

Original Research Article

Effects of different antibiotics injection during spinal anesthesia and Infection management after lower limb surgeries in patients with Beta-lactam Allergy

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ABSTRACT

This study compared cefazolin with second-line antibiotics to assess the prevalence of SSIs within 90 days after joint replacement surgery and interoperative HSRs among patients with a diagnosis of penicillin or cephalosporin allergy.

Demographics, comorbidities, immunomodulatory medications, allergy history, perioperative medications, and laboratory test results were all collected from the electronic health record. Patients who underwent multiple joint replacements in various procedures were counted as separate encounters. Joint replacements on both sides carried out during the same procedure were counted as one encounter. Based on the symptoms that were reported, beta-lactam allergic reaction histories were divided into immediate, delayed, and undetermined categories. There were descriptions of anaphylaxis, respiratory distress, cardiovascular symptoms, edema, and hives among the immediate allergic reactions. Delayed allergic reactions were described as pruritis, nephritis, hepatitis, and blood cell dysfunction (neutropenia, thrombocytopenia), among other dermatological findings and conditions. The causes of all other allergic reactions were labeled as unknown.

The average time from surgery to SSI was 24 days in the cefazolin group and 21 days in the clindamycin and/or vancomycin group. There were fewer superficial incisional infections (0.7% vs 1.9%) and prosthetic joint infections (0.1% vs 1.9%) in the cefazolin group. According to our research, using cefazolin as a perioperative antibiotic for infection prevention during total joint arthroplasty in patients who have been diagnosed as being allergic to beta-lactams is associated with fewer postoperative SSIs without raising interoperative HSRs.

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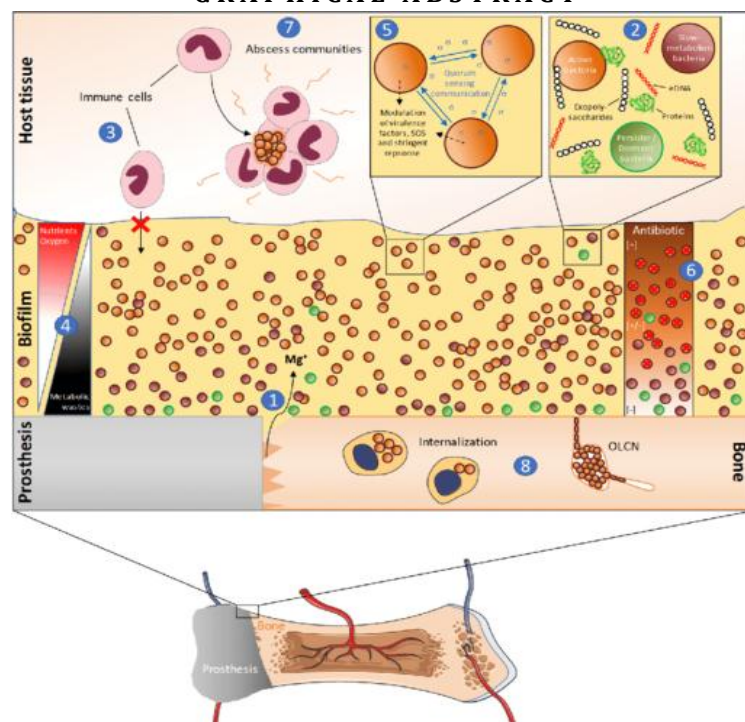
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GRAPHICAL ABSTRACT



1. INTRODUCTION

How much do you know about spinal anesthesia? Every day, many surgeries are performed in the world, in each of them, a special method is used for anesthesia and anesthesia of the patient [1-3]. The choice of method is determined based on the type of surgery, its duration, the patient's physical condition, the doctor's diagnosis, and finally the patient's request [4]. Types of anesthesia include local anesthesia, short-term anesthesia, complete general anesthesia, hypnotic administration, or spinal anesthesia [5-7]. Among these, one of the most common methods used in many surgeries, including cesarean delivery, is called spinal anesthesia. This anesthesia method is performed by an anesthesiologist and the patient is not

completely anesthetized. Spinal anesthesia or spinal anesthesia (spinal anesthesia) is one of various types of anesthesia [8-10]. It actually involves injecting a spinal anesthetic and other painkillers into the space below the dura mater or near the spinal cord. This method is actually a type of anesthesia or local anesthesia in which the anesthetic drug is injected near the spinal cord (Fig 1). The anesthetic is injected through a long needle. To insert the needle, the anesthesiologist first places the patient in a sitting position, and then sterilizes the injection site with a disinfectant solution. Sometimes, the injection area may be first locally numbed with an anesthetic, and then using a special long needle, which is usually 9 cm, he injects the anesthetic [11].

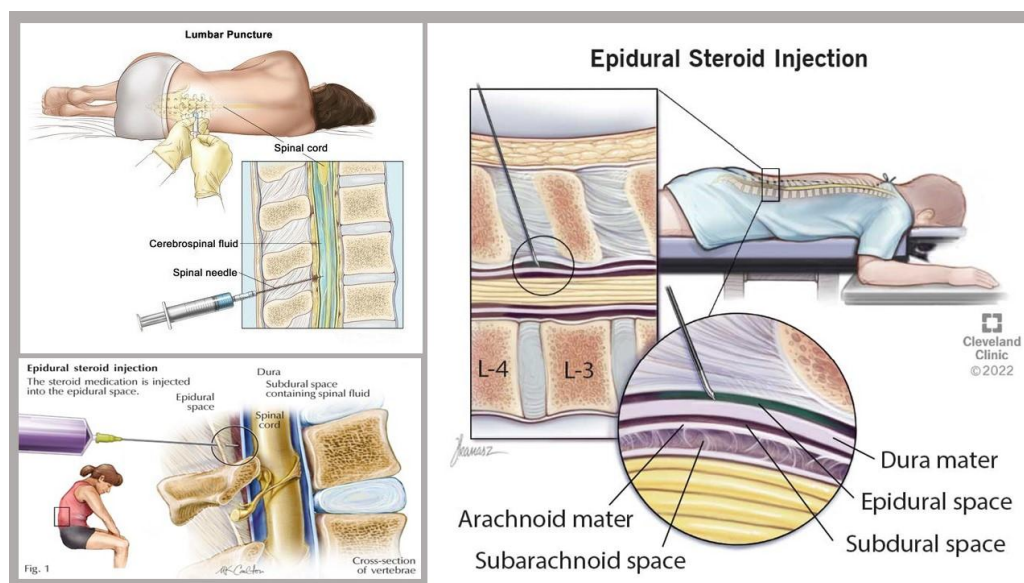


Fig1. How much do you know about spinal anesthesia?

How does spinal anesthesia (spinal anesthesia) work?

By injecting an anesthetic drug into the spinal area, the nerves are numbed so that the pain in certain areas of the body is relieved and not felt. In fact, the space under the dura mater and close to the spinal cord is a bag full of spinal fluid that surrounds the spinal cord and nerves that come out of it. Local anesthetics and other accompanying pain relievers are injected into this space using a fine needle. Immediately after the injection, the drug takes effect and the patient experiences tingling and burning sensation in the legs [12-15]. This warming of the legs and tingling means that the medicine is working and the person is numb. The pulse, blood pressure, and oxygen level of the patient's blood are checked during this procedure. In some cases, sleeping or sedative drugs may be used to control the patient's condition. Spinal anesthesia is usually used for outpatient and short-term procedures performed on the lower body and lower back. In cardiac patients, depending on the type of surgery, spinal anesthesia often replaces

general anesthesia. Especially if the doctor determines that general anesthesia is dangerous for the patient's heart disease [16-18]. For example, spinal anesthesia is used in vascular surgeries such as leg blood vessel surgery and varicose vein surgery. To inject the anesthetic in spinal anesthesia, the anesthesiologist asks the patient to sit or lie on his side. Then, when he is sure that the patient is in a suitable condition, he slowly inserts the needle containing the anesthetic and injects the spinal anesthetic through it. This injection is usually not too painful, but it can be uncomfortable for some people. The duration of spinal anesthesia may vary depending on the operation time. In general, the duration of spinal anesthesia is usually between one and three hours. However, the anesthesiologist injects enough anesthetic through the needle to ensure that the anesthesia lasts longer than the expected duration of the procedure [17].

Benefits of spinal anesthesia

Spinal anesthesia works well for some procedures and surgeries and does not require a

breathing tube to be inserted into the patient's trachea. People usually recover their senses much faster. Sometimes, they have to wait for the anesthesia to wear off before they can walk or urinate. However, in this method, the patient returns to normal faster [18-20]. The risk and danger of spinal anesthesia is much lower. In spinal anesthesia, the risk of lung infection and respiratory problems is less. Patients feel less sleepy and confused and can start eating and drinking sooner after surgery. Bacterial infections and the need for hospitalization are one of the main causes of preventable mortality. Beta-lactam antibiotics (such as penicillins and cephalosporins) and aminoglycosides (such as gentamicin) kill bacteria in different ways. Therefore, the combination of a beta-lactam and an aminoglycoside can lead to more effective treatment for patients with severe infection but with side effects of both antibiotics. According to a study conducted by researchers at Mount Sinai Health System in New York, penicillin-allergic patients who receive a specific type of antibiotic as prophylaxis before surgery are at greater risk of developing a site infection. Allergy patients who were prescribed the non-beta-lactam

antibiotic clindamycin were at greater risk than those who received the beta-lactam antibiotic, wrote the researchers, led by Dr. Daniel Roistacher, an oral and maxillofacial surgery resident at Mount Sinai Health System. There were infections. We found that the increased risk of infection was related to differences in antibiotic prescribing and not to penicillin susceptibility alone. This article entitled: "Penicillin allergy due to receiving non-beta-lactam antibiotics as preoperative prophylaxis was associated with the development of SSI [surgical site infection]" was published in the Journal of Oral and Maxillofacial Surgery [19-21].

Disadvantages of spinal anesthesia

In some cases, even if the intended operation is suitable for spinal anesthesia, there are some medical conditions or medications that make this method of anesthesia unsafe and inappropriate for the person. People with a history of migraine headaches and severe back pain may experience a lot of discomfort after this anesthesia procedure. For example, those with lumbar disc herniations are not good candidates for spinal anesthesia (Fig 2) [21].

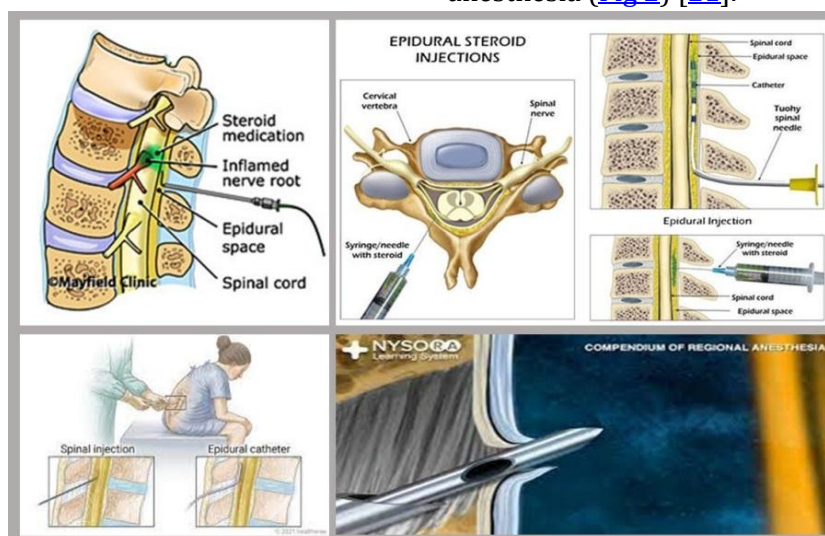


Fig2. Spinal anesthesia

Preparation before spinal anesthesia

For spinal anesthesia, a series of protocols and instructions must be followed. The first thing is to stop eating and drinking before the operation. Usually, depending on the type of operation for spinal anesthesia, patients are told to fast for 10 to 12 hours the night before and not to eat or drink. If you drink alcohol and smoke, you should avoid them the night before and the day of the operation [22].

Care after spinal anesthesia

Post-spinal anesthesia care has a big impact on the complications you feel after the operation, and it is very important to follow these instructions. Patients are usually told not to walk and stay in bed until the sensation in their legs returns [23-25]. Usually patients stay immobile for 12 hours. In many cases, the nurse will ask the patient to urinate to make sure the bladder muscles are working properly.

Complications of spinal anesthesia

Spinal anesthesia, like other methods of general or local anesthesia, can have a series of side effects, some of which are common and some of which are rare. Depending on the type of operation and the patient's condition, there may be a risk of significant permanent damage to the spine. Some patients experience severe back pain after local anesthesia. Spinal failure, low blood pressure, headache, allergic reactions to equipment, substances or injected drugs, itching, difficulty in urination, etc. are some of the side effects of spinal anesthesia. Redness and swelling of the injection site may also be seen in some people [26]. In some more severe cases, it is possible for the anesthetic to spread above the target area, in which case severe pain or even infection around the spine may be seen. Nerve damage, cardiac arrest, spinal abscess, blood clots, paralysis, and death can all be rare side effects of spinal anesthesia.

What is penicillin?

Penicillin is one of the most commonly prescribed antibiotics. This drug is a part of the family of antibiotics called beta-lactams, which includes many drugs in this family, including: penicillin G, penicillin, oxacillin, cloxacillin, dicloxacillin, ampicillin, amoxicillin, carbenicillin, ticarcillin, and piperacillin. Any person who is allergic to one of different types of penicillin should be assumed to be allergic to all of its types and should refrain from using the entire group.

Cephalosporins

Cephalosporins are a class of antibiotics that are very similar to penicillin. Some of the components of this category include cephalexin, cefacler, cefuroxime, cefadroxil, cefradin, cefprozil, loracarb, ceftibuten, cefdinir, ceftoran, cefpodoxime, and cefixime. Patients with a history of penicillin allergy have a low risk of allergic reactions to this drug category. People who have a positive skin test need to be more careful in prescribing these drugs because of the small possibility of allergy to these drugs [27].

What is cefixime?

Cefixime is a strong antibiotic that is effective against a wide range of microbes. This drug is prescribed for the short-term treatment of acute bacterial infections such as urinary tract infections, chest infections, and ear and throat infections. Inhibiting the construction of the cell wall of bacteria destroys them. Some people who are allergic to the different types of penicillin may also be allergic to this drug. Therefore, before starting the treatment, if you are allergic to any antibiotic, remind your doctor of its name. Only 40-50% of an oral dose of cefixime is absorbed slowly. Absorption of this drug is reduced in the presence of food. The peak serum concentration of the drug is reached 2-6 hours after its oral intake. The plasma half-life of the drug is 3-4 hours, which increases in kidney

failure. The metabolism of this drug has not been determined. About 20 percent of the drug is excreted unchanged through the kidneys and 60 percent of the drug through non-renal routes [28]. Given that beta-lactams are broad-spectrum antibiotic drugs and used for most patients, and if a person is allergic to these drugs, he should receive another type of antibiotics, we decided to conduct this study to investigate the effects of different antibiotics injection during spinal anesthesia and infection management after lower limb surgeries in patients with beta-lactam allergy.

2- EXPERIMENTAL

2-1-Material and methods

This study was a double-blind, randomized clinical trial with a control group conducted during the period of 2020-21 in Tabriz University of Medical Sciences. All patients (N=110) who underwent a total knee or hip replacement within the Tabriz University of Medical (UCHealth) system between January 1, 2020, and July 31, 2021, had their medical records reviewed retrospectively. Patients who underwent a primary total knee arthroplasty (TKA) or total hip arthroplasty (THA) and had an antibiotic allergy to penicillin or a cephalosporin recorded in their electronic health record at the time of surgery were included in the study. All interventions were done by Orthopedics surgeon. They also had to be 18 years old or older. Patients were excluded if they had a joint infection prior to surgery, passed away before the 90-day recovery period, underwent a revision surgery, underwent a second TKA or THA, underwent a hemiarthroplasty, or underwent a patellofemoral arthroplasty [22-28].

3- RESULTS AND DISCUSSION

This study started with 110 patients and ended with 110 patients. Side effect is a medical term

that refers to all adverse reactions caused by drugs. Both allergic or non-allergic complications may occur. Non-allergic side effects are more common. Examples of common non-allergic side effects include digestive problems and diarrhea. It is very important to distinguish non-allergic side effects from true allergic side effects. Some people, when faced with non-allergic reactions, report them as allergic reactions, the result of which is that the patient avoids the use of penicillin in a particular infection without needing it, and a drug that is less effective, or it is more toxic for him. This can lead to resistance or treatment failure, which is costly and can lead to longer disease duration. 5 patients were excluded out of a total of 118 procedures from 110 patients. Reasons for exclusion were non-primary surgery including revision (n = 2), hemiarthroplasty (n = 1), absence of beta-lactam allergy label at time of surgery (n = 1), complex surgery beyond scope of total arthroplasty, or a patellofemoral surgery (n = 1), presence of joint infection at time of surgery (n = 3), patient death before 90-day time frame (n = 1), or the patient did not receive perioperative antibiotics (n= 1) (Fig 3). Approximately 10% of patients are allergic to penicillin, but about 90% of these cases are not true allergies. When choosing preoperative antibiotics, knowing the patient's allergy status is very important. Because penicillin sensitivity often precludes the use of penicillin and other beta-lactam antibiotics, these patients are often prescribed broad-spectrum antibiotics, which are associated with antimicrobial resistance and toxicity. Previous research has revealed that penicillin sensitivity is associated with a significantly increased risk of surgical site infection in patients undergoing cardiac, gynecological, orthopedic, and colorectal surgery. This risk is observed in the presence of preoperative antibiotic therapy with alternative antibiotics. Similarly, surgical site infection is a risk for patients undergoing oral and maxillofacial surgery. Because the reported risk

of surgical site infection after orthognathic surgery varied up to 18% and was related to the choice and duration of antibiotic prophylaxis therapy, researchers at Mount Sinai Health System wanted to know whether patients with penicillin allergy, who are subjected to mouth, jaw, and face operations are more prone to infections. To investigate whether penicillin-allergic patients are at greater risk of infection than non-allergic patients, Dr. Roistacher *et al.* conducted a retrospective cohort study of 2,058 patients undergoing oral, maxillofacial surgery,

including dentoalveolar, temporomandibular joint, orthognathic and the third molar tooth extraction. These surgeries were performed in the hospital between 2011 and 2018. Among the patients, 318 (16%) had reported penicillin allergy, the researchers wrote. Their results showed that, compared with patients who did not report a penicillin allergy, the odds of developing a postoperative infection were increased in those who had an allergy (adjusted odds ratio, 2.61; 95% CI , 1.51-4.49; p = 0.001).

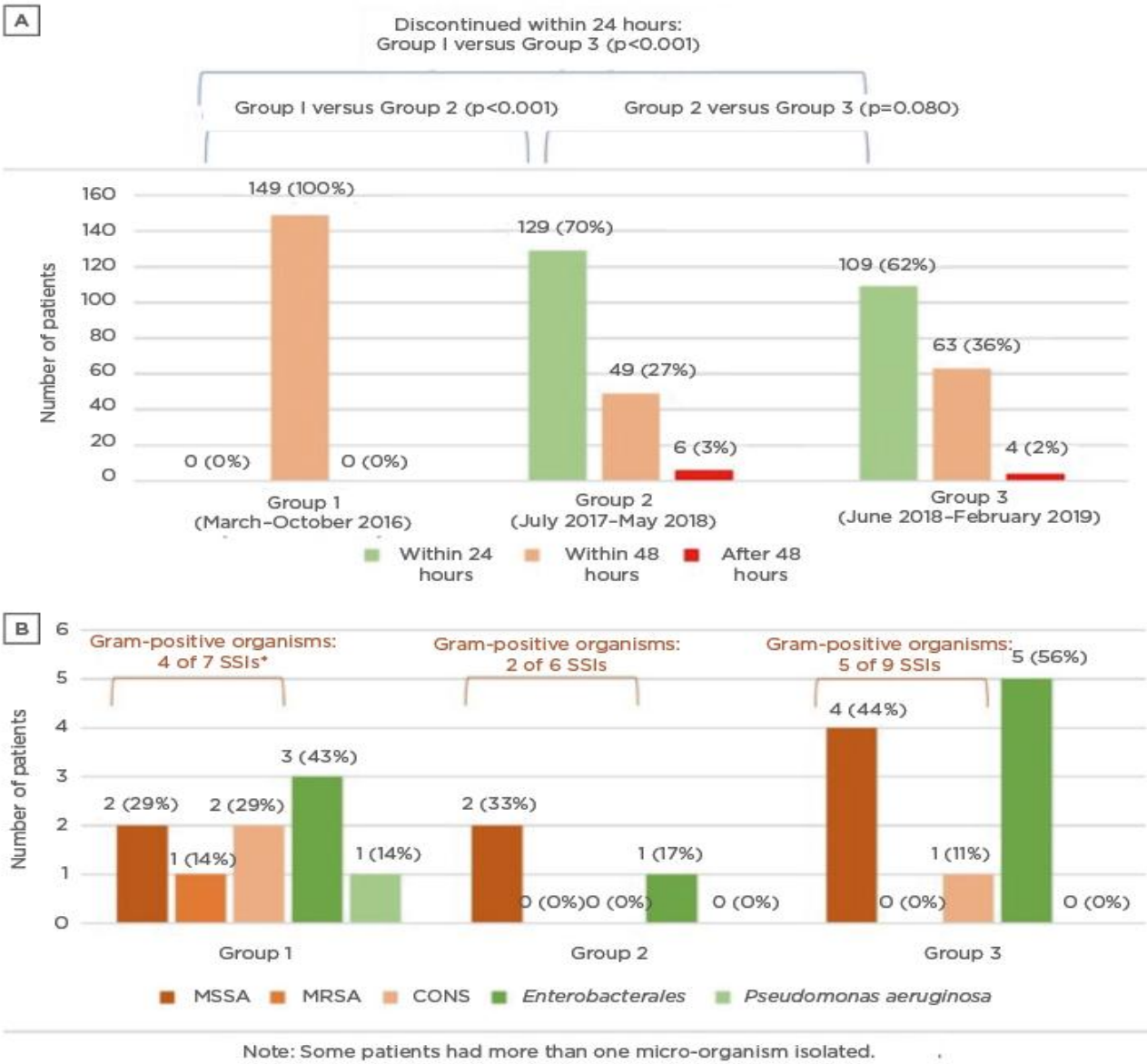


Fig3. Difference of gram in study participant

3-1-Many different types of skin rashes may appear while taking penicillin

Skin rash including hives (raised, with severe itching that appears and disappears within hours) or accompanied by symptoms such as wheezing and swelling of the skin or throat, which indicates a true allergy. Flat skin rashes, in the form of spots and spreads that remain for days, but do not change and do not indicate a dangerous allergy. These rashes usually start after a few days of treatment. It is difficult to distinguish between different types of skin rashes in the past, taking pictures of the rash can always help. After equalizing preoperative antibiotic use between the β -lactam and non- β -lactam groups, penicillin allergy alone was no longer associated with surgical infection, suggesting that antibiotic choice determines outcome. The use of clindamycin was associated with a four-fold increase in surgical site infection compared to the use of beta-lactam antibiotics. Due to the retrospective nature of this study, the results of this study are limited to what was recorded in the medical records of this group of patients. Another limitation of this study was that not all patients were treated by the same surgeon, so possible changes in the surgical method of the patients were not considered in this study. The researchers concluded that the use of non-beta-lactam antibiotics during the preoperative period increases the likelihood of penicillin-allergic patients developing surgical site infections, so dentists should perform allergy testing on these patients before surgery. Dr. Roistacher *et al.* wrote: Referral of patients suspected to be allergic to penicillin for definitive allergy testing should be considered preoperatively as a risk reduction strategy.

3-2-Sefxim recommendations

(1) In some people, taking antibiotics causes red lesions with itching in the mouth or vagina. If these symptoms occur, see your doctor.

(2) Ladies, if you are using birth control pills at the same time as cefixime treatment, if you have any illness accompanied by diarrhea and vomiting that lasts more than 24 hours, it is necessary to use another method of prevention. Use pregnancy (such as condoms) for caution along with birth control pills.

(3) If you intend to have surgery or start drug treatment for another disease, inform your doctor about taking this drug because cefixime can affect the response of some tests (such as the amount of sugar in the urine).

3-3-Common side effects of cefixime

(1) Mild diarrhea at the beginning of treatment is one of the common side effects of cefixime, which resolves on its own. If it occurs, drink enough fluids, but if the diarrhea continues for more than 24 hours and becomes more severe or contains blood, see your doctor.

(2) Feelings of nausea, abdominal pain, and indigestion may occur during treatment with this medicine, to improve it, eating light and simple foods, and taking the medicine after a meal can help.

(3) Headache is a complication that may occur as a result of taking this medicine. In this situation, drink enough water a day, and consult your pharmacist to choose the right painkiller. However, if the headache becomes severe and prolonged, see the doctor.

(4) Taking this medicine may make you feel dizzy, so avoid driving and doing things that require concentration and caution until the effect of the medicine wears off.

(5) If you have symptoms of drug allergy, including red and itchy skin lesions, shortness of breath, swelling of the face or lips, stop taking the drug, and consult a doctor or medical center. 112 surgical procedures were performed on 104 patients in the final cohort. Cefazolin was used as the perioperative antibiotic regimen in 81 surgeries overall (71.7%). Clindamycin and/or vancomycin were used as the perioperative

antibiotic regimen in the 31 remaining surgeries (28.3%). Out of the 31 patients, 14 only received clindamycin, 7 only received vancomycin, and 9 received both clindamycin and vancomycin during the perioperative period (Fig 4).

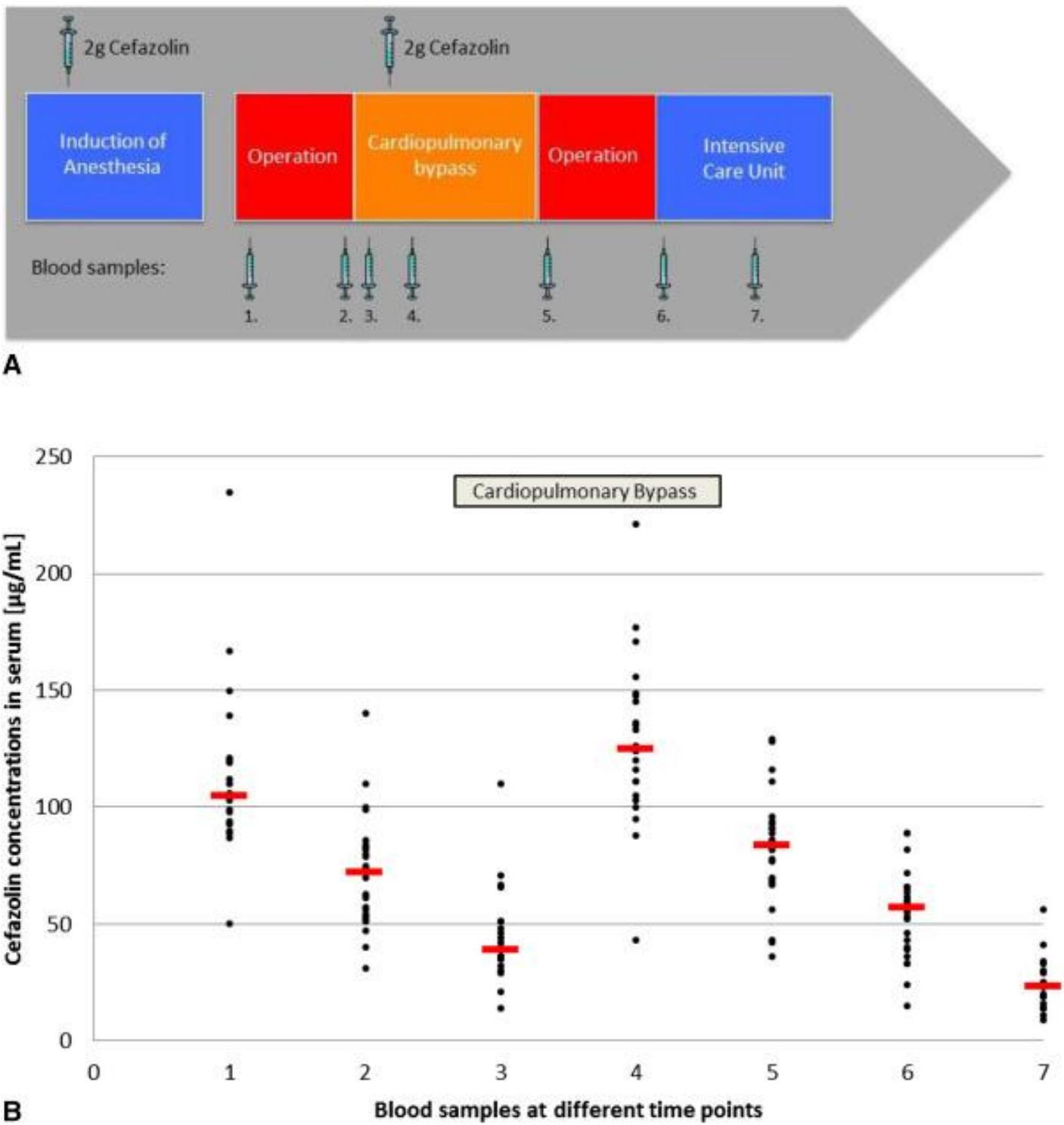


Fig4. Blood sample at different time after surgery

With the exception of surgery length, antibiotic irrigation use, past medical history including cancer, asthma, and fibromyalgia, patient

characteristics between the cefazolin and clindamycin/vancomycin groups were similar (Fig 5).

| | PENICILLIN | AMOXICILLIN | AMPICILLIN | CEPHALEXIN | CEFAZOLIN | CEFUROXIME | CEFOXITIN | CEFTRIAXONE | CEFOTAXIME | CEFTAZIDIME | CEFEPIME | CEFIDEROCOL | AZTREONAM |
|-------------|------------|-------------|------------|------------|-----------|------------|-----------|-------------|------------|-------------|----------|-------------|-----------|
| Penicillin | | + | + | + | | | | | | | | | |
| Amoxicillin | + | | + | + | | | | | | | | | |
| Ampicillin | + | + | | X | | | | | | | | | |
| Cephalexin | + | + | X | | | | | | | | | | |
| Cefazolin | | | | | | | | | | | | | |
| Cefuroxime | | | | | | | X | X | X | | X | | |
| Cefoxitin | | | | | | X | | | | | | | |
| Ceftriaxone | | | | | | X | | | X | | X | | |
| Cefotaxime | | | | | | X | | X | | | X | | |
| Ceftazidime | | | | | | | | | | | | X | X |
| Cefepime | | | | | | X | | X | X | | | | |
| Cefiderocol | | | | | | | | | | X | | | X |
| Aztreonam | | | | | | | | | | X | | X | |

Fig5. B-lactams allergy Rate

Two HSRs were present in the cefazolin group. One patient had skin involvement, and one patient reported having an allergic reaction on their own without any accompanying symptoms. Although there was no record of past reactions, both patients had a history of penicillin allergies. Two of the four HSRs in the clindamycin and/or vancomycin group involved the skin, and the other two had hemodynamic instability. The present study was conducted with the aim of effects of different antibiotics injection during spinal anesthesia and infection management after lower limb surgeries in patients with beta-lactam allergy. Penicillin sensitivity shows itself when the body's defense system becomes sensitive to the drug and attacks the drug. The chemicals in the medicine cause allergic reactions. Another type of drugs called

cephalosporins play a role in causing allergic reactions. If you are allergic to penicillin, you are most likely allergic to cephalosporin drugs. Different types of penicillin belong to a class of antibacterial drugs called beta-lactam antibiotics [29]. These drugs have a similar structure and fight infections by attacking the walls of bacteria. The effects of this problem include bleeding, bruising, and blood clotting. Beta-lactam and sulfamethoxazole cause blood reactions in the body more than other types of antibiotics. Another problem is thrombocytopenia, which means low blood platelet levels. Fluoroquinolone antibiotics such as ciprofloxacin or erythromycin cause such problems. Terbinafine (antifungal) can also have such side effects. Taking some antibiotics causes changes in the blood (Fig 6) [35].

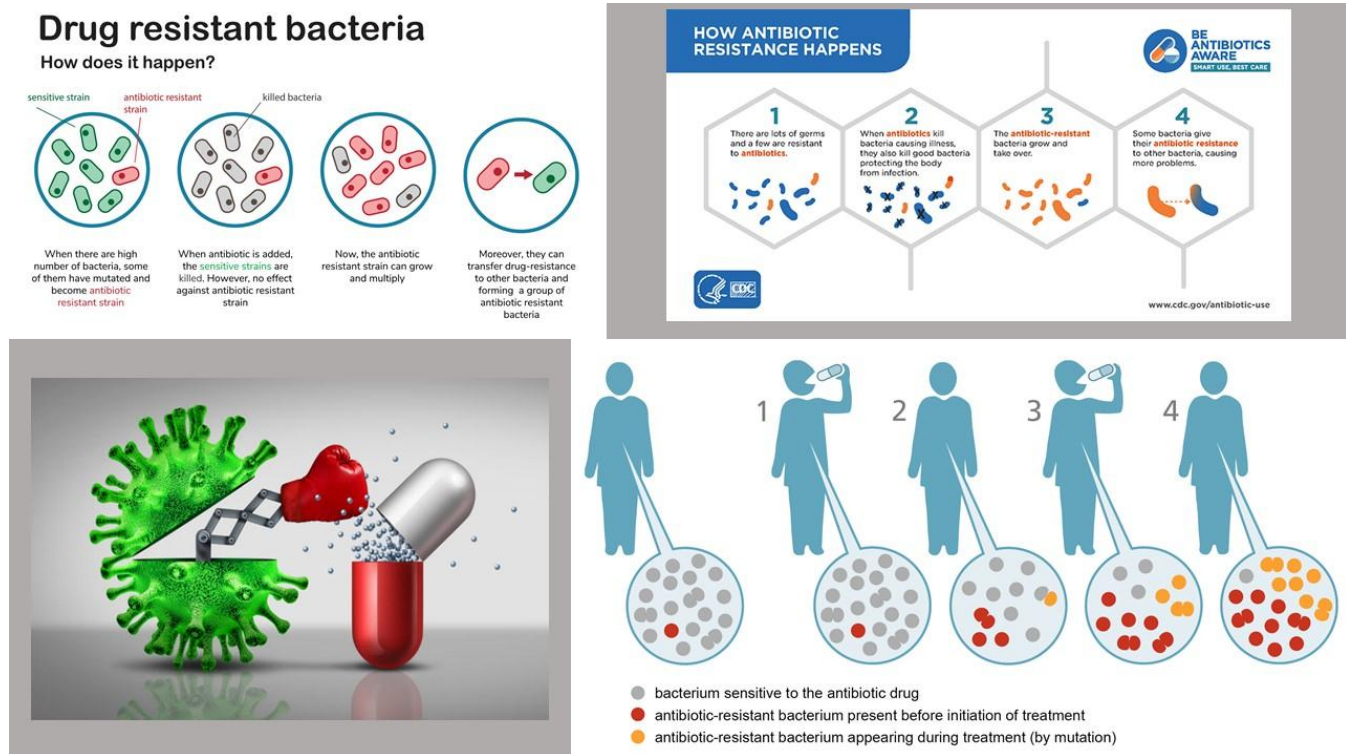


Fig6. Antibiotic resistant bacteria

3-4-Beta-lactam antibiotics

There are a wide group of antibiotics that have a beta-lactam ring in their molecular structure. Penicillins, cephalosporins, monobactams, and carbapenems can be mentioned among the antibiotics using this compound. It has been more than half a century since the beta-lactam family officially entered the field of treatment. The leader of this family is Penicillin G. This drug is quickly removed from the body and it is necessary to use repeated doses of the drug to achieve definitive treatment. The criterion of this value for Clinicin is the level of the drug higher than the MIC of the target bacteria. This drug group is bactericidal, and it is better to use the term MBC instead of the term MIC for this family. One of the reasons for creating resistance to this family is the creation of MIC concentration, which makes the new generation of bacteria resistant to this therapeutic level. Therefore, the

blood level of the drug must be between 3- and 4-times MBC. The binding proteins of this family, especially cephalosporins, are worth mentioning and bind quickly with albumin. Of course, ceftriaxone with this feature can be a suitable treatment for enterobacteriaceae with low blood levels because its renal excretion is reduced and the blood concentration of this drug remains high for a longer period of time. It is mentioned that beta-lactam antibiotics such as penicillin and amoxicillin have PAE (post antibiotic effect). With this effect, after stopping the drugs, the target bacteria cannot grow again for some time. The effect of these antibiotics is highly dependent on time. The main pattern of effectiveness in this antibiotic family is $T > MIC$. Therefore, the longer the contact time of the antibiotic with the target organ (bacteria), the more effective the medicine. Therefore, the first goal of the clinic is to administer the drug at "certain time intervals" to

keep the drug concentration high in the "interval between two administrations".

CONCLUSION

Indiscriminate use of antibiotics in farm animals causes increasing problems for human health. They are used to protect farms against contagious diseases, as a preventive measure to prevent animals from getting sick, or even as "growth promoters" to increase farm profitability. Antibiotics are included in the feed used in aquaculture farms and even in some marine paints to prevent the proliferation of microorganisms in the hulls of ships! Almost 80% of antibiotics used are harmful to human health. This excessive use of antibiotics in animals also greatly contributes to the development of antibiotic resistance. The human gut naturally contains a large number of bacteria. This intestinal flora participates in digestion and immune defense. Antibiotics destroy not only pathogenic bacteria, but also the bacteria that make up the intestinal flora, which leads to an imbalance in this flora and intestinal digestive disorders, especially diarrhea, which may require treatment discontinuation. Rarely, destruction of the normal gut flora allows pathogenic bacteria to multiply in the colon and cause true colon infections, which can be very serious. Certain bacteria that have become resistant due to the excessive use of antibiotics are responsible for relatively common or serious infections such as skin and intestinal infections, in babies, and female cystitis.

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