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Science Editor and Company Editor-in-Chief
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RESPONSE LETTER – ADDRESSING REVIEWER COMMENTS

Manuscript ID-NO: 61761

Dear Prof. Lian-Sheng,

thank you very much for the valuable peer reviewers' comments on our manuscript ID-No 61761 submitted for the category minireview. We are pleased about your preliminar decision of conditional acceptance, if the necessary revisions are completed to your and the peer reviewers' satisfaction.

The feedback has been highly welcomed because of the constructive nature of the comments and critics. After introducing now major revisions in the manuscript in response to the reviewers' suggestions we are convinced that the paper has now substantially improved. Therefore, we hope that the revised manuscript will receive the status "accepted for publication" by the reviewers and by the editorial office and we are looking forward to receive your final evaluation.

Best regards,

Christof Berberich, corresponding author

Responses to Reviewer comments point by point

Reviewer 1

- (1) *From the title we knew this manuscript talked about "rationale of use" and "scientific evidence" of dual-antibiotic ALBC. Unfortunately, the major part of manuscript discussed clinical effect of ready-to-use ALBC in clinical cohorts. We advise that either title or text should be revised to make them matched.*

Thank you for your valuable and important comment. In fact, the manuscript focuses on the rationale and clinical effect of commercial "ready-to-use" ALBC. The reason for that is that most surgeons prefer such an industry tested and mechanically evaluated product (according to ISO norms) if they use the bone cement for fixation purposes. The situation is different if ALBC is used for spacers in the staged treatment of septic cases. In this context bone cement is often manually impregnated with a wide range of different antibiotic combinations based on the knowledge of the PJI-causing pathogen and its antimicrobial resistancies. In addition, the literature search has not revealed outcome studies which compare the PJI risk of in-theatre hand-mixed dual ALBC vs single ALBC.

In order to emphasize the evaluated prophylactic role of dual ALBC and to differentiate its intended use in infection prophylaxis from treatment of septic cases, we have accordingly

added the term “for prophylaxis” to the “TITLE” (Dual antibiotic loaded bone cement in patients at high infection risks in arthroplasty – rationale of use for prophylaxis and scientific evidence). Furthermore, we have added the following sentence to the end of the “INTRODUCTION”:

“[New]...To the best of our knowledge there are no clinical outcome studies published which have compared the PJI rate of hand-mixed (theatre-admixed) dual ALBC vs single ALBC” .

- (2) *There are two kinds of ALBC, commercial ready-to-use products and hand-made ALBC, a mixture of antibiotic and plain cement by surgeons in the theatre. Because of personal preference or economic reasons, hand-made ALBC is still popular worldwide, especially in developing countries. There are many interesting questions remaining unsolved in hand-made ALBC, such as the selection of drug, best drug ratio, method of mix and difference in antibiotic effect compared with commercial products, which are needed to be discussed in the manuscript.*
- (3) *Most of antibiotics have no chemical reaction with bone cement, so the introduction of drug could influence microstructure of cement layer, changing its mechanical properties, a potential risk factor for aseptic loosening. Previous studies have made detailed measurements for this change, which was not seen in the manuscript.*

Again, these are two very helpful comments which we have addressed in combination because of the overlapping contents. Indeed, we agree with the need to insert an entire chapter highlighting the difference between premixed and hand-mixed cement. However, as already pointed out in the answer to comment 1, our literature search did not reveal any outcome studies describing the prophylactic efficacy of hand-mixed ALBC with respect to PJI rates.

Accordingly, we have inserted the following chapter after the “INTRODUCTION”:

“[New] COMMERCIALLY PREMIXED VS. HAND-MIXED DUAL ALBC

There are several Food & Drug Administration (FDA) and European Medicines Agency (EMA) approved ALBC which are available as “ready-to-use” commercial products. According to their antibiotic contents they can be grouped in single low dose ALBC (e.g. impregnated with either 0,5 or 1 g of gentamicin or loaded with 1 g of tobramycin in 40 g PMMA powder) or in dual high dose ALBC (e.g. impregnated with 1 g of gentamicin and 1 g of clindamycin or loaded with 0,5 g of gentamicin and 2 g of vancomycin). In addition, there is widespread non-standardized, off-label and surgeon-directed use involving hand-mixing various antibiotics into bone cement. Reasons for this practice are economic considerations, lack of availability of specific ALBC, limited local regulatory approval or need for specific customized solutions in septic revision arthroplasty^[18]. However, manual admixture of antibiotics into bone cement has raised some concerns with regards to unknown elution kinetics, toxicity, efficacy and mechanical stability of such in-theatre made ALBC^[18]. The latter aspect is particularly important if the cement is intended for fixation. In fact, the manual addition of higher amounts of some antibiotics in powder- or in liquid-form has been shown to affect the fatigue strength of PMMA prompting fears of premature aseptic loosening of the joint^[19]. It should also be noted that some antibiotics are not stable at the bone cement curing temperature (e.g. many beta-lactam antibiotics) or chemically interfere with the polymerization process (e.g. rifampicin)^[20]. Given these uncertainties, the majority of surgeons still prefer the use of commercial single or dual ALBC for prosthesis fixation.

In addition, the 3 new citations [18-20] were inserted in the “LITERATURE” part.

- (4) *This manuscript supported application of dual ALBC in high infection risk patients, but the principles of optimizing these patients (like risk algorithm, evaluation chart, etc.) was absent.*

Thank you for this valuable comment. Although it is correct that this manuscript introduces the idea of a variation of local antibiotic prophylaxis in response to higher infections risks, the focus is rather on the discussion of the rationale of use and clinical evidence than on the description who is a risk patient. Nonetheless, we already described and cited the current state of knowledge in the “INTRODUCTION” (“*..In view of the demographic changes, arthroplasty surgeons today face the challenge to operate on an increasing number of older patients suffering from several major comorbidities. Numerous clinical studies have provided evidence that important patient-related disorders predispose patients to a higher operational risk of infections than usual [9-11]. This is also true for the more complex surgical procedures of revision arthroplasty which is frequently associated with longer operation times and a higher invasiveness leading to a PJI incidence of 5% and more [12]. Significantly increased infection rates of 4-6% are also reported in the frail cohort of femoral neck fracture patients on an emergency trauma track which does not leave time for preoperative health optimization strategies or for decolonization protocols of multi-drug resistant bacteria [13,14]....*”)

In the chapter “LOWER PJI RATE WITH DUAL ALBC (COPAL G+C) - RISK FOR INFECTION PATIENTS IN PRIMARY ARTHROPLASTY” we already provided further explanations who was considered a RFI patient in the discussed study.

“...Patients were defined as risk for infection individuals if they presented a combination of at least two or three major risk factors for total hip arthroplasty and total knee arthroplasty, respectively, using a simple scoring system. The risk algorithm included specific patient-related comorbidities (e.g. severe anemia, severe obesity, diabetes mellitus, chronic immunosuppression) and further general risk factors (e.g. hip-fractures or prior arthroplasty surgeries) [35].”

Further details on the applied risk algorithm in that study from the University Clinic of Madrid can be retrieved from the publication cited in [35].

- (5) *Many antibiotics were metabolized via liver or kidney, so overuse of antibiotics might cause hepatic or renal damage, dual ALBC might worsen this side effect, especially in elder patients with internal diseases. The improvement of antibiotic effect and effect on body should be discussed simultaneously.*

This is again a very important comment. Although mainly reported from septic treatment cases in which high dose hand-mixed ALBC for spacers was used, the concern of more side effects with dual ALBC justifies a closer look. The randomized clinical study from Sprowson et al. [citation 31] in the fragile patient cohort of femoral neck fracture patients provides here interesting insights. We have summarized them in the following sentences at the end of chapter “LOWER PJI RATE WITH DUAL ALBC (COPAL G+C) – HEMIARTHROPLASTY IN FEMORAL NECK FRACTURE PATIENTS”

"[New]...Concerns that the use of a dual antibiotic-loaded cement with higher drug content may trigger more antibiotic-mediated adverse side effects in these fragile patient cohorts could not be confirmed. In fact, the comparison of complications including renal failure or percentage of Clostridium difficile infections did not reveal differences between the standard and intervention group [31]. There was even a statistically significant decrease in the need for critical care treatment in the COPAL G+C group (0,5% vs 4,7%), reflecting the clinical impact of the much lower PJI rate in the intervention group receiving dual ALBC [31].

- (6) *We advise the author to illustrate their searching strategies of literatures so others could made improvement in this topic easily.*

Thank you for this important comment. We totally agree with the suggestion that the literature search terms should be described for reproducibility. Therefore, we have addressed this requirement in the revised manuscript and inserted the following new content at the end of "INTRODUCTION":

"[New]... For that purpose, the PubMed & EMBASE literature databases were screened for publications pertaining to the clinical utilization of dual antibiotics in cement for infection prophylaxis. Use of dual ALBC in treatment of septic cases was excluded from the evaluation. Only four in-vitro and five original clinical studies were identified which met the inclusion criteria. The latter were also stratified by level of clinical evidence (I-IV). The combination of gentamicin and clindamycin in commercial bone cement was the only referenced dual ALBC in these clinical studies..."

- (7) *Some grammar questions could be carefully discussed. For instance, "neck-of-femur" could be revised as "femoral neck" and "orthopaedically relevant pathogens" could be revised as "pathogens related to orthopedic infections".*

Thank you for these suggestions which make the readability of this paper easier. In the revised manuscript we have already changed the terms "neck-of-femur fractures" by "femoral neck fractures" and "orthopaedically relevant pathogens" by "pathogens related to orthopedic infections". In addition, we made the revised manuscript check by two colleagues (one is a teacher of English, the other native English speaker) to further improve ways of spelling and grammar-related issues.

Reviewer 2:

The format of WJO (in the abstract as well as the manuscript) is not followed. - A guideline for reviews (in this case PRISMA) is not followed and described. - A methods section is entirely absent (including search terms, in- and exclusion criteria), which makes it impossible to reproduce. - The results section is not mentioned as such, but several interesting studies are discussed. - The discussion is very short, it lacks a limitations section and any future perspectives.

Thank you very much for these valuable comments which we would like to address in combined form. We would completely agree with the critics that the paper lacks the

traditional structure (Introduction, Methods, Results, Discussion & Conclusions), if the intention had been to publish a systematic review. However, our objective was to evaluate the evidence for a possibly better prophylactic role of dual ALBC in risk for infection patients in form of a literature-based minireview. As a regular reader of the digital WJO issues we let us here guide by the frequently found examples of previous minireviews which are written in a “scientific essay” form (e.g. recent minireview by Sandean. Management of acute spinal cord injury: A summary of the evidence pertaining to the acute management, operative and non-operative management. World J Orthop. 2020 Dec 18; 11(12): 573–583, doi: 10.5312/wjo.v11.i12.573). Our impression is that the readership of the WJO also appreciates this format because it allows to gain a relatively easy overview of the current state of knowledge with respect to a surgical practice or a still controversially discussed topic. Nonetheless, the point is absolutely justified that a short description of the literature search terms including inclusion and exclusion criteria must be provided for reproducibility reasons. Therefore, we have inserted a new paragraph in the “INTRODUCTION” providing an explanation what has been done.

“[New]... For that purpose, the PubMed & EMBASE literature databases were screened for publications pertaining to the clinical utilization of dual antibiotics in cement for infection prophylaxis. Use of dual ALBC in treatment of septic cases was excluded from the evaluation. Only four in-vitro and five original clinical studies were identified which met the inclusion criteria. The latter were also stratified by level of clinical evidence (I-IV). The combination of gentamicin and clindamycin in commercial bone cement was the only referenced dual ALBC in these clinical studies. To the best of our knowledge there are no clinical outcome studies published which have compared the PJI rate in hand-made (theatre-admixed) dual ALBC vs single ALBC.”

We further agree with the critics that the discussion is short (despite the condensed minireview format), it lacks a limitation section and should also point to future perspectives. To address this comment, we have now re-written this chapter and inserted new sentences in “CONCLUSIONS”:

“The current literature including in vitro and in vivo studies supports the additional benefits of dual ALBC, with synergy of drug elution and improved antibacterial activity on a wide range of pathogens related to orthopedic infections. While its therapeutic efficacy on mature biofilm-bacteria is still not entirely clear, more and more data have now demonstrated that it may confer better protection from infection in particularly vulnerable patients or in higher risk procedures (see Fig. 3 for summary of clinical evidence). [New]...However, this conclusion is still based on a mix of prospective and retrospective cohort studies, the latter with a lower evidence level and inherent limitations with regard to possible study bias and higher risk of confounding factors. A generalization of the observed effect of a stronger antibiotic prophylaxis by dual ALBC may be also problematic given that the ready-to-use brands of bone cements differ in their antibiotic elution properties as well as in the nature and amount of pre-mixed antibiotics.

The idea of an infection risk-adapted local antibiotic prophylaxis may be one interesting option among other preoperative optimization protocols to decrease the burden of PJI. In addition to the use of dual ALBC this can be also achieved by temporary or permanent antibacterial implant coatings including surface modifications with silver ions or manual spreading of a fast-resorbable, antibiotic-loaded hydrogel [41]. Both strategies have been

shown to reduce early post-surgical infections in uncemented implants in orthopedic surgery. Further studies are needed to truly elucidate the effect of dual ALBC and other local antibiotic delivery systems for infection prevention and to weigh possible benefits against potential adverse effects and costs.”

Science editor and editorial office comments:

Language quality

A native English speaker has now edited the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability.

Conflict-of-Interest Disclosure Form

Filled-in and separately provided

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Authors contribution statement

Separately provided

Original figure documents

All 3 figures are provided in a separate PPT-document. They are original and have been composed for this manuscript. Fig 1 illustrates the prophylactic anti-biofilm effect of three different commercial ALBCs vs plain cement on two bacterial strains frequently found in orthopedic infections. Fig. 2 illustrates the randomized clinical study design and comparative outcome data in femoral neck fracture patients in relation to the ALBC used. Fig. 3 provides an overview of all five clinical studies which have reported PJI rates in relation to the ALBC used with further details on the indication of use, number of patients analyzed, study design, level of evidence and main result.

Literature

Citations have been carefully checked and PMID & DOI citation numbers provided where still missing. References' numbers in the text have been put in superscript.