Editorial

Local vancomycin powder administration is not the Holy Grail, only on the half way there

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Surgical-site infections (SSIs) is a typical sort of hospital acquired infections (HAIs) which leads to a substantial worse prognosis and high national health expenditure. In the latest issue of Neurosurgery, Arka's prospective observational cohort study with 355 patients (1) showed that vancomycin local use could reduce the incidence of SSIs in patients with craniotomy (0.49% vs. 6%, P=0.002). The study is timely and with great importance due to SSIs after craniotomy may result in significant consequences such as paresis, hydrocephalus and blood stream infections (2). Despite the encouraging results, more concerns with the topical use of vancomycin merit discussion.

Heterogeneity of the baseline

Factors for the development of SSIs sometimes can be multifactorial. These risk factors could be divided into patient-related factors and operation-related factors. Patient-related factors include diabetes mellitus, immunosuppression, malnutrition and so on. Operation-related factors include the status of the wound (clean or contaminated, specially in patients with emergency operation or trauma), type of surgery, duration of operation, drainage or pressure monitoring device placement and etc. (3). All of the factors come together to reduce the patients' ability to stimulate immune response adequately which will prevent SSIs. Unfortunately, these risk factors vary greatly in each group of the studies about topical vancomycin application. In Arka's study, immune or nutritional status of the patients were not compared in the baseline. The number of patients who were placed drainage or pressure monitoring device during the operation was not even mentioned.

SSIs should be classified into deep or superficial infection. The incidence of each type is totally different (4). In Patricia's prospective observational study (5), the incidence of SSIs in patients with craniotomy was 5.14%. Only 7.69% of them were superficial infections while 30.77% were deep infections. Most of the risk factors have not been well evaluated or even not have been mentioned in the baseline of the patients which lead to confounding results of the researches.

Vancomycin minimal inhibitory concentration (MIC) creep

Vancomycin administration in treating infections caused by gram positive bacteria has lasted for several decades. However, with its extensive use, bacterial resistance will always be a potential issue. The balance between benefits and risks must always be taken into consideration. For this reason and the sustained effectiveness of vancomycin on *Staphylococcus aureus* related SSIs, close surveillance is

mandatory.

A large body of evidence have demonstrated that local vancomycin powder showed the beneficial effect in decreasing SSIs while few studies accounted for the changes of vancomycin MICs. The rise of drug-resistant bacteria gained international attentions. One multi-center study revealed that the shift in vancomycin MICs from <0.5 to 1.0 μg/mL had been observed in the past decade (6). Local use of antibiotics is a main cause of this consequence as well as the intravenous administration.

The optimal dosage is uncertain

Among the studies of vancomycin topical treatment (1,7-9), almost all the patients in the intervention group received vancomycin 1 g in spite of the wound size and the operation duration. Some patients received vancomycin powder while other might receive vancomycin solution in the surface of the wound. It is predictable that different wound size might lead to different vancomycin concentration. The uncertain concentration might be above the MICs to the gram positive bacterial or not. Even though the area of the wound could be measured, the concentration of local vancomycin could not be evaluated precisely. What is the most important, it is an undeniable fact that there is currently no evidence to support vancomycin 1 g is the optimal dosage. The only one retrospective study by Abode-Iyamah (10) with different dosage of vancomycin powder (from 0.5 to 2 g) showed that there was no difference of SSIs incidence (vancomycin group 6.5% *vs.* no-vancomycin group 5.4%, P=0.72). Since there is a lack of head-to-head comparisons between different dosage groups, it is largely unknown what is the best dosage of vancomycin powder for the prevention of SSIs.

Other alternative antibiotics

Antibiotics chosen for prophylaxis of SSIs should cover the pathogens which are commonly associated with the infection. Meanwhile, it should be at a relative low price with less side effects. As some of the investigations revealed (5,11) that *Staphylococcus* species were frequently isolated from the patients with SSIs, we therefore hypothesize that cefazolin or cefradin might also be an option. Sulfamethoxazole is another alternative which can cover the *Staphylococcus* species well with lower MICs to it. All the antibiotics listed above have a relatively low medical expenditure than vancomycin.

Vancomycin administration sometimes leads to side effects which is unavoidable. The adverse effects include nephrotoxicity, nausea, vomiting and hypotensive which can result in ischemic diseases (12). It is unwise to use vancomycin indiscriminately. Sulfamethoxazole, first generation cephalosporin or even clindamycin could be as a replacement of vancomycin for SSIs prophylaxis.

Pathogens of SSIs are various

A huge number of microorganisms reside on the human skin, including bacteria, fungi and virus. Some of the commensal bacteria can prevent pathogens to colonize on the skin surface via competing nutrients, releasing chemicals or stimulating the host's immune system (13). The colonized pathogens are potential sources of SSIs. It has been found that *Staphylococcus hominis*, *Staphylococcus aureus*, *Enterococci*, some type of gram-negative bacteria and even *Candida* were more frequently to be isolated in the damaged skin (14).

In Shi's retrospective study (11), the incidence of SSIs was 6.8% in 5,723 consecutive craniotomy patients. Among them, 42.7% (167 patients) had positive results of cerebrospinal fluid (CSF) or wound secretion. Gram positive pathogens were dominant (82.0%) while the gram negative was 16.8% (*Klebsiella pneumoniae* was the most common pathogen). Ten patients of them suffered from mixed pathogens including *Candida spp*. Another study with 1,200 spinal deformity reconstruction patients revealed that the incidence of SSIs was 2.83% (8). Of the total 34 patients with SSIs, gram positive cocci could be isolated in 10 samples while gram negative rods were 11. Also, *Candida albicans* was detected in two mixed infection patients. So pathogens of SSIs are various and numberous, gram positive bacteria is just one component.

There is an interesting phenomenon that the prevalence of SSIs caused by *Pseudomonas* is increasing. Whether it can indirectly reflect the effectiveness of local vancomycin administration is still unknown. Large sample studies on pathogens of SSIs are necessarily needed in order to prove the assumption.

Limitations of published meta-analysis

The incidence of SSIs depends on many factors including antibiotics prophylaxis or decolonization with chlorhexidine. The real effect of topical vancomycin treatment is still in controversy. Most of all, it is a off-lable application which

is not approved by Food and Drug Administration and no practice guidelines or recommendations for the application till now.

It is noticed that two meta-analysis about topical vancomycin application have been published (15,16). However, limitations could be found in these studies. In the first place, most of the studies involved were singe-center, observational with a lower sample size. The incidence of SSIs is much less which leads to a low power to detect the real effect of topical vancomycin on decreasing the already lower SSIs rate in a small population. Then, the definition of SSIs was not unitary in these studies. Surgical site (Spine surgery, neurosurgery and joint surgery were mixed up) and postsurgical follow up were always various which all led to the confounding results. Third, the form of topical vancomycin administrated was diverse. Vancomycin powder and vancomycin solution or even the vancomycin sponges might not have the same effect although the mechanism of drug action was unclear. Above all, two studies (17,18) which revealed that topical vancomycin was invalid in preventing SSIs were not included in the two early meta-analysis.

Conclusions

The role of vancomycin topical application to prevent SSIs is unclear and the exact population who can obtain a benefit from the treatment is not easy to define. Furthermore, more attentions should be paid to MICs before widespread use of vancomycin intrawound and more prospective studies are needed to clarify the optimal dose of topical vancomycin treatment. Anyhow, there is still a large space for the improvement of antibiotics prophylaxis to prevent the incidence of SSIs.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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