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**Use of topical vancomycin powder in total joint arthroplasty: Why the current literature is inconsistent?**

Mancino F *et al.* Vancomycin powder in TJA

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**Abstract**

Periprosthetic joint infection (PJI) is a catastrophic complication in hip and knee arthroplasty, and the use of topical vancomycin powder (VP) has been investigated as a tool to potentially reduce its incidence. However, there remains no consensus on its efficacy. Therefore, the aim of this review is to provide an analysis of the recent evidence underlying the conflicting conclusions. Seven systematic reviews and meta-analyses on topical VP in hip and knee arthroplasty were published in international peer-reviewed journals between January 2020 and December 2022 reporting conflicting outcomes. Apart from all being limited by the quality of the included studies (mostly level III and IV), some pooled in their analysis confounding variables that may have led to contradictory results. If taken into consideration the exclusive use of VP in isolation, the available data, although very limited, suggest that it does not reduce the infection rate in routine primary hip and knee arthroplasty. However, conflicting results from multiple meta-analyses and systematic reviews do not allow a clear conclusion to be drawn. A large multicentre randomized-controlled trial is indicated to clarify the role of VP in hip and knee arthroplasty. Based on the analysis of the current evidence, the use of topical VP appears to be safe when used locally in terms of systemic adverse reactions, hence, if proven to be effective, it could bring great benefits due to its low cost and accessibility.

**Key Words:** Periprosthetic joint infection; Vancomycin powder; Total knee arthroplasty; Total hip arthroplasty; Infection; antibiotic

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**Core Tip:** Vancomycin powder (VP) is a hot topic in total joint arthroplasty (TJA), however, the published results are conflicting. The aim of this study was to thoroughly analyze the available literature and provide a valid explanation on why such contrasting outcomes and describe the current knowledge on VP in TJA.

**INTRODUCTION**

Periprosthetic joint infection (PJI) is one of the leading causes of revision in total joint arthroplasty (TJA) accounting for up to 15% of all revision total hip arthroplasty (THA) and up to 25% of all revision total knee arthroplasty (TKA)[1]. Its incidence has been reported between 1% to 4% after primary TKA and 1% to 2% after primary THA[2]. The number of primary implants performed every year is expected to grow, and therefore the number of revisions is expected to increase proportionally[3]. In particular, the incidence of revisions for PJI is projected to increase by 176% between 2014 and 2030 in THA, and by 170% in TKA[4]. The economic burden is massive, the yearly cost associated with PJI in the United States was approximately one billion United States dollars in 2017, and as the prevalence of primary implants is projected to double in the next 10 years, the economic impact will probably reach almost two billion United States dollars by 2030[5].

Multiple strategies have been pursued to try to reduce the PJI rate in TJA, including preoperative screening, patient optimization, modified intraoperative techniques, and enhanced postoperative surveillance[6]. The topical application of vancomycin powder (VP) has been investigated to reduce the incidence of PJI by providing a high concentration of antibiotic in a specific surgical site. However, despite being considered a “hot topic”, recent meta-analyses have reported conflicting conclusions.

The aim of this review is to provide a thorough analysis of the results previously reported in the literature, in order to clarify the current evidence for the use of topical VP in TJA.

The United States National Library of Medicine (PubMed/MEDLINE), EMBASE, and the Cochrane Database of Systematic Reviews were queried for publications utilizing various combinations of the search terms “VP”, “THA”, “TKA”, “primary”, and “revision” in combination with the Boolean operators (AND, OR, \*) since January 2020 to December 2022. Two authors (Fabio Mancino and Christopher W Jones) independently conducted all the searches and screened the titles and abstracts to identify relevant studies. Differences were resolved by consulting a third senior reviewer (Piers J Yates). Only abstracts that evaluated the outcomes of VP in primary and/or revision TJA were reviewed. If the title and abstract of each study contained insufficient information, the full manuscript was reviewed. An additional search was conducted by screening the references list of each selected article. Inclusion criteria were any systematic review and/or meta-analysis that pooled the results on the application of VP in TJA, analyzing the outcomes in terms of infection rate. Exclusion criteria were cohort studies, clinical trials, case reports, surgical technique reports, expert opinions, letters to editors, biomechanical reports, instructional course lectures, studies on animals, cadaver or *in vitro* investigations, book chapters, abstracts from scientific meetings, unpublished reports, and studies written in a non-English language. Two independent reviewers (Fabio Mancino and Christopher W Jones) separately examined all the identified studies and extracted data. During the initial review of the data, the following information was collected for each study: Title, first author, year of publication, study design, number of studies included, number of patients included, type of joint replacement, methods of application of VP, complications related to VP, superficial and deep infection rates.

**BURDEN OF PERIPROSTHETIC JOINT INFECTION**

PJI is a devastating complication associated with extensive economic, physical, and psychological costs. Mortality is significantly greater in patients undergoing surgery for PJI compared with those undergoing aseptic revisions, with mortality rates reported as five times higher at one year[7,8]. Moreover, when methicillin-resistant Staphylococcus aureus (MRSA) is involved, the mortality rate has been reported up to 24% at 5 years[9]. In addition, after the first case of PJI, the reinfection rate is up to 8.5% in THA and up to 16% in TKA[9], showing that the long-term consequences can be devastating. Kapadia *et al*[10], reported that patients with PJI had a significantly higher number of readmissions (3.6 *vs* 1.2; *P* < 0.001), length of hospitalization, clinic visits and sum-total episode cost than patients who had a non-infected primary implant (US$96,166 *vs* US$21,654; *P* < 0.001). When considering the economic burden, the cost of a revision for PJI is up to five times higher than a primary TJA ($116,382 *vs* $28,249)[11]. Moreover, managing this complication often requires a two-stage revision strategy, costing approximately US$60,000 more than revisions for mechanical failure and/or aseptic loosening[12].

Currently, the only consensus recommendation for the use of antibiotics in TJA by international authorities is systemic perioperative administration[13].

**VANCOMYCIN POWDER IN ORTHOPAEDIC SURGERY AND TJA**

Gram-positive bacteria, particularly staphylococcal species, are the most common pathogenic organisms involved in post-operative orthopaedic infections[14]. Vancomycin is a tricyclic glycopeptide antibiotic with activity against gram-positive bacteria initially derived in 1953 from a compound produced by *Amycolatopsis orientalis*, a soil bacterium discovered within mud collected from a Borneo forest. The compound nicknamed “*Mississippi mud*” because of its appearance prior to purification became vancomycin (after the word “*vanquish*”) and nearly 70 years later still retains antimicrobial activity against the majority of gram-positive organisms and remains the most commonly used antibiotic in the United States for the treatment of serious gram-positive infections, including those caused by MRSA[15]. The topical application of this antibiotic has been widely adopted in different fields of orthopaedic surgery with promising results. Sweet *et al*[16], demonstrated a significant reduction in postoperative deep wound infection rates (0.2% *vs* 2.6%; *P* < 0.0001) in posterior instrumented thoracolumbar spinal fusions with the adjunctive application of 2 g of VP before wound closure. Similar findings were reported by O'Neill *et al*[17], when analyzing 110 patients that underwent posterior spinal stabilization of traumatic injuries. The authors noted that the infection rate was significantly reduced (13% *vs* 0%; *P* = 0.02) when 1 g of vancomycin was applied before wound closure. Moreover, similarly reduced infection rates were reported both by Molinari *et al*[18] and by Bakhsheshian *et al*[19] when studying the effect of topical VP in instrumented and uninstrumented spine surgery.

The use of VP has been also investigated in tibial fractures, considered to be at high risk of infection, in an open-label multicentre randomized clinical trial reporting that the application of 1 g of VP was associated with a reduced risk of deep surgical site infection due to gram-positive organisms (risk difference, -3.7%; 95%CI, -6.7% to -0.8%; *P* = 0.02), in line with the activity of the antibiotic[20].

Considering these promising results, VP has been introduced in TJA with the hope of significantly reducing the risk of PJI (Figure 1). Weight-based (15 mg/Kg) intravenous (IV) vancomycin is already widely adopted as a second-line prophylaxis instead of first- or second-generation cephalosporin in case of allergies to penicillin, history of MRSA, or positive preoperative MRSA nasal-swab culture[21]. However, considering the better results associated with cephalosporins, the International Consensus on PJI recommended that these antibiotics can be safely used in case of non-anaphylactic penicillin allergy[22] since the cross-reactivity risk has been proven to be as low as 1%[23].

The rationale behind the topical application of VP is to maximize the local concentration while minimizing the systemic adverse effects[24], especially when the surgical wound often consists of areas of local hematoma or seroma and tissue ischemia that may not be reached by the systemically administered antibiotics. In a rat model, the use of intra-articular VP combined with IV antibiotics resulted in the complete eradication of MRSA bacteria from contaminated implants[25]. Johnson *et al*[24] studied vancomycin concentration both locally and systemically after the administration of 2 g of VP (1 g intra-articular and 1 g in superficial tissues) in 34 THA reporting the different serum levels at 90 min, 3 h, 12 h, and 24 h, and the local levels at 3 h, 12 h, and 24 h. The authors reported that the mean serum concentration peaked at 12 h (4.7 mcg/mL; max observed 12.7 mcg/mL at 3 h) while never reaching the systemic therapeutic levels of 15-20 mcg/mL. The intra-wound half-life was estimated to be 7.2 h with mean wound levels > 900 mcg/mL at 3 h while maintaining the local concentration over 200 mcg/mL for 24 h. Finally, the authors estimated that it would take up to 64 h for intrawound levels to drop below the minimum inhibitory concentration for *S. aureus* of 2 mcg/mL (Table 1).

Despite the potential benefits, there are also theoretical drawbacks. Firstly, the low systemic concentration of vancomycin may induce the development of resistant species of gram-positive bacteria colonizing the body. The Infectious Disease Society of America recommended serum levels > 10 mcg/mL to avoid the potential development of resistance[26]. Given the short half-life of the antibiotic when administered parenterally (4-6 h), this is not problematic when administered as a single dose of prophylactic IV antibiotic providing coverage for the first 24 h, but maybe a factor during ongoing and prolonged systemic absorption of intra-articular antibiotics. Secondly, a potential third body wear mechanism has been hypothesized between crystalline vancomycin and implant components since the solubility of vancomycin may vary in an intra-articular environment compared to saline solution. Nevertheless, Qadir *et al*[27] reported no appreciable difference in wear rates after 10 million simulated cycles between ultra-high-molecular-weight-polyethylene and Cobalt-Chrome alloy with the addition of VP. Lastly, vancomycin may have negative effects on the proliferation of viable cells including osteoblasts. Braun *et al*[28], reported the *in-vitro* effect of vancomycin on osteoblasts, endothelial cells, fibroblasts and skeletal muscle cells showing that the toxic effects were time (from day-3) and concentration-dependent (> 0.01 mg/mL). However, such results are yet to be proven *in-vivo*, and as shown by Johnson, no such concentrations have been reported at the 3-d mark. Therefore, based on the aforementioned studies, topical administration of VP can reasonably be considered clinically safe when used in TJA. Finally, if proven to significantly impact the PJI rate, VP would be highly cost-effective as its price has been reported from $2.50 to the highest of $44.00 per gram[29].

**CURRENT LITERATURE FOR VP IN TJA**

The application of VP has become a “hot topic” among researchers. Between January 2020 and December 2022, seven systematic reviews and/or meta-analyses have been published in contemporary international peer-reviewed orthopaedic journals[30-36]. Among them, 2 were published one-year apart in two of the most relevant orthopaedic journals. However, despite similar methodologies, the 2 studies reported conflicting results[30,31] (Table 2).

Movassaghi *et al*[30], reported in a meta-analysis published in 2022 that intrawound VP may reduce the risk of PJI in primary and revision TJA while not leading to systemic complications. The authors included in their analysis 16 studies and 17164 TJA that received intrawound VP reporting an overall decreased rate of PJI (OR 0.46, *P* < 0.05), a decreased rate when considering TKA and THA separately (OR 0.41, *P* < 0.05 and OR 0.45, *P* < 0.05, respectively), and a decreased rate when considering primary implants only (OR 0.44, *P* < 0.05). However, it is worth pointing out that most of the results came from the outcome of primary TKA (14,262 of 17164 joints, 83%) and that among them, 69% of the primary TKA (9884 of 14262 primary knees) came from a single study[37] where the authors used the so-called “VIP protocol”, consisting in 0.35% povidone-iodine (PI) (17.5 mL in 500 mL saline) solution lavage followed by 1 g of VP deep to the fascia and 1 g superficial to the fascia. When looking at PI lavage, data is once again not clear. We know from Kim *et al*[38], that the results of a systematic review of 7 studies and 8861 TJA showed no difference between PI and saline in reducing the PJI rate. However, more recent studies showed efficacy in revision TJA reducing the PJI rate from 3.4% to 0.4% (*P* = 0.038, 478 revisions)[39], and efficacy in reducing the rate of any infection over 3232 TJA (OR 0.45, *P* < 0.05) or superficial site infections (SSI, OR 0.3, *P* < 0.05)[40]. Finally, Shohat *et al*[41] recently reported on the outcomes of 31331 cases showing a 2.34 times lower rate of PJI when comparing PI lavage with saline in TJA (0.6% *vs* 1.3%) with an absolute risk reduction of 0.73% and a number needed to treat of 137 patients. Therefore, the positive outcomes reported by Movassaghi *et al*[30] may have been influenced by the inclusion of iodine lavage.

Similarly, Liao *et al*[35], recently published in strong favor of VP suggesting that, according to their results, VP has a clear effect on preventing PJI in primary TKA. The authors reported on 11292 TKAs where VP was used with a Risk Ratio (RR) of 0.41 (95%CI 0.29 to 0.58, *P* < 0.001) when compared to cases where VP was not used. However, as previously mentioned, 46.7% of their results came from two studies[37,42] where VP was used in combination with a PI solution, potentially having a significant effect on the final results and recommendations.

On the other hand, Wong *et al*[31]discouraged the application of VP in primary TJA after systematically analysing the outcomes of 9 studies and 3371 TJA in which VP was used compared with 2884 in which it was not. Only studies with similar procedures and those limited to the application of VP were included. The authors reported that only one of the studies included[43] was associated with significant improvement while the remaining eight had OR that broadly bracketed the line of no difference (range, 0.09 to 1.97). In addition, the authors noted insufficient evidence on the question of safety, therefore, their final statement was against the use of topical VP in routine THA and TKA unless adequately powered, multicentre, prospective trials demonstrate clear evidence. However, despite the methodology and the inclusion criteria being well defined to include only studies using topical VP in isolation, no meta-analysis was conducted to verify the statistical significance of such a conclusion, thereby limiting the strength of their results.

Conversely, in the same year (2021) another meta-analysis was published on the same topic[32] but this time, the authors stated that “the local application of VP could significantly decrease the rate of SSI and PJI in primary TJA” and that “we recommend topical administration of the VP before wound closure”. The meta-analysis included once again nine studies, six of which were also included in the research by Wong *et al*[31]. However, the remaining 3 studies[41,43,44], representing a weight on the result of 44%, did not involve only the application of topical VP, therefore, their inclusion could be misleading. One of these[42], reported on the combined application of PI lavage and VP showing that administration of local antibiotics was preventative for PJI only in the primary TKA (OR 0.28, 95%CI 0.09–0.89). The other two[43,45], reported on the application of VP on the surface of cementless implants in THA and TKA and not in the soft tissue deep or superficial to the fascia/capsule, therefore, a completely different way of using VP.

In another systematic review and meta-analysis by Xu *et al*[34], the authors reported that “the current literature suggests that intrawound vancomycin used in primary hip and knee arthroplasty may reduce the incidence of PJI, but it may also increase risk of aseptic wound complications”. Nine studies were included in their final analysis with 4605 TJA, 2497 of which were treated with VP. The authors reported a reduced PJI rate in the VP group (1.20% *vs* 2.75%) with an OR of 0.44 (95%CI 0.28 to 0.69, *I*² = 0.0%), a comparable risk of SSI (OR 0.60, 95%CI 0.17 to 2.12), and a higher incidence of aseptic wound complications (2.15% *vs* 0.96%, OR 2.39, 95%CI 1.09 to 5.23). However, when considering the aseptic wound complications, only four of the nine studies reported on such events (1069 treated cases), and all of them had different methodology protocols in terms of the amount of VP used, placement of the VP (deep to the fascia, superficial, or both), and the application of a drain for up to 48 h post-operative. Therefore, the conclusion that VP is associated with an increased risk of aseptic wound complications, based on such results, may require stronger evidence.

Moreover, another systematic review and meta-analysis published in 2020[33], stated that topical antibiotics led to a moderate reduction in PJI in primary TJA, with no significant impact on SSI rates but that it may be associated with a moderate increase in aseptic wound complication. However, once again, four of the nine studies reported mixed results considering the combined activity of PI lavage and VP[42], the application on cementless implants[44,45], or did not consider only the application of VP in TJA but more generally the use of topical antibiotics[46].

Lastly, Martin *et al*[36] recently pooled together the studies using VP alone (7 studies) and in combination with PI lavage (7 studies) reporting a significant reduction of PJI rate (RR 0.39, 95%CI 0.27 to 0.56, *P* < 0.001) in primary and revision THA and TKA when compared with a control group. However, there remain doubts on the contribution of the PI lavage as we are still missing clear results on the VP alone used with standardized methods and compared with a control group. Interestingly, the authors reported a reduced aseptic wound complication rate in the treatment pool (110/2903, 3.79% *vs* 98/1512, 6.48%), though, still considering the combined effect of VP and PI lavage.

**CONCLUSION**

PJI in TJA is certainly one of the biggest challenges that the orthopaedic community is now facing with tremendous impact on the patient, the treating multi-disciplinary team, and the health care system. There are potential risks regarding the development of antimicrobial resistance following the administration of VP. From the available data, we can conclude though that the application of topic VP appears to be safe in terms of other systemic complications as the serum levels reached are proven to be below the ones associated with the risk for toxicity (> 15-20 mcg/mL). Moreover, the evidence that supports the perceived increased risk of aseptic wound complications is limited, therefore stronger data are probably necessary to clarify such a conclusion.

However, despite an apparently adequate safety profile, the efficacy of topical VP in reducing PJI is yet to be proven. Evidence remains lacking, as previous studies have been mostly retrospective level III and IV, with varying methodologies and important technical differences (amount of VP, placement deep or superficial to the fascia, use of drain). The most recent literature shows contrasting results; positive outcomes appear only to have been reported when the additional application of PI is considered together with VP. However, for studies considering only the strict use of VP, authors have recommended against its use in TJA, but have failed to provide sufficient statistical justification to support that recommendation. It must also be noted that the use of intraoperative antimicrobial irrigation (*e.g.* deep or subcutaneous tissues), or the application of antimicrobial agents (*e.g.* ointments, solutions, or powders) to the surgical incision for the prevention of SSI are not currently recommended by The Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection[47]. Again, this is due to a lack of evidence supporting these practices.

Therefore, despite the multiple studies recently published, the efficacy of VP in TJA for reducing PJI is still essentially unknown. To overcome this issue, a large multicentre randomized controlled trial with homogeneous methodology and exclusion of additional confounding variables (such as PI lavage) is required.

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**Figure Legends**



**Figure 1 Vancomycin powder used in 1-st stage revision total knee arthroplasty.**

**Table 1 Serum and local levels of vancomycin at different post-wound closure collection times**

|  |  |
| --- | --- |
| **Procedure** | **Serum levels after wound closure of VP intrawound administration (μg/mL)** |
|  | **1.5 h (mean ± SD; max)** | **3 h (mean ± SD; max)** | **12 h (mean ± SD; max)** | **24 h (mean ± SD; max)** | **Highest level observed across the 24-h period** |
| THA (*n* = 15) | 3.8 ± 3.9; 9.5 | 4.9 ± 4.5; 12.7 | 5.1 ± 3.3; 8.4 | 3.5 ± 3.5; 8.0 | 6.6 ± 3.8; 12.7 |
| TKA (*n* = 19) | 1. ± 2.5; 8.7
 | 1.8 ± 3.2; 9.8 | 4.4 ± 3.1; 7.3 | 3.5 V 3.6; 10.4 | 5.2 ± 3.4; 10.4 |
| THA + TKA (*n* = 34) | 2.2 ± 3.4; 9.5 | 3.2 ± 4.1; 12.7 | 4.7 ± 3.2; 8.4 | 3.5 ± 3.5; 10.4 | 5.8 ± 3.6; 12.7 |
|  | **Local levels after wound closure of VP intrawound administration, *n* (μg/mL)** |
|  | **-** | **3 h (mean ± SD)** | **12 h (mean ± SD)** | **24 h (mean ± SD)** | **-** |
| THA | - | 988 ± 628 (12) | 769 ± 1059 (11) | 280 ± 436 (11) | - |
| TKA | - | 877 ± 455 (18) | 288 ± 203 (16) | 163 ± 220 (18) | - |
| THA + TKA | - | 922 ± 523 (30) | 484 ± 716 (27) | 207 ± 317 (29) | - |

VP: Vancomycin powder; THA: Total hip arthroplasty; TKA: Total knee arthroplasty.

**Table 2** Main characteristics and results of the recent literature on the topic vancomycin powder

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Type of study** | **No. of studies** | **No. of cases (Control / Intervention)** | **PJI Rate/RR (Control *vs* Intervention)** | **SSI/Aseptic wound complications (Control *vs* Intervention)** | **Authors’ Conclusions** |
| Martin *et al*[36]*,* 2022 | Systematic review and meta-analysis | 7/7 | 144724/8029 | RR 0.39 (95%CI 0.27-0.56, *P* < 0.001) | 6.48% *vs* 3.79% | VP ± PI lavage reduced PJI rate in primary and revision THA/TKA. Associated with reduced aseptic wound complications |
| Liao *et al*[35]*,* 2022 | Systematic review and meta-analysis | 14 | 7720/1292 | RR 0.41 (95%CI 0.29-0.58, *P* < 0.001) | - | VP recommended in primary TKA |
| Movassaghi *et al*[30]*,* 2022 | Systematic review and meta-analysis | 16 | 3731/17164 | 1.65% *vs* 0.87% (*P* < 0.05) | - | Local VP may reduce the risk of PJI in primary and revision TJA |
| Wong *et al*[31]*,* 2021 | Systematic review | 9 | 6255/3371 | - | No difference | Recommend the surgeons not to use VP in routine THA and TKA |
| Peng *et al*[32]*,* 2021 | Systematic review and meta-analysis | 9 | 4512/2354 | RR 0.37 (95%CI 0.23- 0.60, *P* < 0.001) | RR = 0.40, 95%CI 0.27-0.61 (*P* < 0.001) | Local VP could significantly decrease the rate of SSI and PJI in primary TJA |
| Saidahmed *et al*[33]*,* 2021 | Systematic review and meta-analysis | 9 | 3714/1985 | 3.5% *vs* 1.6%, RR 0.53 (95%CI 0.35-0.79, *P* = 0.002, *I*2 = 0.0%) | No difference1.6% *vs* 0.7%, RR = 0.61, 95%CI 0.17-2.12, (*P* = 0.43, *I*2 = 0.0%) | Local antibiotic application results in a moderate reduction in deep infection rates in primary TJA, with no significant impact on SSI rate |
| Xu *et al*[34]*,* 2020 | Systematic review and meta-analysis | 9 | 4607/2497 | 2.75% *vs* 1.20% (OR 0.44, 95%CI 0.28-0.69, *I*2 = 0.0%) | No difference 1.60% *vs* 0.67% (OR 0.60, 95%CI 0.17-2.12, *I*2 = 0.0%) | VP used in primary hip and knee arthroplasty may reduce the incidence of PJI but it may increase the risk of aseptic wound complications |

RR: Relative risk; SSI: Superficial site infection; VP: Vancomycin powder; PI: Povidone iodine; PJI: Periprosthetic joint infection; THA: Total hip arthroplasty; TKA: Total knee arthroplasty; TJA: Total joint arthroplasty; OR: Odds ratio.