PHARMACY

Antibiotics consumption in neurosurgery versus appendectomy: a call for antibiotic stewardship initiatives

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Abstract

Background and aims. Surgical site infection (SSI) remains a significant global health concern, including in Indonesia. The administration of prophylactic antibiotics plays a pivotal role in the prevention and the reduction in mortality rates associated with SSIs. Prophylactic antibiotic use is recommended in surgical procedures that are at risk of infection, including in clean surgical operations that last more than three hours and clean-contaminated surgeries. The objective of this study was to analyze the quantity of prophylactic antibiotic consumption and to compare the consumption of antibiotics between neurosurgery (clean surgery) and appendectomy (clean-contaminated surgery).

Methods. Data in this observational study were obtained from the medical records of patients who underwent neurosurgery and appendectomy at two hospitals in Surabaya: one private and one public hospital. The quantity of antibiotic consumption will be analyzed descriptively and presented as a defined daily dose (DDD) per 100 bed days.

Results. Research findings revealed a higher quantity of antibiotic consumption in elective neurosurgery, representing 47.43 DDD/100 bed-days, in comparison to 21.26 DDD/100 bed-days and 76.34 DDD/100 bed-days in elective and emergency appendectomy, respectively. The most frequently used antibiotics were broad-spectrum antibiotics, which included cefixime (36.91 DDD/100 bed-days) and ceftriaxone (5.45 DDD/100 bed-days) in elective neurosurgery; and ceftriaxone (14.94 vs 50.86 DDD/100 bed-days) and metronidazole (5.75 vs 19.16 DDD/100 bed-days) in elective and emergency appendectomy, respectively.

Conclusion. The consumption of prophylaxis antibiotics remains a significant concern. In order to develop strategies to prevent bacterial resistance through an antibiotic stewardship program, it is essential to evaluate antibiotic consumption and monitor trends over time.

Keywords: antibiotic prophylaxis, neurosurgery, appendectomy, antimicrobial stewardship, drug evaluation

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Background and aims

The prevalence of surgical site infections (SSIs) represents a significant global public health concern in the context of surgical procedures. The incidence of SSIs varies among countries, with a global incidence rate of 5-10% [1]. Additionally, SSIs are becoming more prevalent in low- and middle-income countries, with an incidence rate that could exceed 15% [2-4]. Indonesia is one of the low-middle income countries, with a reported SSI incidence ranging from 13.10% to 56.7% [5-8].

SSIs have been identified as one of major risk factors of 30-day postoperative mortality, which further make SSI listed as the third leading cause of death globally [9-11]. Moreover, SSIs have been linked to an increased length of stay, higher healthcare costs, increased morbidity, poorer therapeutic outcomes, and a longer course of antibiotic therapy [3,12,13]. Hence, in order to prevent the incidence of SSI, antibiotic prophylaxis is required in surgical procedures, especially clean surgery and clean-contaminated surgery [14]. Clean surgery is defined as a surgical procedure that is planned and performed in uninfected anatomical areas, without opening the gastrointestinal, biliary, urinary, or respiratory tracts. These procedures typically involve primary skin closure, with or without the application of closed drains. On the other hand, clean-contaminated surgery refers to operations involving hollow organs, such as the gastrointestinal, biliary, urinary, respiratory, or reproductive systems (excluding the ovaries), or surgeries where contamination is not evident. In general, the administration of prophylactic antibiotics is not required for clean surgery, unless the procedure is performed within a body cavity which, if infected, would pose a significant risk, such as neurosurgery or clean surgery lasting more than three hours [14].

Neurosurgery is classified as a clean surgery, with a relatively high incidence of surgical site infections [14-17]. A systematic review and meta-analysis conducted by Lee et al. (2024), revealed that the incidence of SSIs at one and three months post-neurosurgery was 4.03% and 6.17%, respectively. Furthermore, the study indicated that 13.9% of patients were readmitted and 16.3% required reoperation due to SSI post-neurosurgery [18]. It is worth emphasizing that SSIs in neurosurgery could result in significant complications, including meningitis, encephalitis, epidural abscess, subdural empyema, and brain abscess, which can be life-threatening [19-21].

Another type of surgical procedure is the appendectomy, which is classified as clean-contaminated surgery [14]. The global incidence of surgical site infection (SSI) in patients undergoing appendectomy is comparatively high, with a range of 6.4% to 7.7% [22-25]. Notably, this incidence is even higher in low-middle income countries, including Indonesia, reaching rates up to 11% [22]. The SSI post-appendectomy can be caused by the presence of a large number of normal flora within the intestine, which may enter and infect the surgical wound [22,23].

To reduce the prevalence of SSI in surgical procedures, including neurosurgery and appendectomy, antibiotic stewardship programs (ASPs) should be implemented [26-28]. These programs are systematic initiatives designed to promote the responsible use of antimicrobials, enhance treatment efficacy, limit the emergence of resistance, and control the spread of infections caused by resistant microorganisms [29,30]. A commonly used metric in ASPs is the defined daily dose (DDD), which was developed by the World Health Organization (WHO). Within the framework of ASPs, the DDD is used to quantify the antibiotic consumption, monitor and evaluate patterns of antibiotic use, identify trends, and detect potential overuse or misuse in clinical practice [29-31].

Prior to the present study, the available published research on the quantity of prophylactic antibiotic use in patients undergoing neurosurgery and appendectomy was relatively limited. The study by Nasare et al. (2023) revealed an increase in the consumption of antimicrobial agents in neurosurgery from 125.7 to 155.5 DDDs/100 days within a five-year observation. The consumption of Watch group antibiotics, as defined by the WHO AWaRe classification, was higher than that of Access group antibiotics in both the intensive care unit (ICU) and in patient department settings, representing over 75% of the total antibiotic consumption [32]. Effort to prevent SSI by relying heavily on the use of antibiotic should be taken with precaution because antibiotic consumption was associated with the developmental of antibiotic resistant pathogens [28,33].

A relatively limited number of studies aiming to identify the use of antibiotic prophylaxis in an Indonesian setting have been documented in the published literature [34,35]. Majority of the studies were specifically conducted among adult patients undergoing surgery and ceftriaxone was found as the most common used antibiotic for prophylaxis in both neurosurgery and appendectomy surgery [34-36]. It should be mentioned that the profile of antibiotic use in pediatric patients in an Indonesian setting is yet to be explored.

In light of the potential risk of SSIs and the pivotal role of responsible antibiotic use, it is essential to assess the utilization of antibiotics. The most common method of evaluating antibiotic use is to assess the quantity of antibiotics using the defined daily dose (DDD) [28,33,37,38]. Based on the classification of the surgical procedure, the quantity of antibiotics administered during clean surgery (neurosurgery) is expected to be lower than in clean-contaminated surgery (appendectomy). However, no studies have been conducted to compare the antibiotic consumption in both types of surgery, especially in Indonesia. Thus, this study aims to analyze the quantity of prophylactic antibiotic consumption and to compare the consumption of antibiotics in patients undergoing neurosurgery (clean surgery) and appendectomy (clean-contaminated surgery).

Methods

Study design and setting

This research is a descriptive observational study with retrospective data collection. Data were collected from medical records in two tertiary care hospitals in Surabaya, i.e one private hospital and one public hospital. The private hospital has 205 beds, whereas public hospital has 293 beds. This research has been reviewed by the Institutional Ethical Committee of the University of Surabaya and obtained a research ethics permit (letter number 013/KE/KEPK/2020 and 142/KE/XI/2020).

Population and sample

The population in this research consists of all patients who underwent neurosurgery or appendectomy from January 2019 to November 2020. The research sample was selected using a purposive sampling technique. Patients who met the research criteria were included in this research. The inclusion criteria in this research were: (1) patients aged over 5 years; (2) patients who received prophylactic antibiotics before surgery; and (3) patients with complete medical records.

Data collection

Data were collected using a standardized data collection form consisting of two sections: patient characteristics and antibiotic profile. Patient characteristics included sex, age, diagnosis and length of stay (LOS), type of surgical procedure. The type surgical procedure may be categorized as either elective or emergency surgery. Elective surgery is defined as a surgical procedure that is not an emergency and can be scheduled in advance. In contrast, emergency surgery is defined as a surgical procedure that must be performed without delay in order to save the life of a patient. Antibiotic profile in this study included type of antibiotics, dosage, route of administration, and Anatomical Therapeutic Chemical (ATC) code.

Data analysis

Data were analyzed descriptively. Patient characteristics were collected and presented in tables and graphs, followed by descriptive explanations. Antibiotic quantity profiles were classified using the ATC system to obtain DDD values for each antibiotic and analyzed using the Defined Daily Dose (DDD)/100 days, according to the following formula [40]:

$$\text{DDD/100 bed-days} = \frac{\text{Antibiotic consumption (g)}}{\text{WHO DDD antibiotic (g)}} \times \frac{100}{\text{total patients' length of stay}}$$

In addition, antibiotics prophylaxis in this study were also classified according to the 2021 WHO AWaRe classification [40].

Results

A total of 180 medical records were reviewed in this research, consisting of 142 records from patients who had neurosurgery and 38 records from patients who had an appendectomy. Of the 38 patients who underwent appendectomy, 23 patients had uncomplicated appendicitis and 15 patients had complicated appendicitis. The majority of patients undergoing neurosurgery and appendectomy with uncomplicated appendicitis were female (more than 60%), whereas the majority of patients with complicated appendicitis were male (73%). Most neurosurgery patients (81.69%) were over 46 years old. Out of 180 patients, 18.33% were patients under 17 years old (Table I).

All patients included in this study underwent elective neurosurgery. The antibiotic with the highest defined daily dose (DDD) per 100 bed-days in patients undergoing neurosurgery is cefixime (36.91 DDD/100 bed-days), which implies that, on average, each patient receives 0.36 DDD of cefixime per inpatient day. According to the 2021 WHO AWaRe classification, most antibiotics used in neurosurgery were categorized as ‘Watch’ and ‘Access’ antibiotics, each accounting for 37.5%. In addition, two reserve antibiotics were found to be administered in patient underwent neurosurgery: tigecycline (2.58 DDD/100 bed-days) and meropenem (0.16 DDD/100 bed-days). A detailed description of the antibiotics used in neurosurgery could be found in table II.

Table I. Patients characteristics (N=180).

Characteristics	Clean surgery (N=142)	Clean-contaminated surgery (N=38)	
	Neurosurgery (n, %)	Uncomplicated appendicitis[1] (n, %)	Complicated appendicitis[2] (n, %)
Gender			
• Male	48 (33.80)	9 (39.13)	11 (73.33)
• Female	94 (66.20)	14 (60.87)	4 (26.67)
Age (years)			
• 6 – <12	2 (1.41)	3 (13.04)	1 (6.67)
• 12 – <17	3 (2.11)	4 (17.39)	2 (13.33)
• 17 – <26	4 (2.82)	2 (8.70)	2 (13.33)
• 26 – <36	3 (2.11)	3 (13.04)	4 (26.67)
• 36 – <46	14 (9.86)	6 (26.09)	2 (13.33)
• 46 – <56	35 (24.65)	4 (17.39)	1 (6.67)
• 56 – <65	36 (25.35)	1 (4.35)	2 (13.33)
• 65<	45 (31.69)	0	1 (6.67)
Total LOS (days)	4,072	87	86

[1] – acute appendicitis (K.35), acute appendicitis unspecified (K35.8); [2] – generalized peritonitis (K35.2), perforation (K35.3), peritoneal abscess (K35.3); LOS: length of stay

Table II. Prescribed prophylactic antibiotics for neurosurgery in DDD/100 bed-days.

Variable	ATC code	WHO AWaRe classification	DDD/100 bed-days
Elective			
Tigecycline	J01AA12	Reserve	2.58
Meropenem	J01DH02	Reserve	0.16
Ceftriaxone	J01DD04	Watch	5.45
Cefixime	J01DD08	Watch	36.91
Moxifloxacin	J01MA14	Watch	0.80
Gentamicin	J01GB03	Access	1.06
Amikacin	J01GB06	Access	0.25
Metronidazole	J01XD01	Access	0.22
Total			47.43
Emergency	-	-	-

Table III. Prescribed prophylactic antibiotics for appendectomy in DDD/100 bed-days.

Variable	ATC code	WHO AWaRe classification	Type of appendicitis		
			Uncomplicated appendicitis[1]	Complicated appendicitis[2]	Total
Elective					
Cefuroxime	J01DC02	Watch	0.57	-	0.57
Ceftriaxone	J01DD04	Watch	14.94	4.65	19.59
Metronidazole	J01XD01	Access	5.75	4.65	10.40
Total			21.26	9.30	30.56
Emergency					
Cefotaxime	J01DD01	Watch	-	0.58	0.58
Ceftriaxone	J01DD04	Watch	50.86	61.63	112.49
Cefixime	J01DD08	Watch	4.02	0.58	4.60
Ciprofloxacin	J01MA02	Watch	-	4.36	4.36
Cefazolin	J01DB04	Access	2.30	1.55	3.85
Metronidazole	J01XD01	Access	19.16	54.65	73.81
Total			76.34	123.35	199.69

[1] – acute appendicitis (K.35), acute appendicitis unspecified (K35.8); [2] – generalized peritonitis (K35.2), perforation (K35.3), peritoneal abscess (K35.3); A – WHO Access classification; Wa – WHO Watch classification; Re – WHO Reserve classification.

The patients with appendicitis included in this study underwent either elective or emergency appendectomy. Ceftriaxone is the most commonly used as a prophylactic antibiotic both in elective and emergency appendectomy with 19.59 DDD/100 bed-days and 112.49 DDD/100 bed-days, respectively. The antibiotic recommended for appendectomy prophylaxis by American Society of Health System Pharmacist (ASHP) guideline and the Ministry of Health Republic Indonesia guideline published in 2021 is cefazolin, either alone or in combination with metronidazole. Metronidazole was identified as the second most commonly used antibiotic in both elective (10.40 DDD/100 bed-days) and emergency appendectomy procedures (73.81 DDD/100 bed-days). In contrast, the use of cefazolin in emergency appendectomy cases accounted for only approximately 2% of the total DDD (3.85 out of 199.69 DDD/100 bed-days; table III). According to the 2021 WHO AWaRe classification, antibiotics for both elective and emergency appendectomies are mainly categorized as 'Watch'.

The use of prophylactic antibiotic in clean surgery (elective neurosurgery) was found to be two times higher than in clean-contaminated surgery (elective appendectomy), with 47.43 DDD/100 bed-days compared to 21.26 DDD/100 bed-days. A detailed description of the antibiotics used in neurosurgery, compared with those used in appendectomy, can be found in table II and table III.

Antibiotics for patients with appendicitis were administered at a relatively various points of time in the surgical process, including before, during, and after surgery. The quantity of antibiotic use in patients with uncomplicated appendicitis before, during, and after surgery was 12.64 DDD/100 bed-days, 27.30 DDD/100 bed-days, and 57.66 DDD/100 bed-days, respectively. In contrast, patients with complicated appendicitis showed a markedly increased quantity of antibiotic use before, during, and after surgery, reaching 13.28 DDD/100 bed-days, 23.45 DDD/100 bed-days, and 95.93 DDD/100 bed-days, respectively. The use of antibiotics after elective appendectomy surgery (beyond 24 hours after the procedure) is 1-4 times higher than during surgery. Furthermore, antibiotic use for emergency appendectomy after surgery is 2-5 times higher compared to during surgery (Table IV).

Table IV. Prescribed antibiotic for appendectomy.

Variable	ATC code	Uncomplicated[1] – Complicated[2]		
		Before	During	After
Elective				
Cefuroxime (Wa)	J01DC02	0.00 – 0.00	0.57 – 0.00	0.00 – 0.00
Ceftriaxone (Wa)	J01DD04	2.30 – 1.16	3.45 – 1.16	9.20 – 2.33
Metronidazole (A)	J01XD01	0.00 – 1.16	0.00 – 1.16	5.75 – 2.33
Total		2.30 – 2.32	4.02 – 2.32	14.95 – 4.66
Emergency				
Cefazolin (A)	J01DB04	0.00 – 0.78	2.30 – 0.78	0.00 – 0.00
Cefotaxime (Wa)	J01DD01	0.00 – 0.00	0.00 – 0.58	0.00 – 0.00
Ceftriaxone (Wa)	J01DD04	6.90 – 7.56	17.53 – 11.63	26.44 – 42.44
Cefixime (Wa)	J01DD08	0.00 – 0.00	0.00 – 0.00	4.02 – 0.58
Ciprofloxacin (Wa)	J01MA02	0.00 – 0.87	0.00 – 0.58	0.00 – 2.91
Metronidazole (A)	J01XD01	3.45 – 1.74	3.45 – 7.56	12.26 – 45.35
Total		10.35 – 10.95	23.28 – 21.13	42.72 – 91.28

[1] – acute appendicitis (K.35), acute appendicitis unspecified (K35.8); [2] – generalized peritonitis (K35.2), perforation (K35.3), peritoneal abscess (K35.3); A – WHO Access classification; Wa – WHO Watch classification; Re – WHO Reserve classification.

Discussion

A number of different types of antibiotics are used in neurosurgery for prophylaxis and cefixime is the most frequently used antibiotic in patients undergoing neurosurgery. Furthermore, ceftriaxone is the second most commonly used antibiotic in neurosurgery. Cefixime and ceftriaxone are classified as the third-generation cephalosporin antibiotics with a broad spectrum of activity [41]. In accordance with the national antibiotic guidelines provided by ASHP guideline and the Ministry of Health Republic Indonesia guideline, cefazolin at a dose of 2 grams intravenously is the recommended prophylactic antibiotic for patients undergoing neurosurgery, including craniotomy, spinal cord surgery, and cerebrospinal fluid shunting [14,42]. The published evidence indicated that the use of third-generation cephalosporins was not superior compared to conventional antibiotics (cefazoline, trimethoprim/sulfamethoxazole, ampicillin/sulbactam, vancomycin and gentamicin) as a prophylaxis in neurosurgery. It was documented that the overall incidence of surgical site infections (SSIs) following neurosurgery was not statistically different between the use of third generation cephalosporins and conventional antibiotics (OR 0.94; 95% CI 0.59-1.52). The results of the study regarding the incidence of SSIs, such as osteomyelitis, meningitis, intracranial infection and disc space also demonstrated a non-significant difference between third generation cephalosporins and conventional antibiotics (OR 0.88; 95% CI 0.45-1.74) [43]. In addition to the lack of superiority in efficacy, it should be emphasized that the overuse of third-generation cephalosporins can result in the emergence of third-generation cephalosporin-resistant Enterobacterales (3GCRE) due to the production of beta-lactamases, particularly extended-spectrum beta-lactamases (ESBL). This phenomenon could potentially lead to the incremental of last-resort antibiotics utilisation, including carbapenems, which could exacerbate the global resistance problem [44,45]. The World Health Organization (WHO) has previously identified third-generation cephalosporin-resistant Enterobacterales (3GCRE) as a critical priority with the highest priority for monitoring in terms of resistance issues globally [45].

Ceftriaxone and metronidazole are two types of prophylactic antibiotics that are commonly employed in patients undergoing appendectomy, both in elective and emergency surgery. The recommended antibiotic for prophylaxis in patients undergoing appendectomy is cefazoline, administered intravenously at a dose of 2 grams alone [14,42] or in combination with metronidazole, administered intravenously at a dose of 500 mg [46-48]. A review of the literature reveals no studies that have directly compared the efficacy and safety of cefazoline-metronidazole and ceftriaxone-metronidazole as prophylactic antibiotics for appendectomy. A number of published studies have demonstrated that the combination of ceftriaxone with metronidazole represents the optimal antibiotic choice for patients presenting with complicated or perforated appendicitis [49-52]. As previously described, the inappropriate use of ceftriaxone as a prophylactic antibiotic has the potential to result in the emergence of 3GCRE bacteria [44,45].

The consumption of antibiotics in elective neurosurgery (clean surgery) demonstrated a higher quantity than that observed in appendectomy (clean-contaminated surgery) which 47.43 DDD/100 bed-days compared to 21.26 DDD/100 bed-days. In general, prophylactic antibiotics are not indicated for clean surgeries, except in procedures with higher risk of infection, including neurosurgery and surgeries that exceed 3 hours in duration. In the national antibiotic guidelines provided by the Ministry of Health in 2021, the recommended antibiotics for patients undergoing neurosurgery and appendectomy are Cefazoline 2 grams intravenously as a single dose, which may be re-administered if the surgical procedure exceeds 3 hours [14,42]. The increased consumption of antibiotics in neurosurgery that classified as clean surgery can be attributed to a number of factors. Primarily, the duration of neurosurgery is longer than that of appendectomy, which increases the likelihood of re-administration of antibiotics (repeat antibiotic treatment). Secondly, neurosurgeons tend to administer antibiotics following surgery to prevent the occurrence of surgical site infections, which can lead to an increased risk of postoperative mortality [53].

The quantity of antibiotics administered after surgery was found to be greater than that administered during surgery, in both elective and emergency surgical procedures. This suggests that the practice of administering antibiotics for an extended period following the patient's discharge from the hospital is common. The practice of administering postoperative antibiotics has also been demonstrated in several published studies [54-56]. A number of published studies found that patients who received postoperative prophylactic antibiotics did not show a significantly lower incidence of SSIs compared to patients who did not receive postoperative antibiotics [55,57-59]. A summary of systematic review of 44 trials comparing the use of prolonged antibiotics compared to no postoperative antibiotics in different types of surgery revealed that only three trials demonstrated a reduced risk of surgical site infection (SSI). In the context of appendectomies, a review of five trials revealed a non-significant difference (OR 0.71; 95% CI 0.41-1.23) in the incidence of SSI between prolonged antibiotic administration and single-dose prophylactic antibiotic administration [60].

The findings of this research are crucial for advancing both future research and clinical practice. The results revealed that the types of prophylactic antibiotics used in neurosurgery and appendectomy varied and did not fully comply with the guidelines established by the ASHP and the Ministry of Health of the Republic of Indonesia. These findings should prompt further research involving interprofessional collaboration among all healthcare workers in hospitals to identify effective strategies for enhancing adherence to prophylactic antibiotic guidelines in surgical procedures [26-28]. Additionally, the findings of this study could provide a basis for the development of hospital policies regarding the rational use of prophylactic antibiotics.

The limitations of this study are inherent to its cross-sectional research design, which provides a description of antibiotic consumption only for a specific period. Consequently, further research is required to quantify antibiotic consumption on a continuous basis, thus providing data that can be used to predict the incidence of bacterial resistance, assist in the selection of optimal antibiotics for patients and effective antibiotic stewardship program. In addition, we included all patients, those with out of pocket expenses and patients covered by health insurance. The different payment methods of medical services could impact on the prescribing behavior of intra-hospital physicians [61,62]. Lastly, antibiotic consumption is influenced by the patient visiting the hospital during a specific period, which may result in differences in antibiotic consumption patterns between these two tertiary care hospitals and other hospitals.

Conclusion

The use of broad-spectrum antibiotics, including the third-generation cephalosporins and metronidazole, as a prophylaxis in neurosurgery and appendectomy were a common practice in our research sites. Moreover, some of restricted antibiotics were also found as the prophylaxis antibiotics for neurosurgery and appendectomy. Owing to the further negative consequences of these prescribing practices, effort should be made to facilitate the successful implementation of an antibiotic stewardship program.

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