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ANTIBACTERIAL THERAPY OF ENDOMETRITIS AFTER CESARIAN SECTION: OPTIMIZING THE DOSING REGIME

N.A. Korobkov, N.V. Baculina, M.A. Repina

North-Western State Medical University named after I.I. Mechnikov, Saint Petersburg, Russia

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◆ ***Purpose.*** To study the pharmacokinetics of β-lactam antibiotics in the development of endometritis after cesarean section to select the optimal dosage regimen.

Methods. A prospective, randomized, single-center study included 52 women in puerperas with endometritis after a caesarean section, divided into four groups. The patients of the first group (n = 17) received a course of ceftriaxone bolus in a single dose of 2.0 g (n = 10) and in the mode of prolonged perioperative infusion (n = 7). The patients of the second group (n = 10) received cefepim bolus at a dose of 2.0 g 2 times a day (n = 5) and in the extended infusion mode (n = 5). The patients of the third group (n = 14) received amoxicillin / clavulanic acid (Amoxiclav® 1000 mg + 200 mg) bolus at a dose of 1.0 g 3 times a day (n = 7) and in the extended infusion regimen (n = 7). The patients of the fourth group (n = 11) received ampicillin / sulbactam (Ampisid® 1000 mg + 500 mg) bolus at a dose of 1.0 g 4 times a day (n = 6) and in the extended infusion regimen (n = 5). We have compared the concentration of the studied antibiotics in the uterine cavity in the four groups using high performance liquid chromatography.

Results. The effective bactericidal concentration (C > 4×MIC) was not maintained throughout the entire dose interval in any of the treatment groups. The clinical efficacy and safety of the studied antibiotic regimens were similar. However, prolonged infusion of cefepime and aminopenicillins provided significantly higher concentrations in lochia.

Conclusion. Prolonged intravenous infusion of cefepime, ceftriaxone, amoxicillin / clavulanic acid and ampicillin / sulbactam in the treatment of endometritis after a caesarean section improves the pharmacokinetic / pharmacodynamic characteristics of these β-lactams in the uterine cavity, compared with the traditional bolus administration.

◆ **Keywords:** endometritis; cesarean section; β-lactam antibiotics; anti-bacterial agents; intermittent dosing; pharmacokinetics; pharmacodynamics; bolus administration; extended infusion; lochia.

АНТИБАКТЕРИАЛЬНАЯ ТЕРАПИЯ ЭНДОМЕТРИТА ПОСЛЕ КЕСАРЕВА СЕЧЕНИЯ: ОПТИМИЗАЦИЯ РЕЖИМА ДОЗИРОВАНИЯ

Н.А. Коробков, Н.В. Бакулина, М.А. Репина

Федеральное государственное бюджетное образовательное учреждение высшего образования
«Северо-Западный государственный медицинский университет имени И.И. Мечникова»
Министерства здравоохранения Российской Федерации, Санкт-Петербург

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◆ ***Цель*** — изучить фармакокинетику β-лактамных антибиотиков при развитии эндометрита после кесарева сечения для выбора оптимального режима их дозирования.

Методы. В проспективное рандомизированное одноцентровое исследование были включены 52 родильницы с эндометритом после кесарева сечения, разделенные на четыре группы. Пациентки первой группы (n = 17) получали курс цефтриаксона болюсно в дозе 2,0 г однократно (n = 10) и в режиме продленной

периоперационной инфузии (n = 7); пациентки второй группы (n = 10) — цефепим болюсно в дозе 2,0 г 2 раза в сутки (n = 5) и в режиме продленной инфузии (n = 5); пациентки третьей группы (n = 14) — амоксициллин/клавулановая кислота (Амоксиклав® 1000 мг + 200 мг) болюсно в дозе 1,0 г 3 раза в сутки (n = 7) и в режиме продленной инфузии (n = 7); пациентки четвертой группы (n = 11) — ампициллин/сульбактам (Амписид® 1000 мг + 500 мг) болюсно в дозе 1,0 г 4 раза в сутки (n = 6) и в режиме продленной инфузии (n = 5). Проведено сравнение концентрации исследуемых антибиотиков в полости матки в четырех группах методом высокоэффективной жидкостной хроматографии.

Основные результаты. Эффективная бактерицидная концентрация ($C > 4\times$МПК) не сохранялась на протяжении всего междозового интервала ни в одной из групп лечения. Клиническая эффективность и безопасность исследуемых режимов введения антибиотиков была сходной. Однако продленная инфузия цефепима и аминопенициллинов обеспечивала их значимо более высокие концентрации в лохиях.

Заключение. Продленная внутривенная инфузия цефепима, цефтриаксона, амоксициллина/клавулановой кислоты и ампициллина/сульбактама при лечении эндометрита после кесарева сечения позволяет улучшить фармакокинетические/фармакодинамические характеристики данных β-лактамов в полости матки по сравнению с традиционным болюсным режимом введения.

◆ **Ключевые слова:** эндометрит; кесарево сечение; β-лактамные антибиотики; антимикробные препараты; интермиттирующий режим введения; фармакокинетика; фармакодинамика; болюсное введение; продленная инфузия; лохии.

Introduction

Problems associated with an increase in the level of antibiotic resistance of hospital pathogens and a decrease in the supply of antibiotics with new mechanisms of action into clinical practice have necessitated additional studies of existing antimicrobial drugs [1]. In recent years, the issues of their optimal dosage and administration mode have been actively developed based on pharmacodynamic and pharmacokinetic properties to increase antibiotics' activity [2–5].

Due to a wide range of antimicrobial activity and a high level of safety during lactation, β-lactams are still preferred as etiotropic therapy for postpartum infection [6]. It has now been established that the maximum effect of antimicrobial drugs of this group depends on the time (t) during which the concentration (C) of the drug remains above the minimum inhibitory concentration (MIC) for pathogenic microorganisms. Therefore, such a parameter as $t >$ MIC is the most important in predicting β-lactams' antimicrobial activity [7, 8].

β-lactams' maximum bactericidal effect is achieved at a concentration four times higher than the MIC and does not contribute to a further increase in antimicrobial activity [9]. Long-term infusions purportedly enable the maintenance of target concentrations between drug injections while the $t >$ MIC value increases. Continuous administration of β-lactams has been analyzed in several studies [7, 8]. However, there is no convincing evidence of the efficacy of this alternative mode of administration. The professional literature provides scant information on β-lactam antibiotics' puerperal pharmacokinetics or pharmacodynamics.

This study aims to analyze β-lactam antibiotics' pharmacokinetics in the development of endometritis after cesarean section to select the optimal dosage regimen.

Materials and methods

A single-center, prospective, randomized, comparative study was performed. 52 puerperas with endometritis after cesarean section were examined. Their clinical symptoms met the criteria for postpartum endometritis (standard epidemiological case definition) [6].

The noninclusion (exclusion) criteria for female patients in the study were kidney and liver diseases, medication intake that affects the pharmacokinetic parameters of β-lactam antibiotics, predisposition to allergic reactions (hypersensitivity to the antibiotics under study), and a body mass index between 18 and 30 kg/m^2. The criteria for study withdrawal were the patient's refusal and non-compliance with the treatment regimen.

Aminopenicillins and cephalosporins as recommended by the federal clinical protocol [6]

were investigated, namely ceftriaxone, cefepime, as well as amoxicillin and ampicillin protected by β-lactamase inhibitors. The protocol for the administration of these antibiotics is standard of clinical practice in obstetrics.

The patients who received these antibiotics (according to the instructions) were randomized into the following groups:

— the group 1 (n = 17) received a ceftriaxone bolus injection at a dose of 2.0 g once (n = 10) and in the extended infusion mode (n = 7);
— the group 2 (n = 10) received a cefepime bolus injection at a dose of 2.0 g administered two times a day (n = 5) and in the extended infusion mode (n = 5);
— the group 3 (n = 14) received an amoxicillin/clavulanic acid (Amoxiclav® 1000 mg + 200 mg) bolus injection at a dose of 1.0 g administered three times a day (n = 7) and in the extended infusion mode (n = 7);
— the group 4 (n = 11) received ampicillin/sulbactam (Ampisid® 1000 mg + 500 mg) bolus injection at a dose of 1.0 g administered four times a day (n = 6) and in the extended infusion mode (n = 5).

The groups were well-balanced regarding demographic and baseline characteristics. The patients of all groups were comparable concerning weight and height parameters, anamnesis, parity, creatinine clearance, blood loss volume, and perioperative infusion.

The extended infusion was performed using a perfusor [Perfusor® fm (MFC); B. Braun, Melsungen AG, Germany]. The antibiotic under study was administered by microstream infusion for 2 hours. This time period was chosen for two reasons. First, this mode of administration did not affect the compliance of the puerperas during lactation and did not significantly limit their mobility. Second, the duration of the microstream infusion is limited by the manufacturer's guaranteed stability of aminopenicillins at room temperature in the prepared solution.

The antibiotics investigated can remain stable for a relatively long time in solution at room temperature after dilution, except for aminopenicillins. Manufacturers guarantee the absence of biodegradation and preservation of the activity of aminopenicillins for 3–4 hours. All antimicrobial chemotherapy drugs used are compatible with other drugs administered simultaneously through the same venous catheter during standard pharmacotherapy of endometritis after cesarean section.

The β-lactams concentrations studied in the lochia samples were measured by high performance liquid chromatography combined with diode array and mass selective detection using an Agilent 6400 high performance liquid chromatograph (Agilent Technologies, USA) at the Research Laboratory of Toxicology and Drug Monitoring, Research Department of Bioindication of the A.M. Nikiforov All-Russian Center for Emergency and Radiation Medicine, Emergency Control Ministry of Russia (the laboratory head was Professor G.G. Rodionov, MD, PhD). Metroaspirate was taken on day two from the start of antibiotic therapy at the end of the dosing interval (immediately before the next administration of the antibiotic). Since β-lactams are time-dependent antibiotics, their residual concentration level at the inflammation focus was assessed. Lochia was taken directly from the uterine cavity using a special aspiration catheter.

A comparative assessment of the MIC of the studied drugs was performed in relation toco the most significant pathogens of postoperative infectious complications in case of obstetric interventions, namely enterobacteria, staphylococci, and streptococci. The ceftriaxone MIC for sensitive pathogens ("wild strains") of wound infection is lower than 8 μg/ml [9]. Even W. Craig in his classic work showed that a concentration that is four times higher than the MIC is recognized as extremely effective for β-lactam antibiotics [10] in the eradication of microorganisms with sensitivity intermediate to them. Therefore, the indicator 4 × MIC = 32 μg/ml was used for further analysis as a "critical" level.

The safety of β-lactam therapy was assessed by clinical symptoms (diarrhea, rash, vomiting, and seizures), and by changes in laboratory parameters during treatment (transaminases, alkaline phosphatase, bilirubin, platelets).

The study results were analyzed using the Statsoft STATISTICA 10 and Microsoft Excel 2016 software packages. According to the Kolmogorov–Smirnov test, the main characteristics and statistical criteria for their comparison were selected after studying the distribution of the characteristic and its comparison with the Gaussian distribution. Since the revealed distribution of the values of the parameters under study

differed from the normal one, nonparametric methods were used to present the data obtained. Quantitative data were described as Me (Q_{25}; Q_{75}), where Me is the median; Q_{25} and Q_{75} are lower and upper quartiles, respectively; comparison in groups was performed using the nonparametric Mann-Whitney test.

Qualitative parameters were presented as the frequency of characteristics as a percentage of the total number of patients, and the values were compared using the chi-square test.

Differences were considered statistically significant when p did not reach the threshold value of the statistical significance level of the null hypothesis (alpha) equal to 0.05.

Results

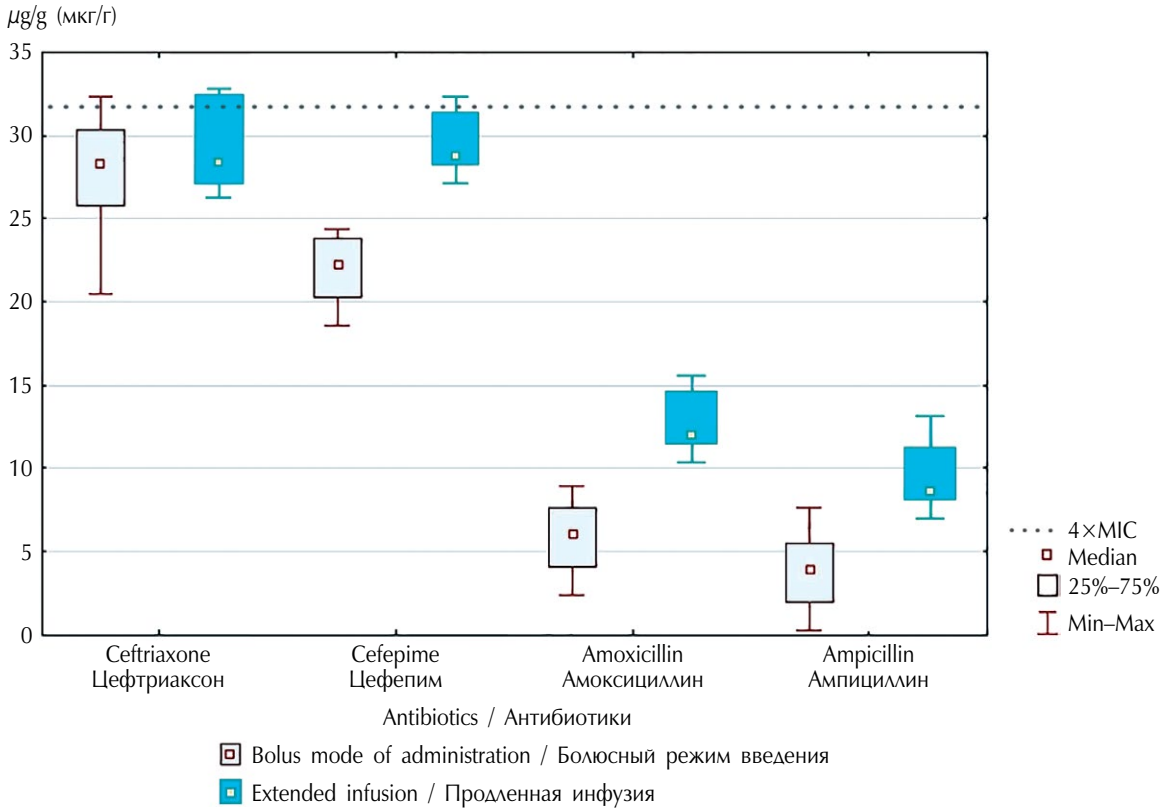
The concentrations of the antibiotics studied in lochia at the end of the dosing interval for different modes of administration are presented in Figure.

In patients receiving cefepime and aminopenicillins, the residual drug concentrations at the end of the dosing interval in the extended infusion mode were significantly higher ($p < 0.05$).

The levels of ceftriaxone with different modes of administration were also different, but the differences were not statistically significant ($p = 0.087$), which was apparently due to the peculiarities of the pharmacokinetic characteristics of ceftriaxone, namely higher variability of concentrations in peripheral blood and a long half-life period ($T^1/_2$) of ceftriaxone compared to other drugs under study.

At the same time, for all modes of administration, the "critical" level of 4 × MIC of the drugs under study was not achieved. Only in patients who received ceftriaxone and cefepime in the extended infusion mode, the concentration of antibiotics in the uterine cavity was close to the target value,

Clinical cure rates for patients with endometritis from different treatment groups were



Concentrations of the investigated cephalosporins and inhibitor-protected aminopenicillins in lochia of parturient women with endometritis after a cesarean section at the end of the dosing interval for various modes of administration. * $p < 0.05$

Концентрации исследуемых цефалоспоринов и ингибиторозащищенных аминопенициллинов в лохиях родильниц при эндометрите после кесарева сечения в конце интервала дозирования при различных режимах введения. * $p < 0,05$

comparable. All postpartum women recovered without hanging the antibiotic, transferring to the septic department, or having surgery.

Possible side effects due to β-lactams were rare, and the incidence did not differ between the two groups. There were no statistically significant intergroup differences in laboratory deviations associated with the safety of the antibiotics used. However, both groups of patients who received β-lactams had an increased in the concentration of hepatic enzymes compared with the baseline level. The initial signs of cubital phlebitis were recorded in one postpartum woman during the course of etiotropic treatment in a bolus mode and two postpartum women with an extended infusion mode.

Discussion

In our study, the effective bactericidal concentration ($C > 4 \times$ MIC) was not maintained throughout the entire inter-dose interval in any of the treatment groups. The clinical efficacy and safety of the studied antibiotic administration modes were similar. However, extended infusion of cefepime and aminopenicillins provided significantly higher concentrations in lochia. In contrast, the $t > 4$ MIC parameter will indirectly tend to the target time values of the dosing interval, which is important for predicting the efficacy of the studied time-dependent antibacterial drugs [11].

In the case of a bolus mode, with a lower concentration of antibiotic in the uterine cavity between injections and peak increase in concentration after injection (in the absence of an increase in the antimicrobial activity of β-lactams), there is a supposedly greater probability of the resumption of microbial pathogen propagation and clinical treatment failure. With extended infusion, such a "selection window" can exist only at its creation. The loading dose enables the quick achievement of the required concentration of the antimicrobial drug and avoids the initial period of propagation of pathogens with higher MIC values. It also reduces the probability of selection of resistant strains [7, 8]. However, further research is required to assess the possible prospects for this strategy.

In our opinion, the study results are largely consistent with the hypothesis of the advantage of extended infusion in achieving a "critical" level of concentrations of antimicrobial drugs at the focus of infection. Longer (daily) infusions will probably improve the determining index $t > 4$ MIC, which will better result in the treatment of postoperative infectious complications.

Thus, the study demonstrated the advantage of extended infusion in at least one parameter, better antibiotic penetration into the site of infection. This method of maintaining a stable bactericidal concentration is a promising strategy. At the same time, in many clinical situations (when pathogens do not have multidrug resistance), it is not necessary to strive to achieve $t > 4$ MIC of 100%. Therefore, intervals between infusions are possible to provide full care for the newborn and conduct medical and diagnostic procedures.

Conclusions

Extended intravenous infusion of cefepime, ceftriaxone, amoxicillin/clavulanic acid, and ampicillin/sulbactam in the treatment of endometritis after cesarean section improves the pharmacokinetic/pharmacodynamic characteristics and antibacterial activity of these β-lactams in the uterine cavity regarding pathogens with a higher MIC (moderately resistant strains) compared with the traditional bolus mode of administration. This mode of administration thereby increases the probability of eradicating pathogens and enhances the efficiency of etiotropic therapy.

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◆ **Information about the author** *(Адрес автора для переписки)*

Nikolay A. Korobkov / Николай Александрович Коробков
https://orcid.org/0000-0001-7279-2535
E-mail: nikolai_korobkov@mail.ru