ADVERSE DRUG REACTIONS TO LOCAL INTRAWOUND VANCOMYCIN APPLICATION AFTER POSTERIOR LUMBOSACRAL FUSION

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Objective. To analyze the types and frequency of adverse drug reactions to local intrawound application of vancomycin powder in patients after posterior decompression and stabilization in the lumbosacral spine.
Material and Methods. Clinical series published in 2011—2017 were analyzed. At the first stage, Medline and PubMed databases were searched for English-language literature sources using the keywords «intrawound vancomycin», «surgical site infection», and «posterior lumbar fusion», and e-Library for Russian-language sources using «local application of vancomycin powder», «infection in the surgical site», and «posterior decompression and stabilization». At the second stage, abstracts of articles were examined, and publications that did not meet the research criteria were excluded. At the third stage, the full texts of the selected articles were reviewed for compliance with inclusion criteria, as well as references for relevant studies.
Results. Nineteen clinical studies (16 retrospective and 3 prospective) with a total of 13,077 patients were selected for a systematic review. In 55.3 % (7,236) of posterior lumbosacral surgery cases, vancomycin powder was applied locally to prevent surgical site infection. Among the entire cohort of patients, unwanted drug reactions were detected in 2.19 % of patients.
Conclusions. Local application of vancomycin powder is associated with a low incidence of unwanted drug reactions.
Key Words: lumbosacral spine, surgical site infections, posterior decompression and stabilization, vancomycin, local application, adverse drug reactions.

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Surgical site infections (SSIs) in spinal neurosurgery are the most common cause of adverse outcomes of surgical treatment and prolonged hospitalization in patients after spine surgery [1, 32]. According to the literature data [14, 23], the incidence of SSIs after posterior decompression and stabilization in the lumbosacral spine varies from 3 to 5 %. Nevertheless, SSI cases reach up to 15–20 % in a series of somatic diseases (coronary heart disease, arterial hypertension, diabetes mellitus, and obesity) as well as in the presence of certain intraoperative factors (more than 3-hour duration of surgery, blood loss of more than 1000 ml, staged surgeries) [3, 20].

To date, international clinical practice guidelines for antibiotic prophylaxis of SSIs in spinal neurosurgery, including posterior lumbosacral fusion, have been established. A special role in these clinical guidelines is attributed to local application of vancomycin powder, a natural antibiotic of the glycopeptide group produced by soil actinomycetes. Vancomycin was first isolated from *Actinobacteria species* by Edmund Kornfeld in 1953 and was first introduced into clinical practice in the form of intravenous infusions in 1958 [7]. However, local application of vancomycin powder for SSI prevention was first used in cardiac and thoracic surgery [7].

The high efficiency of local application of vancomycin powder for SSI prevention in cardiac and thoracic surgery led to the active use of this antibacterial drug in other types of surgeries, including spinal neurosurgery. According to the world literature data [13, 14], local application of vancomycin powder in patients after spinal surgery allows reducing SSI incidence from 4.1 to 1.3 %. In addition, the economic costs of practical healthcare have been reduced significantly. For instance, Theologis et al. [29] demonstrated that local use of vancomycin powder for SSI prevention in patients after thoracic and lumbosacral spine surgeries can significantly reduce the cost of practical healthcare (an average of 244,402 $ cost saving per 100 surgeries).

The main advantage of local application of vancomycin powder is that it allows a higher minimum inhibitory concentration (MIC) of the drug in the wound while avoiding its accumulation in the blood plasma and, as a conse-

quence, reducing the systemic effect of the antibacterial drug. Plasma concentration of vancomycin was shown to be maintained at the therapeutic (15–20 μg/ml) or subtherapeutic levels upon its local administration with its concentration in the wound exceeding the MIC required for the treatment of most bacterial infections [2]. It is important to note that the increased plasma concentration of vancomycin in its local application is associated with a series of unwanted drug reactions, the most adverse of which is nephrotoxicity. The frequency of this type of unwanted drug reactions reaches 6 % [24].

Despite the absence of large multicenter studies on the local intrawound application of vancomycin powder for the prevention of SSI in spinal neurosurgery, this antibacterial drug is widely used in many neurosurgical clinics around the world. There have been only a few reports on the types and frequency of unwanted drug reactions in the local application of vancomycin powder in spinal neurosurgery, with the results of these studies being largely ambiguous.

The aim of the study is to analyze the types and frequency of adverse drug reactions to local intrawound application of vancomycin powder in patients after posterior decompression and stabilization in the lumbosacral spine.

Material and Methods

Clinical series of local application of vancomycin powder for SSI prevention in patients after posterior decompression and stabilization surgeries published in the period of 2011–2017 were analyzed.

In order to analyze the types and frequency of adverse drug reactions to local application of vancomycin powder after posterior lumbosacral fusion, the following criteria were defined for inclusion of the literature data in this systematic review:

1) English- and Russian-language clinical series on the local application of vancomycin powder for SSI prevention in patients after posterior decompression and stabilization in the lumbosacral spine published in 2011–2017;

2) study design – prospective and retrospective analysis;

3) comparison of two groups (group with local application of vancomycin powder and group without administration of the antibacterial drug);

4) recorded dosage of intrawound drug administration and the incidence of SSI;

5) data on the types and frequency of adverse drug reactions to the local application of vancomycin powder.

Exclusion criteria:

1) *in vitro* and/or animal studies devoted to analysis of the efficacy of local application of vancomycin powder in SSI prevention;

2) case–control studies;

3) descriptive studies (studies devoted to the features of surgical technique, and recommended methods of SSI prevention after spinal fusion without indications on the effectiveness of these methods).

The stages of searching and filtering data for the systematic review are shown in Fig. At the first stage, Medline, PubMed, and e-Library databases were searched for literature sources using keywords "intrawound vancomycin", "surgical site infection", and "posterior lumbar fusion" for English-language sources, while keywords "local application of vancomycin powder", "infection in the surgical site", and "posterior decompression and stabilization" were used for e-Library database. In addition, manual selection of the articles based on the title and according to the inclusion criteria was used. At the second stage, abstracts of articles were examined, and publications that did not meet the research criteria were excluded. At the third stage, the full texts of the selected articles were reviewed for compliance with inclusion criteria, as well as references for relevant studies. The data obtained from the articles were recorded in a table and analyzed. Thus, due to the lack of domestic studies when searching for the literature sources using these keywords, a total of 16 retrospective and 3 prospective foreign studies were systematized.

Results

Nineteen (16 retrospective and 3 prospective) clinical studies with a total of 13,077 patients were selected for a systematic review as a result of the search and selection of literature data. In 55.3 % (7,236) of posterior lumbosacral surgery cases, vancomycin powder was applied locally to prevent surgical site infection.

The average incidence of SSI in patients without local application of vancomycin powder and in the group with antibiotic administration was 6.56 and 1.74 %, respectively. Among all the patients under study, who had been subjected to local preventive administration of vancomycin powder, unwanted drug reactions were detected in 2.71 % of patients in the form of nephropathy (0.17%), ototoxicity with short-term hearing loss (0.23 %), systemic effect of the antibacterial drug, predominantly pseudomembranous colitis (0.10 %), pseudoarthrosis (0.52 %), and seroma formation (1.68 %, Table).

Discussion

It is no coincidence that we specifically chose posterior decompression and stabilization in the lumbosacral spine. Posterior and posterolateral surgical approach to the lumbosacral spine are known to involve incision of the skin, subcutaneous fat and bulky musculoaponeurotic system located in this spinal region. Surgical interventions in spinal neurosurgery are not possible without the use of special retractors that hold the entire soft tissue mass. Retractors that hold soft tissues throughout the surgery create local compression and microcirculation dysfunction in these structures. In such conditions, ischemic tissue is more vulnerable to various pathogenic and opportunistic microorganisms. For this reason, local application of antibacterial drugs is a promising method for preventing SSI in patients after posterior spinal fusions.

It is worth mentioning that the obtained value of frequency rate of adverse drug reactions in local application of vancomycin powder is not strict-

ly reliable. This is due to the fact that most of the studies included in the current systematic review are of retrospective nature and also due to a number of limitations affecting the results of statistical analysis. Nevertheless, this allows us to claim that adverse drug reactions in the local application of vancomycin powder is a rare phenomenon in spinal neurosurgery.

To date, there are two major clinical studies on the efficacy of local application of vancomycin powder for SSI prevention in patients after posterior decompression and stabilization in the lumbosacral spine. For instance, only one out of 1512 operated patients suffered adverse drug reactions (nephropathy) with the use of local application of vancomycin powder in the clinical series by Molinari et al. [19]. Vancomycin was used at the same dose (1 g, local intrawound application) for all patients. In the observation by Devin et al. [4], unwanted drug reactions (nephropathy, ototoxicity) developed in two out of 2056 patients subjected to the local application of vancomycin powder for preventive purposes.

The studies on the pharmacokinetic features of vancomycin show that its plasma concentration rarely reaches supratherapeutic values upon local application, and the drug is completely eliminated from the body in one day. For instance, Armaghani et al. [2] revealed cases with supratherapeutic levels of vancomycin in blood plasma. However, no systemic toxic effect of the drug was noted. Gans et al. [7] did not find a reliable correlation between the plasma concentrations of vancomycin and elevated level of creatinine in patients who underwent posterior surgery in the lumbosacral spine.

The main infectious agent of SSI is methicillin-resistant *S. aureus* (MRSA). Ghobrial et al. [8] in their clinical series proved high efficacy of vancomycin powder in the prevention of SSI in patients with risk factors for the development of this complication after surgical interventions on the spine. The study included 981 patients, 786 (80.1 %) of which were operated on the lumbosacral spine through posterior approach. The incidence of SSI was 5.2 %, the prevalence of unwanted drug reactions (seromas) in the local application of vancomycin was verified in 1.5% of cases. The analysis of wound microbiology in SSI revealed mostly polymicrobial associations and only two cases of fungal infection. Polymicrobial associations are represented mainly by Gram-negative pathogenic and conditionally pathogenic microflora: *Pseudomonas, Proteus, Escherichia Coli, Corynebacteria*. Tomov et al. [30] conducted a retrospective study on the efficacy of local application of vancomycin powder in SSI prevention in 2,325 patients after spinal surgeries. The authors demonstrated that this antibacterial drug allows achieving a significant reduction in the incidence of SSI caused by Gram-positive microorganisms, particularly MRSA. The researchers also noted a statistically significant reduction in the prevalence of SSI in patients after spinal fusions, which are caused by Gram-negative bacteria and polymicrobial associations.

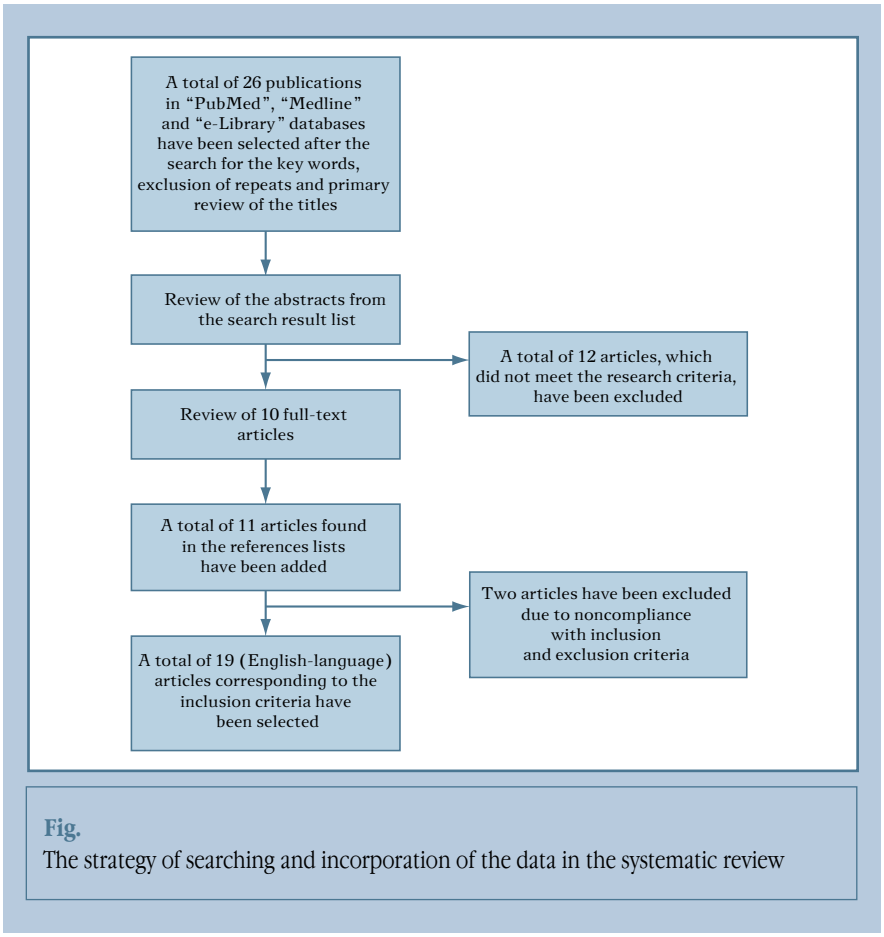

Fig.
The strategy of searching and incorporation of the data in the systematic review

Nevertheless, widespread use of vancomycin in surgical practice both for prevention and treatment of bacterial infections has led to the development of resistance of microorganisms to this antibacterial drug. None of the studies included in this systematic review mentioned cases of SSI caused by vancomycin-resistant microorganisms after spinal surgery. Nevertheless, world literature describes cases of SSI caused by vancomycin-resistant *S. aureus* (VRSA) after thoracic surgeries [10, 22]. *In vitro* study by Tarai et al. [28] clearly demonstrated that *S. aureus* culture acquires resistance to vancomycin at its dosage less than 4 μg/ml in the wound. For this reason, the most important feature of local application of vancomycin powder for prevention of SSI is the creation of an adequate concentration of the drug in the wound cavity.

To date, there are no works devoted to the study of optimal doses of vanco-

Table 1
Clinical series on the efficiency of local application of vancomycin powder for SSI prevention in patients after decompression and stabilization in the lumbosacral spine

Authors of the study	Study design	Patients, n	Patients with local application of vancomycin, n	SSI incidence in control patients, %	SSI incidence in patients with local application of vancomycin powder, %	Vancomycin dosage applied, g	Type and frequency of adverse drug reactions
Mirzashahi et al. [18]	Prospective	380	380	–	2.7	2	0.52 % (pseudarthrosis)
Lee et al. [16]	Retrospective	571	275	10.4	5.4	2	No reactions noted
Devin et al. [4]	Retrospective	2056	966	5.1	2.2	2	0.2% (nephropathy. ototoxicity)
Tomov et al. [30]	Retrospective	2425	1173	2.2	1.3	1	0.16% (seromas)
Heller et al. [11]	Retrospective	683	342	3.8	1.1	0.5–2	No reactions noted
Emohare et al. [6]	Retrospective	303	303	3.4	0	1	No reactions noted
Theologis et al. [29]	Retrospective	215	151	10.9	2.6	2	No reactions noted
Martin et al. [17]	Retrospective	306	156	5.3	5.1	2	No reactions noted
Ghobrial et al. [8]	Retrospective	981	981	–	5.2	Mean 1.3	1.52% (seromas)
Hill et al. [12]	Retrospective	300	156	4.0	0	1	No reactions noted
Armaghani et al. [2]	Retrospective	25	25	–	0	1	No reactions noted
Godil et al. [9]	Retrospective	110	56	13.0	0	1	No reactions noted
Tubaki et al. [31]	Prospective	907	302	1.68	1.61	1	0.11% (pseudomembranous colitis)
Kim et al. [15]	Retrospective	74	34	12.5	0	1	No reactions noted
Strom et al. [26]	Retrospective	300	156	4.0	0	1	No reactions noted
Gans et al. [7]	Prospective	87	87	–	3.4	0.5	No reactions noted
Molinari et al. [19]	Retrospective	1512	1512	–	1.20	1	0.07% (nephropathy). 0.13% (ototoxicity)
Sweet et al. [27]	Retrospective	1732	156	2.6	0.2	2	No reactions noted
O'Neill et al. [21]	Retrospective	110	25	13.0	0	1	No reactions noted

mycin powder in its local application in humans. In the experimental observation by Eder et al. [5], a negative dose-dependent effect of local application of vancomycin powder on osteoblast activity was shown. Vancomycin powder was added to the culture of osteoblasts at the following doses: 0, 3, 6 and 12 mg/cm^2. In all cases when vancomycin concentration exceeded 3 mg/cm^2, there was a sharp decrease in pH and osteoblast activity, which was confirmed by a decrease in the enzymatic activity of alkaline phosphatase and calcium deposition in cells. Most of the osteoblasts died at vancomy-

cin concentration of 6 mg/cm^2, which is directly related to a sharp decrease in pH value of the medium. However, some osteoblasts retained their activity after administration of vancomycin at a concentration of 12 mg/cm^2. It is the decrease in osteoblast activity and their death that lead to the development of pseudarthrosis, which is one of the main adverse drug reactions to vancomycin [25]. The dose of vancomycin powder in its local application for SSI prevention in patients after spine fusions varies from 1 to 2 g in various clinical series, but most researchers agree that the drug should be evenly distributed throughout the entire surface of the wound area [6, 9, 11, 12, 15, 17, 21, 27, 31]. Further in vivo studies are required in order to determine the optimal dose of vancomycin powder in its local application alongside with maintaining its high antibacterial activity and leveling the adverse drug reactions. An important issue is the assessment of the effect of vancomycin on the rate of bone block formation while taking into account its negative effect on bone tissue itself, especially when vancomycin is used in combination with osteoinductive drugs. For instance, Strom et al. [26] revealed no significant differences in the rate of bone block formation between the group with local application of vancomycin and the control group.

The studies included in this systematic review have a number of limitations:

1) most of the clinical series are retrospective and include a small number of patients, which cannot help affecting the results of statistical data processing;

2) no results of bacteriological analysis of the wound content are presented;

3) no relation between the doses of the antibacterial drug and the types and frequencies of adverse drug reactions was determined;

4) the factor of the effect of active drainage of the postoperative wound was not taken into account in any of the cited clinical series, which could serve as a reason for reduction in the local concentration of vancomycin powder;

5) the role of the somatic status of patients (chronic heart failure, chronic renal failure, diabetes mellitus, obesity, and etc.) has not been defined. There is no doubt that it is necessary to conduct further large multicenter studies on a larger number of respondents with a detailed study of all the above mentioned parameters in order to overcome these limitations.

Conclusion

Local application of vancomycin powder is a relatively safe and effective method of preventing SSI in patients after posterior lumbosacral fusion. There is no doubt that the difference among studies in design, total number of patients and the number of groups, as well as inclusion and exclusion criteria, cannot help affecting the results of this systematic review. Nevertheless, we can state that local application of vancomycin powder is associated with a low incidence of adverse drug reactions. On the other hand, the use of this antibacterial drug for SSI prevention should be strictly individual while taking into account all possible risk factors, since there are still no large multicenter prospective studies in the world literature.

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