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A multi-center study on the prophylactic application of antibiotics in aseptic operations

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ABSTRACT. To understand the application of antibacterial agents in aseptic operations and to provide evidence for their rational use and management, the antibiotic use statuses of six types of aseptic operations (306 cases from 4 tertiary hospitals) were retrospectively analyzed. Of 312 patients, 306 (65.08%) were treated with antibacterial agents in the perioperative period. Four categories of antibiotics including cephalosporins, penicillins, nitroimidazoles, and fluoroquinolones were administered (descending sequence). Administration time: preoperative >2 h, 15 cases; preoperative 0.5-2 h, 20 cases; postoperative: 265 cases. Drug withdrawal time: postoperative 1-3 days: 33 cases; 3-7 days: 255 cases; 7-15 days: 12 cases. The prophylactic use of antibacterial agents in aseptic operations suffers from non-strict mastered medication indication, improper drug selection, aimless drug combinations, inappropriate administration timing, and over long medication duration.

Key words: Antibacterial agent; Aseptic operation;
Prophylactic application

INTRODUCTION

Class I (aseptic) incision operations, which are performed outside the areas of inflammation, the respiratory tract, the urogenital tract, and blunt trauma, do not normally require antibacterial agents. According to the Cruse statistics, the infection rates of aseptic incision operations, aseptic-contaminated incision operations, contaminated incision operations, and severely contaminated-infected incision operations are 1, 7, 20, and 40%, respectively (Surgery Branch of the Chinese Academy of Medical Sciences, Editorial Board of the Chinese Journal of Surgery, 2006). Only those patients undergoing massive, long-duration, and high-risk of infection aseptic operations require administration of antibacterial agents. Perioperative use of antibacterial agents significantly prevents postoperative infections; however, they are commonly misused (Bucher et al., 2011). As such, the prophylactic use of antibiotics in six types of aseptic operations in four tertiary hospitals in China (306 cases) was retrospectively analyzed.

MATERIAL AND METHODS

Data sources

Class I medical records from January to June 2012 (306 cases) were randomly selected from the Departments of General Surgery, Hepatobiliary Surgery, and Bone Surgery in four tertiary hospitals.

Investigation questionnaire

A questionnaire, including patient age, gender, disease diagnosis, length of hospital stay, records of disease history and infection risk factors, and the preoperative, intraoperative, and postoperative use of antibiotics, was designed.

Evaluation criteria

Evaluation criteria were established referring to the GAUCP [Guidelines for Antimicrobial Use in Clinical Practice (2004) No. 285, China's Ministry of Health] and document No. 38 (Notification on the clinical application and management of antimicrobial agents issued by the Ministry of Health, 2009) (Chinese Medical Association, Pharmacy Professional Advisory Committee of the Chinese Hospital Association, Hospital Pharmacy Advisory Committee of the Chinese Pharmaceutical Association, 2005).

RESULTS

General information

Among the 306 cases, 61, 53, 50, 53, 48, and 41 cases were of thyroid operations, splenectomies, breast operations, closed fracture operations, abdominal external hernia operations, and gallbladder operations, respectively. The ages of the patients (150 males, 156 females) ranged from 6 to 80 years old, their hospitalization time ranged from 1 to 30 days, and their operation time ranged from 0.5 to 6 h. Most of the 306 patients (98.1%) were administered antibacterial agents perioperatively (Table 1).

Table 1. General information of patients.

Operation	Gender		Age	Average age	Length of stay (days)	Infection risk factors			Fervescence in perioperative period
	Male	Female				>70 years	Malignancy	Diabetes mellitus	
Thyroid	26	35	20-79	63.44	5-13	3	-	5	9
Breast	-	50	12-80	38.50	1-21	3	2	1	5
Gallbladder	26	15	16-80	55.66	8-28	5	1	4	-
Abdominal external hernia	42	6	28-78	53.42	9-30	6	2	3	1
Splenectomy	26	27	10-68	45.21	3-10	-	1	2	20
Closed fractures	30	23	6-80	52.34	9-27	4	1	3	1

Type and utilization frequency of antimicrobial agents

The 306 patients were treated with four categories of antibacterial agents a total of 482 times in the perioperative period in the following descending order: cephalosporins > penicillins > nitroimidazoles > fluoroquinolones (Table 2).

Table 2. Type and utilization frequency of antimicrobial agents.

Operation	Cephalosporins				Fluoroquinolones	Nitroimidazoles	Penicillin
	First-generation	Second-generation	Third-generation	Fourth-generation			
Thyroid	12	10	6	1	15	-	41
Breast	7	15	7	-	9	-	23
Gallbladder	12	20	4	1	8	7	25
Abdominal external hernia	7	10	5	-	7	6	18
Splenectomy	9	16	7	3	-	46	19
Closed fractures	14	25	10	2	28	19	8

Thyroid operation: In 61 cases of thyroid operation, antibacterial agents were used a total of 85 times.

Splenectomy: In 53 cases of splenectomy, antibacterial agents were used a total of 100 times.

Breast and abdominal external hernia operations: In 50 and 48 cases of breast and abdominal external hernia operation, respectively, antibacterial agents were used a total of 61 and 53 times.

Bone closed fracture operation: In 53 cases of bone closed fracture operation, antibacterial agents were used a total of 106 times.

Gallbladder operation: In 41 cases of gallbladder operation, antibacterial agents were used a total of 77 times.

Polypharmacy

Among the 306 cases, 6, 160, 130, and 10 cases were treated without antibacterial agents (2.0%), with one (52.3%), with two (42.3%), or with three (3.3%) types of antibacterial agents, respectively. The antibacterial agents were altered in 15 cases (4.9%). The use of antimicrobial agents and their combinations in the six aseptic operations are shown in Table 3.

Table 3. Polypharmacy conditions.

Operation	No drug (%)	Single drug (%)	Two-drug combination (%)	Three-drug combination (%)	Combination method
Thyroid	1.6	74.1	24.3	-	Penicillins/Cephalosporins + Nitroimidazoles
Breast	4.0	75.0	21.0	-	Cephalosporins/Penicillins + Fluoroquinolones
Gallbladder	2.4	52.7	38.5	7.4	Penicillins/Cephalosporins + Fluoroquinolones/Nitroimidazoles
Abdominal external hernia	4.2	64.0	25.0	4.8	Penicillins/Cephalosporins + Fluoroquinolones/Nitroimidazoles
Splenectomy	-	21.9	75.4	2.7	Cephalosporins/Penicillins + Nitroimidazoles
Closed fractures	-	25.0	68.8	6.2	Cephalosporins + Fluoroquinolones/Nitroimidazoles

Administration methods of antibacterial agents

All 300 patients who received antibacterial agents were intravenously infused (100%), the doses of 97.3% of the patients did not exceed the specified ones; excessive doses were used in 8 cases (2.6%), and 24 cases were daily administered irrationally (8.0%).

Administration timing and duration

When examining the timing of administration of the antibacterial agents, 15, 20, 265, and 6 patients were administered more than 2 h before their operations (4.9%), 0.5-2 h before their operations (6.5%), after their operations (88.3%), and were not administered (2%), respectively. Furthermore, 33, 255, and 12 of the 300 patients were treated with antibacterial agents continuously for 1-2 days (10.8%), 3-7 days (83.3%), and 7-15 days (3.9%) after their operations, respectively (Table 4).

Table 4. Administration timing and duration.

Operation	Administration timing			Postoperative administration duration			No. drugs
	Preoperative		Postoperative				
	>2 h	0.5-2 h	2 h	1-2 days	3-7 days	7-15 days	
Thyroid	2	3	55	6	45	1	1
Breast	2	3	43	5	43	-	2
Gallbladder	2	2	36	4	35	1	1
Abdominal external hernia	2	2	42	6	39	1	2
Splenectomy	4	5	44	7	41	5	-
Closed fractures	3	5	45	5	44	4	-

DISCUSSION

Indications for prophylactic use of antibacterial agents

In general aseptic operations, the prophylactic use of antibacterial agents during the perioperative period aims to prevent bacteria from entering the blood circulation through wounds as well as secondary infection. Antibacterial agents are commonly not needed unless dealing with massive and long-duration operations or those involving vital organs, foreign body implantation, or patients with high risks of infection (e.g., the elderly, or patients with diabetes, cancer, etc.) (Uckay et al., 2011; Tanaka et al., 2012). In the 53 cases of closed fracture operation, 28 and 25 patients underwent hip replacement and open reduction plus internal fixation, respectively, which all involved the implantation of foreign bodies. The spleen is the most important immune organ, without which patients may suffer simultaneous infections and hemorrhage owing to their weakened immunity, which significantly increase the opportunities of explosive infection (Rodriguez Gomez et al., 1998). Therefore, all the closed fracture and splenectomy patients were indicated for the prophylactic use of antibacterial agents. In total, 98.1% of the 306 patients were administered antibacterial agents, and 165 cases (53.9%) had high-risk factors and relevant indications. In addition, some small-area and short-duration (<1 h) operations also used antibacterial agents. Thus, the prophylactic medication indications were apparently not strictly mastered (Pope et al., 2008). The misuse of antibacterial agents not only enables the drug resistance of bacteria to develop, but also unnecessarily incurs cost (Maragakis et al., 2008).

Selection of the types of antibacterial agents

The prophylactic use of antibacterial agents aims to eliminate bacteria that may contaminate incisions. Principally speaking, broad-spectrum and secure bactericides are preferred, of which cephalosporins are the most suitable (Zhang and Harvey, 2006; Butt et al., 2012). According to the requirements released by the Ministry of Health, first-generation cephalosporins are recommended in thyroid, breast, and abdominal external hernia operations, of which cefazolin or cefradine are given priority (Esposito et al., 2006; Avenia et al., 2009; Rodriguez-Caravaca et al., 2011). In the 159 cases of these operations, first-generation cephalosporins were used in only 14 cases (8.8%), whereas second-, third-, and fourth-generation cephalosporins were used in 74 cases (46.5%). *Staphylococcus aureus* and other Gram-positive bacteria could contaminate the incisions of these three operations. First-generation cephalosporins ought to be given priority as they target gram-positive bacteria (Poon et al., 2012), whereas second- and third-generation cephalosporins have lower antimicrobial activities (Griffith et al., 2003). One patient who underwent thyroid operation and was not indicated to receive prophylactic medication was treated with cefepime to prevent potential infections. Cefepime, a fourth-generation cephalosporin (Sprauten et al., 2003), is characteristic for its remarkable antibacterial activity and β-lactam enzyme stability. However, cefepime is expensive and is associated with a heavy economic burden. Penicillins were used in 71 cases (44.7%). Nevertheless, the penicillin-type drug to which *Pseudomonas aeruginosa* is resistant was mainly utilized (Hocquet et al., 2011), thus wasting medical resources. Patients undergoing orthopedic operations could be infected by *S. aureus* (Lee et al., 2010), for which the first- and second-generation cephalosporins are commonly advocated (Fujita et al., 2007). Thus, the use of first- and second-generation cephalosporins in 42.0% of the fracture patients was reasonable. In contrast, the use of the third-generation cephalosporins (45.0%) was not a cost-effective strategy. In addition, some patients were administered with excessively effective drugs at the very beginning, which were subsequently altered frequently and without reason. For example, one patient after thyroidectomy exhibiting normal body temperature and blood indexes that had been treated with mezlocillin/sulbactam for 1 day was then administered cefoxitin and amoxicillin/flucloxacillin on the 2nd and 3rd days, respectively. Such frequent changes of medication shorten the time that an effective concentration of each antibacterial agent is maintained in the blood, resulting in the development of bacterial drug resistance (Cordero et al., 2012).

Polypharmacy

Polypharmacy should include drugs with synergetic or additive antimicrobial effects, and are permitted in severe infections in which the pathogenic bacteria have not been identified, and that individual antimicrobial agents cannot control, that are caused by a mixture of aerobic and anaerobic bacteria, and that need long-term treatment to limit toxic reactions. In general, polypharmacy is not recommended in aseptic operations (Higuchi et al., 2011). In this study, two and three types of antibacterial agents were combined in 42.3 and 3.3% of the patients, respectively. Penicillins or second- and third-generation cephalosporins were combined with fluoroquinolones in 20 cases of thyroid and breast operations. These drugs are broad-spectrum overlapping antibacterial agents, and their administration is irrational for incision infections after aseptic operations (Micek et al., 2010). Fluoroquinolones, which are

resistant to Gram-negative bacilli have been misused in China (Jean and Hsueh, 2011), and are generally not suitable for prophylaxis unless sensitivity tests have verified their effectiveness. Therefore, the use of fluoroquinolones as prophylaxis during the perioperative period has been strictly controlled by the Ministry of Health since March, 2009. A combination of three types of antibacterial agents is only allowed under special circumstances in order to prevent mixed infections. Generally, combining two types of antibacterial agents in aseptic operations is sufficient (Cammarota et al., 2012). For instance, one 67-year-old patient with Type II diabetes who had undergone an abdominal external hernia operation was administered combined ceftezole, lavo-ofloxacin, and metronidazole, which is excessive. Furthermore, patients who are treated with polypharmacy are subject to increased side effects (Stinner et al., 1998).

Administration method

Patients should be treated with undiluted antibacterial agents intravenously within 20-30 min during the perioperative period, aiming to maintain effective concentrations (Tamby-raja et al., 2004). Therefore, the intravenous administration in the 306 cases was rational, but a small number of patients were administered excessive medication. For example, two patients with normal body temperatures, blood indexes, and without high-risk of infection, who underwent breast adenofibroma ectomy and splenectomy were intravenously infused with 3 g bid cefmetazole (recommended dose: 1-2 g *iv*, bid) and 3 g bid cefuroxime sodium (recommended dose: 0.75-1.5 g, tid), respectively. β-Lactam antibacterial agents with a short half-life, such as penicillin G and cefmetazole, were used for 25 patients once daily. However, effective concentrations of β-lactams are not maintained in the human body because they are time-dependent antibacterial agents, therefore bacteria are prone to becoming drug resistant in such cases.

Administration timing

It has been mandated that patients undergoing an aseptic operation should be administered antibacterial agents 0.5-2 h before operations or at the beginning of anesthesia. If the operation lasts for more than 3 h or more than 1500 mL blood is lost, a second dose of medicine should be given. The use of antibacterial agents should effectively cover the entire operation and 4 h thereafter. The overall prophylactic administration time is less than 24 h, which may be extended to 48 h occasionally. Patients undergoing aseptic operations of less than 2 h only need a single administration. In this study, most (86.7%) of the 306 patients were treated after their operations, and only 6.5% of them were treated 0.5-2 h before their operations. In other words, the optimal administration timing was missed. Conversely, the treatment of 10.8 and 83.3% of the 306 patients was discontinued within 2 days and 3-7 days, respectively. In particular, the treatment of some patients ceased after 15 days, which is apparently too long. It has been previously reported that the administration of antibacterial agents continuously for uninfected incisions for more than 48 h was invalid, and could result in drug resistance that might induce uncontrollable infections (Spicher et al., 2003; Oz et al., 2010).

In short, this multi-center study has demonstrated that the indication of prophylaxis for aseptic operations during the perioperative period is not managed strictly, drug types are not selected appropriately, administration timing is often inappropriate, and postoperative administration too long, all of which have attracted great attention from the corresponding hospitals. Therefore, it is imperative to focus efforts on rationalizing the use of antibacterial agents by establishing warning/management systems and regularly training doctors.

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