scratch wounds, and there is no significant difference in infection rate from amoxicillin-clavulanate.

Keywords: Bite wound, Antibiotic prophylaxis, Wound infection, Amoxicillin, Amoxicillin-clavulanate

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Many patients present at the emergency department (ED) with animal bites of which the common causes worldwide are dog and cat bites[(1,2)]. In Thailand, there are an estimated 400,000 dog bites each year leading to mortality and severe health consequences, such as infection, tetanus, and rabies[(3,4)]. Wound infection is the most common complication, occurring in 3% to 25% of dog bites and 30% to 50% of cat bites[(1,5)]. Most of the causative organisms are *Pasteurella* species, *Staphylococcus aureus* including methicillin resistant *S. aureus* (MRSA), *Streptococcus* species, and anaerobic bacteria. *Capnocytophaga canimorsus* and *Bartonella* species occur in bites and scratch wounds. They can lead to severe infection, particularly in immunocompromised patients. Many species isolated from the infected wounds are beta-lactamase producers[(6-10)].

The World Health Organization (WHO) recommends early medical management, prophylactic antibiotics for the high-risk wounds or immunodeficiency people, tetanus vaccine and rabies treatment in patients with animal bites[(1)]. Many guidelines suggest antibiotic administration especially in high-risk injuries, but the options of antibiotics are different and various. Amoxicillin-clavulanate is generally considered the first-line prophylactic treatment as a broad-spectrum antibiotic

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and effective against beta-lactamase organisms[2,11-16]. However, amoxicillin is a recommended antibiotic prophylaxis in the Queen Saovabha Memorial Institute Guideline[17].

However, most evidence and guidelines suggest that amoxicillin-clavulanate is more appropriate than amoxicillin[11-16,18]. The authors' previous study conducted at Banbung Hospital retrospectively between January 2015 and December 2017 reported that the rate of antibiotic prescribing was 82.1% in patients with dog and cat bite or scratch wounds. Amoxicillin was the most used antibiotic (82.4% of all patients with antibiotics prescribed), followed by amoxicillin-clavulanate, which was prescribed for severe injuries, such as large or deep wound[19]. Additionally, Mahasarakham Hospital reported the most common antibiotic use was amoxicillin in bite wound patients[20]. The purpose of the present study was to compare the infection rates in patients, at ED in Banbung Hospital, receiving amoxicillin versus amoxicillin-clavulanate as a prophylactic antibiotic in dog and cat bite or scratch wounds.

Materials and Methods

Study design

The present report was a prospective, single-blinded, true experimental study conducted at ED in Banbung Hospital, a 90-bed community hospital in Chonburi Province, Thailand, between February 2018 and May 2018. Chonburi Provincial Public Health Office approved the present research ethics.

All patients received the usual care at ED, such as dressing, suture, and vaccination by nurses and physicians. ED staffs, physicians, and researcher enrolled the patients as inclusion and exclusion criteria. Researcher generated a random allocation sequence with a random number table. ED physicians did not know the randomized allocation and were consulted for antibiotic prescribing by the researcher after the patients gave informed consent. Participating patients were allocated with a 1:1 randomization, based on blocks of four, into two different treatment approaches (amoxicillin versus amoxicillin-clavulanate for five days in doses as follows, amoxicillin 1,000 mg twice daily or amoxicillin-clavulanate 875 over 125 mg twice daily for adult, or 45 mg per kg per day of amoxicillin twice daily for children). All patients received advice and instruction sheet for wound cleaning, signs of infection, and proper antibiotic using. The primary outcome was wound infection, which was evaluated according to the infection criteria on the third day and the seventh day by the nurses or the physicians. The secondary outcomes were adverse drug reaction, drug adherence, and medication cost. The medication adherence was determined with the patients reports and pill count method by the pharmacist.

The participating patients were contacted directly at the follow-up visit schedule or in a follow-up phone call from the researcher. All study protocols were explained to the physicians, nurses, and staffs at the ED. A wound swab culture was not taken from the patients in general practice but would be done in patients with severe infection, who do not respond to treatment, or who are resistant to an antibiotic.

Operative definitions of the present study were defined as follows, Infected wound met one of three major criteria (fever with temperature greater than 38.0°C, abscess, and lymphangitis) or four of five minor criteria (erythema extended at more than 3 cm from the edge of the wound, tenderness, swelling, purulent drainage, and white cell count of more than 12,000 per mm^3)[6], Wounds at the risk of rabies exposure category III, according to WHO definition, were bites or scratches on broken skin and caused blood appearing or contamination of mucous membrane with saliva[21], High-level immunocompromised hosts include those with combined primary immunodeficiency disorder, within two months after solid organ transplantation, receiving cancer chemotherapy, HIV infection with a CD4 T-lymphocyte count of less than 200 cells per mm^3 for adults and adolescents and less than 15% for infants and children, receiving daily corticosteroid therapy of 20 mg or more of prednisone or equivalent for 14 days or longer, or receiving biologic immune modulators[22].

Patient recruitment and data collection

The present study included Thai patients presenting with dog or cat bite or scratch wounds at the risk of rabies exposure category III that reached the hospital within 24 hours after injury, aged two years or older, and gave informed consent. The following cases were excluded, already infected wound, high-level immunocompromised patients, tendon, bone, joint, or nerve involvement, perineum wounds, HbA1C more than 8.5% within the past six months in diabetes patients, inpatients, delivered case to referral hospital, ineligible case from physician evaluation, penicillin allergy, taking antibiotic within past seven days, receiving medical treatments from other healthcare provider except wound dressing, and unconscious patients.

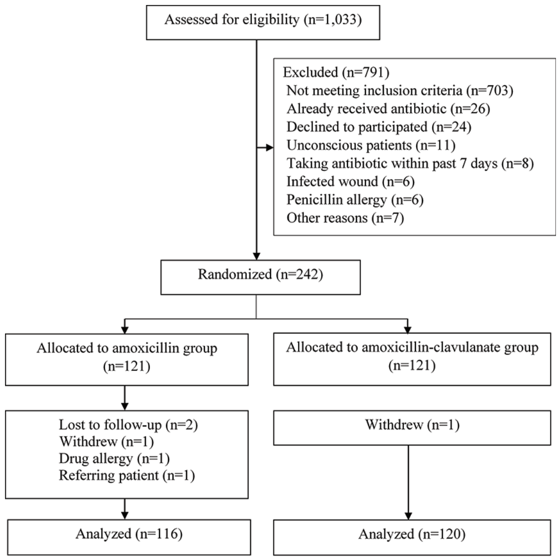

Figure 1. Study flow chart.

Data collected from the patients and medical records included demographics, wound characteristics, antibiotic treatment, wound care, infected wound, adverse drug reaction, and cost of treatment.

The infection rate of amoxicillin-clavulanate in animal bites was reported as 30%[18]. It was estimated that the infection rate of amoxicillin was 50%. Thus, a sample size of 93 patients in each group would be needed for a 5% type I error and 80% statistical power to detect differences in the infection rate between both groups. Therefore, 220 patients were enrolled to compensate for a 10% loss to follow-up.

Data analysis

Data were analyzed by descriptive statistics, chi-square test or Fisher's exact test and independent t-test. Categorical variables were presented as proportions or percentages. Chi-square test or Fisher's exact test was performed for evaluating the association between two paired of categorical variables; odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to estimate the strength of association. The data were analyzed using IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, NY, USA) and p-value less than 0.05 were considered as statistically significant.

Results

Between February 2018 and May 2018, 242 patients participated in the present study. Two patients withdrew from the study, two patients were lost to follow-up, one patient was excluded due to drug allergy, and another patient was referred to another hospital. Consequently, 116 and 120 patients in the amoxicillin and amoxicillin-clavulanate groups were analyzed, respectively. Flow diagram of the present study is shown in Figure 1.

Table 1. Baseline characteristics of the patients

Characteristics	Amoxicillin (n=116) n (%)	Amoxicillin-clavulanate (n=120) n (%)	p-value
Female	62 (53.4)	63 (52.5)	0.884
Age (years); mean±SD	39.0±20.2	39.7±22.0	0.796
Underlying disease	36 (31.0)	40 (33.3)	0.706
Hypertension	19 (16.4)	23 (19.2)	0.576
Dyslipidemia	11 (9.5)	9 (7.5)	0.585
Diabetes mellitus	13 (11.2)	4 (3.3)	0.019
HIV	1 (0.9)	3 (2.5)	0.622
Cancer	1 (0.9)	0 (0.0)	0.492

SD=standard deviation; HIV=human immunodeficiency virus

Of the 236 patients, 53% were females with a mean age of 39.4 years (SD 21.1 years, range 2.0 to 84.2 years), and 67.8% had no underlying disease. Diabetes mellitus patients in the amoxicillin group were significantly more than in the amoxicillin-clavulanate group (11.2% versus 3.3%, p=0.019). Patient characteristics in the amoxicillin and amoxicillin-clavulanate groups are shown in Table 1.

Most wounds were caused by dog bites (75%), followed by cat bites (18.2%) and scratches (6.8%). Most of the wounds were located on the leg and abrasion wound was the most common type. Only 14 patients received wound sutures (5.9%). Wound characteristics are shown in Table 2.

Seven patients developed wound infection (3%), four patients were bitten by dogs and two of which received amoxicillin, three patients were bitten by cats and received amoxicillin-clavulanate. The infection rates were low in both antibiotic groups and were not significantly different [1.7% in amoxicillin group versus 4.2% in amoxicillin-clavulanate group (OR 2.478, 95% CI 0.471 to 13.03), p=0.447]. Among the infected patients, six patients were treated with appropriate wound care as outpatient. One patient denied additional therapies and then was lost to follow-up after diagnosed as wound infection, so the outcome after treatment of this patient was unknown. Two of the infected patients received amoxicillin-clavulanate as treatment antibiotic for five and seven days. Clinical features, antibiotic use, and treatment outcomes of infected patients are summarized in

Table 2. Wound characteristics

Characteristics	Amoxicillin (n=116) n (%)	Amoxicillin-clavulanate (n=120) n (%)	p-value
Cause			0.025
Dog bites	78 (67.2)	99 (82.5)	
Cat bites	28 (24.1)	15 (12.5)	
Cat scratches	10 (8.6)	6 (5.0)	
Duration from injury to visiting ED (hours)			0.962
<1	33 (28.4)	36 (30.0)	
1 to 3	48 (41.4)	48 (40.0)	
≥4	35 (30.2)	36 (30.0)	
Location of wound*			
Leg	47 (40.5)	59 (49.2)	0.182
Hand	31 (26.7)	22 (18.3)	0.123
Arm	14 (12.1)	15 (12.5)	0.920
Foot	12 (10.3)	15 (12.5)	0.603
Head and face	9 (7.8)	9 (7.5)	0.940
Body	5 (4.3)	4 (3.3)	0.746
Type of wound*			
Abrasion wound	72 (62.1)	62 (51.7)	0.107
Laceration wound	40 (34.5)	54 (45.0)	0.099
Puncture wound	32 (27.6)	33 (27.5)	0.988
Wound suture	4 (3.4)	10 (8.3)	0.112

ED=emergency department

* Data considered from patients with multiple wounds

Table 3. Subgroup analysis in 150 patients with laceration or puncture wounds found that the infection rates of amoxicillin and amoxicillin-clavulanate groups were 3% (2 of 67 patients) and 6% (5 of 83 patients), respectively [(OR 2.083, 95% CI 0.391 to 11.095), p=0.461].

Adverse drug reactions were reported in 33 patients (14%), and diarrhea was the most frequent event occurring in 20 patients (60.6%). The patients in the amoxicillin-clavulanate group had more adverse drug reaction than those in the amoxicillin group [17.5% versus 10.3% (OR 1.838, 95% CI 0.859 to 3.934), p=0.113]. Most of the reactions were minor. However, one patient in the amoxicillin-clavulanate group discontinued taking the drug three days after participating because of severe vomiting, but the wound was cured. One hundred fifty patients followed the direction for taking antibiotics as prescribed (63.6%). Non-adherence patients were in the amoxicillin group more than in the amoxicillin-clavulanate group [42.2% versus 30.8% (OR 0.61, 95% CI 0.357 to 1.04), p=0.069]. The reasons for non-adherence were dose missing (27.5%), incorrect frequency or dose administration (7.2%), and drug discontinuation (1.7%). Medication adherence was mostly determined from the patients' reports and only 37.7% of the patients were determined by pill count method since many patients did not bring their medicines in the follow-up visit. The comparison of infection outcome, adverse drug reaction, and medication adherence in both antibiotic groups are shown in Table 4. The infection rates were not significantly different between adherence (5 of 150 patients; 3.3%) and non-adherence patients (2 of 86 patients; 2.3%), respectively [(OR 0.69, 95% CI 0.131 to 3.638), p=1.000].

The total medical expenses for 236 patients attending at ED were 521,218 baht, 75.6% of the total expenses was the cost of rabies immunoglobulin. Average prices for taking amoxicillin and amoxicillin-clavulanate for five days were 40 and 70 baht per

Table 3. Clinical features, antibiotic use, and treatment outcomes of infected patients (n=7)

Sex/ age (years)	Comorbidity	Cause/ duration (hours)	Location/ type of wound	Suture	Prophylactic antibiotic	Treatment antibiotic	Outcome after treatment
F/35.5	None	Dog bite/1	Leg/LW	No	Amoxicillin	None	Cure
F/37.2	Allergies	Dog bite/4	Leg/LW, AW	No	Amoxicillin	None	Cure
F/33.2	None	Dog bite/0.3	Foot/PW, AW	No	Amoxicillin-clavulanate	Amoxicillin-clavulanate	Cure
M/44.2	HT	Dog bite/3	Foot/LW	No	Amoxicillin-clavulanate	None	Cure
M/82.3	HT, DM, CKD, DLP, gout	Cat bite/4	Hand/PW	No	Amoxicillin-clavulanate	None	Cure
M/41.0	HT, DLP	Cat bite/0.2	Hand/PW	No	Amoxicillin-clavulanate	Amoxicillin-clavulanate	Cure
F/69.7	None	Cat bite/0.7	Arm/PW, LW	Yes	Amoxicillin-clavulanate	Denied treatment	Unknown

F=female; M=male; HT=hypertension; DM=diabetes mellitus; CKD=chronic kidney disease; DLP=dyslipidemia; LW=laceration wound; AW=abrasion wound; PW=puncture wound

Table 4. Outcomes of infection, adverse drug reaction, and medication adherence

Outcome	Amoxicillin (n=116) n (%)	Amoxicillin-clavulanate (n=120) n (%)	Odds ratio (95% CI)	p-value
Infected wound	2 (1.7)	5 (4.2)	2.478 (0.471 to 13.036)	0.447
Adverse drug reaction	12 (10.3)	21 (17.5)	18.38 (0.859 to 3.934)	0.113
Diarrhea	8 (6.9)	12 (6.9)	1.500 (0.590 to 3.815)	0.392
Nausea	2 (1.7)	5 (4.2)	2.478 (0.471 to 13.036)	0.447
Vomiting	0 (0.0)	3 (2.5)	-	0.247
Dizziness	2 (1.7)	2 (1.7)	0.966 (0.134 to 6.975)	1.000
GI discomfort	1 (0.9)	1 (0.8)	0.966 (0.060 to 15.634)	1.000
Non-adherence	49 (42.2)	37 (30.8)	0.610 (0.357 to 1.040)	0.069

CI=confidence interval; GI=gastrointestinal

person, respectively. Antibiotic prescription was 2.5% of the total medical costs.

Discussion

Among all ED presentations with bite or scratch wounds in the present study, the overall wound infection rate was very low at 3%. The infection rates in dog bite and cat bite wounds were 2.3% and 7%, respectively. The three infected patients from cat bites presented with the puncture wound. The infection rate of cat bite wound was higher than dog bite because of the deeper wound from slender and sharp teeth, which could easily penetrate into tissues, bones, and joints, leading to serious complications[23]. The infection rate in the amoxicillin-clavulanate group was lower than in the previous studies[18,24]. However, those studies were heterogeneous and had different infected wound definition. In the present study, a rigid criteria of wound infection was used, which required one of the major criteria or four of five minor criteria to be diagnosed. Additionally, abrasion wounds were the most type of wounds in the present study and were at the low-risk of infection in comparison with laceration and puncture wounds[25]. That probably led to fewer infection compared with other studies.

Prescribing amoxicillin and amoxicillin-clavulanate twice daily for five days in the dog and cat bite or scratch patients showed that the infection rates were not significantly different in both antibiotic groups. In previous studies, the microbiology of infected wound has shown that *Pasteurella* species are the most common pathogens and some of them were beta-lactamase producers, so amoxicillin-clavulanate is an appropriate choice for prevention and treatment. Nonetheless, no strong evidence supports using amoxicillin-clavulanate in bite wound, and recommendations on antibiotic choice are based on in vitro susceptibility data[26,27]. Additionally, the susceptibility of common bite isolates has shown that penicillin and ampicillin have activity against *Pasteurella* spp., *Capnocytophaga* spp., and Streptococci[10]. Thus, in the cases where the pathogen is isolated without beta-lactamase activity, amoxicillin is also an effective antibiotic. However, the wound culture at the time of injury might fail to isolate organisms and cannot predict whether the wound will be infected, so that the wound cultures should not be obtained in bite wound without infection[28,29].

At Banbung hospital, the ED physicians in general practice did not swab culture before prescribing antibiotic according to Queen Saovabha Memorial Institute and Rational Drug Use Guideline, Thailand, which recommend prescribing antibiotic for prophylaxis infection in bite wound without the requirement of wound culture[13,17]. Thus, there were not provided microbiological data in the present study, which might cause reporting bias and could not determine the proper antibiotic choice from the susceptibility of causative pathogens. Additionally, antibiotic options may be based on the results of drug resistance in each area. The isolated pathogen from the infected wound has shown antibiotic-resistant *S. aureus* especially MRSA that was a cause of severe infection[5,15]. National Antimicrobial Resistance Surveillance Center of Thailand found the higher report of MRSA in Bangkok (18.6% to 22.5%) and Region 10 Health provider in Northeastern of Thailand (11.4% to 18.4%). Region 6 Health provider in Eastern of Thailand, including Chonburi, reported 13.7% MRSA in 2017 and decreased to 11.1% in 2019[30]. Thus, no statistically significant difference in infection rates between both groups was found. This might be because of the low incidence of drug resistance in this setting area.

Patients in the amoxicillin group seemed to have more infected wounds than in the amoxicillin-clavulanate group since patients in the amoxicillin group had higher diabetes and non-adherence patients. However, the infection rate in the amoxicillin group was lower but not significantly different from the amoxicillin-clavulanate group.

The wound at the risk of rabies exposure category III, which were broken skin wound and caused blood to appear or contamination of mucous membrane with saliva, were reported as the highest infection rate in the authors' previous retrospective study (6%)[19]. Although patients with this wound category were included in the present study, but many patients presented only with abrasion wound and did not develop infections. Subgroup analysis in the high-risk patients with laceration or puncture wounds found that the infection rate was higher but also not significantly different in both antibiotic groups.

In the present study, 220 patients were needed for a 5% type I error and a 80% statistical power for finding the statistically significant difference in wounds infection between both antibiotic groups. While the present study collected enough sample size with 236 patients, the infection rates were lower than the authors' estimation and previous study[18]. The results could not detect an important difference in the primary outcome. This might be because of the low infection rate and low incidence of antibiotic resistance as discussed above.

An adverse reaction occurred in the amoxicillin-clavulanate group more frequently than in the amoxicillin group but was not significantly different (p=0.113). Both antibiotics have been associated with gastrointestinal side effects, such as diarrhea, nausea, and vomiting. In addition, amoxicillin-clavulanate reported higher adverse events according to the results in the present study[31,32]. Some patients did not take the antibiotics as prescribed, which might have affected the infection outcomes. However, there was no significant difference in infection rates between the adherence and non-adherence groups. The authors determined medication adherence from patient report and pill count methods. However, many patients were evaluated by interviewing. Therefore, the outcomes might be less accurate for estimating the patient's drug-taking behavior.

Prescribing amoxicillin as a prophylactic antibiotic for five days costed less than amoxicillin-clavulanate. Nevertheless, the present study excluded high-risk status of infection such as tendon, nerve, or bone injury, and high-level immunocompromised host, physicians might consider broad-spectrum antibiotic to these patients depending on the patient and wound characteristics in the individual case.

There were some limitations of the present study. Both antibiotics showed different appearances and drug labels, so the patients were not blinded. The present study did not provide microbiological data. The results could be applied in those meeting the inclusion and exclusion criteria, but the use of amoxicillin in the patient with complicated wounds or high-risk status would require further investigation. Additionally, differences in antibiotic resistance incidence in each setting area might have affected the application of the present study.

Conclusion

Wound infection rates in the dog and cat bite or scratch patients were low and not significantly different between the amoxicillin and amoxicillin-clavulanate groups. The present finding indicated that amoxicillin could be an antibiotic choice for preventing infection in dog or cat bite or scratch wounds in the patient at the risk of rabies exposure category III with low cost and less adverse events in comparison to amoxicillin-clavulanate.

What is already known on this topic?

Amoxicillin-clavulanate is considered as the first-line prophylactic antibiotic in dog and cat bite or scratch wounds but amoxicillin is still a recommended antibiotic choice in some local guidelines.

What this study adds?

Amoxicillin can be used as a prophylactic antibiotic in dog and cat bite or scratch wounds without increasing the rate of wound infection in comparison with amoxicillin-clavulanate.

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Conflicts of interest

The authors declare no conflict of interest.

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