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The impact of adjuvant antibiotic hydrogel application on the primary stability of uncemented hip stems

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ABSTRACT

Objectives To assess the effect of adjuvant antibiotic-loaded hydrogel application on the primary stability of implanted uncemented hip stems.
Design Biomechanical study.
Setting An electro-mechanic material test system (#5866, Instron, Norwood, MA, USA) equipped with a 10-kN load cell was used. A staircase loading protocol was applied via quasi-static ramped compression loading at 0.005 mm/s and six different load levels between 500 N and 3000 N in 500 N intermittent load increase steps.
Participants 12 artificial femora were prepared and received a collarless uncemented standard offset stem (Corail; DePuy Synthes, Zuchwil, Switzerland).
Interventions The two groups were prepared with or without the antibiotic-loaded hydrogel.
Main outcome measures Construct stiffness was determined from the recorded load-displacement curves and stem subsidence was measured via motion tracking.
Results Construct stiffness (control: 4176±240 N/mm; intervention: 4588±448 N/mm) was not significantly different between the groups (p=0.076). Stem subsidence increased significantly over the increasing load levels in each separate group (p≤0.002) and remained not significantly different between the groups (p=0.609).
Conclusions The application of antibiotic-loaded hydrogel was associated with non-inferior performance in terms of primary uncemented hip stem stability. This finding makes the prospect of adjuvant antibiotic-loaded hydrogel application potentially feasible; however, it requires further investigations prior to translation in the clinical practice.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ To our knowledge, there are no existing biomechanical studies investigating the effect of antibiotic-loaded hydrogel on primary stability of uncemented femoral components.

WHAT THIS STUDY ADDS

⇒ There was no significant effect in primary uncemented femoral stem stability, irrespectively of whether the hydrogel was used or not.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Adjuvant antibiotic-loaded hydrogel application is potentially feasible in uncemented stems. Further studies are required, prior to its translation in the clinical practice.

INTRODUCTION

Primary total hip arthroplasty (THA) has been proven to improve function and relieve pain in patients with hip pathology and primarily osteoarthritis.[1 2] It has increased in popularity, with over 100 000 procedures performed in 2019 in the UK.[3] Prosthetic joint infection (PJI) is a devastating complication and a common reason for revision.[3 4] It requires an extensive workforce, involving a multidisciplinary approach, multiple procedures, and a long duration of antibiotic treatment.[5–7] It is a costly treatment with an estimated burden of $390 000 in the USA.[8]

Antibiotics are a main part of managing PJI, and empirical and targeted antibiotics are used when sensitivities and organisms are known. Both systemic and local delivery of antibiotics are used for this stage.[9 10] Local antibiotics are delivered using bone cement at high concentration, although this can affect pharmacokinetics, cement properties and need for reoperation.[7 11] In terms of organisms, *Staphylococcus aureus* remains the most common organism identified. The ability of bacteria to form a biofilm and be unaffected from the host's defences and antibiotic treatment also adds on the complexity of treatment.[4 12 13]

PJI treatment is challenging with either a single-stage revision involving thorough debridement, antibiotics and implant replacement, or a two-stage revision including two operations using a spacer and delaying the definitive prosthesis implantation until bacterial eradication.[14] The two-stage approach carries a longer morbidity for the patient and recent studies support equivalent outcomes with the one-stage approach.[14–16] The use of a spacer is usually augmented with high dose of antibiotic-loaded cement as a local therapy.[7]

Hydrogels are a new form of a bioabsorbable local delivery of antibiotics with increased doses up to 10–100 compared with bone cement, limiting systemic effects.[4 6] The application of an antibiotic-loaded hydrogel in fracture-related infection with *S. aureus* has been related to good treatment with no detectable interference to fracture healing.[17] Furthermore, the combination of gentamicin and vancomycin in the hydrogel has demonstrated effectiveness to methicillin-resistant *S. aureus* in two-stage and one-stage revision.[6 18] In general, hydrogels can be used as vehicles for delivery of other anti-infective treatments, of drugs with other functions, or for biologics to enhance tissue healing or integration.

With their application directly at the bone-implant interface, hydrogels may affect the stability as the primary function of THA. Therefore, studying the impact of hydrogel application on the mechanical competence of orthopedic devices is a key to determine their applicability in these contexts. This aspect has remained unexplored, with no existing biomechanical studies investigating the effect of antibiotic-loaded hydrogel on primary stability of uncemented femoral components in THAs.

Therefore, the aim of this study was to assess the effect of adjuvant antibiotic-loaded hydrogel application on the primary stability of implanted uncemented hip stems. This investigation focused on the application in synthetic bones to maximize reproducibility.

METHODS

Specimens and study groups

12 mid-size artificial right femora (# 2200, Synbone AG, Zizers, Switzerland), measuring 465 mm in length, with a neck shaft angle of 135°, an anteversion angle of 15°, and canal diameter of 9.5 mm, were prepared to receive a size 10 collarless uncemented standard offset stem (Corail; DePuy Synthes, Zuchwil, Switzerland). The artificial nature of the specimens allows for standardization of outcomes, with removal of anatomical differences that might occur when cadaveric bones are used. They are identical synthetic copies and mimic normal bone architecture and properties, although they are not bone.

The femoral specimens were assigned to two groups of 6 specimens each (n=6)—intervention and control—for treatment with or without antibiotic-loaded hydrogel, respectively. The emulsion-based hydrogel was prepared according to a previously described protocol.[19] The gel has previously been evaluated for its viscoelastic properties to identify its rheological behavior and a viscosity curve has been produced. This has revealed that the gel is shear thinning with a viscosity of 760±20 Pas at a shear rate of 0.1 s^{-1} and 1.5±20 Pas at a shear rate of 100 s^{-1}. The final gel was subsequently prepared by mixing four parts hydrogel with one part aqueous solution of gentamicin sulfate and alcian blue yielding a final concentration of 1% and 0.01% gentamicin sulfate and alcian blue, respectively. The mixing was performed by connecting two syringes, one filled with gel and one with 1 mL of water/antibiotic solution, and then repeatedly extruding the resulting mixture back and forth about 20 times. A total amount of 60 mL was prepared and distributed in 10 mL syringes, each one of them serving for application to one specimen in group intervention.

The sample size was chosen based on an a priori power analysis with the assumption that the SD of the biomechanical test results in each group would not be larger than 60% of the minimum difference in mean values between the groups. This was a biomechanical study using sawbones; hence, Institutional Review Board approval was not sought or required.

Surgical technique

The artificial femora were secured and a line marked 10 mm proximal from the center of the lesser trochanter was set to standardize the cut performed at 45° angle relative to the shaft axis using the corresponding cutting guide provided in the Corail instrument set. Maintaining normal anteversion, the femoral canal was broached to hip stem size 10, ensuring that the used broach was flush to the calcar. A size 10 standard offset Corail uncemented collarless stem was inserted until axial and rotational stability was achieved. In group intervention, 10 mL of the antibiotic-loaded hydrogel agent was evenly distributed to all four surfaces of the stem and the canal prior to implantation, ensuring that most of the hydrogel was retained. The femora were cut 180 mm distally to the tip of the greater trochanter and the distal 60 mm were embedded in a polymethylmethacrylate (PMMA, SCS-Beracryl D-28, Swiss Composite, Jägenstorf, Switzerland) cylindric form in preparation for biomechanical testing. Prior to embedding, the distal canal was obstructed to avoid cement interference. A 36-mm ceramic head was attached to the stem. Finally, optical markers were attached to the femoral shaft and the neck region of the hip stem for optical motion tracking. The antibiotic-loaded hydrogel femora were assessed radiologically and clinically for homogeneity of the hydrogel.

Biomechanical testing

An electro-mechanic material test system (#5866, Instron, Norwood, MA, USA) equipped with a 10 kN load cell was used. The specimens were mounted in 20° adduction relative to the machine loading axis according to a previously established test setup that was adapted for the present study[20 21] (figure 1). Load transmission was performed via a steel indenter attached to the machine transducer and featuring a hemi-spherical cavity fit pairing with the ceramic head and being attached to the machine transducer. Distally, the cylindrical shaft embedding was firmly connected to the machine base via a custom-made holder.

A staircase loading protocol was applied via quasi-static ramped compression loading at a rate of 0.005 mm/s and six different load levels between 500 N and 3000 N in 500 N intermittent load increase steps. The ramp at each load level was repeated three times. The maximum load value of 3000 N was well above the reported hip joint

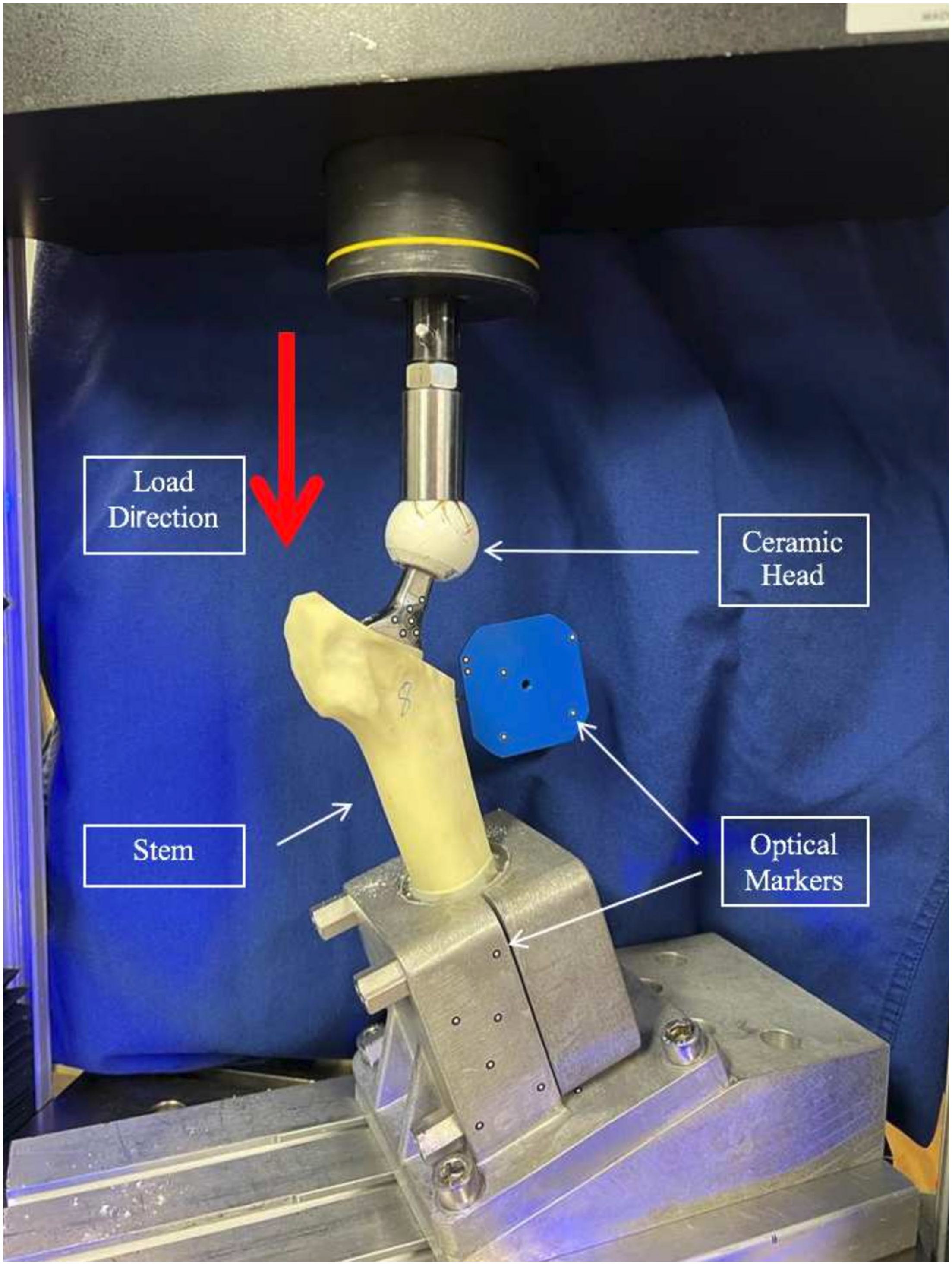

Figure 1 Setup with an instrumented specimen mounted for biomechanical testing.

reaction forces acting in the average 75 kg patient during walking.[22]

Data acquisition and analysis

The machine transducer and load cell were operating at a rate of 20 Hz. The displacement of the machine transducer corresponded to the machine displacement along its axis. The load cell was attached to the transducer. Data of both were continuously acquired from the machine's internal acquisition system, which is also referred to as transducer. Based on the data within the third loading ramp of the first staircase load level, the axial stiffness of each construct was determined from the initial linear slope of the load-displacement curve within the range 300–400 N.

The positions of the optical markers were continuously recorded at 20 Hz by a stereographic camera system (Aramis SRX, GOM Zeiss Metrology GmbH, Leipheim, Germany) operating at 12-megapixel resolution. The maximum acceptance error ranges 0.004–0.02 mm.[23] Based on the motion tracking data, the subsidence of the stem along the femoral shaft axis relative to the bone was calculated throughout testing. The trajectory of the axis was defined by alignment of the shaft markers with it. Peak subsidence values were considered from the third loading cycle of each load level.

Statistical analysis was performed using SPSS software (V27; IBM SPSS Statistics, IBM, Armonk, NY, USA). Normality of data distribution and homogeneity of variance were proven with Shapiro–Wilk and Levene tests, respectively. Outcome measures for stiffness and subsidence were investigated via Independent-Samples T-tests and General Linear Model Repeated Measures tests, respectively. Level of significance was set at 0.05 for statistical tests.

Patient and public involvement

No patients or public were involved, as this is a biomechanical study of a novel antibiotic-loaded hydrogel in an artificial femora.

RESULTS

Axial stiffness was 4176±240 (mean value±SD) N/mm in group control and 4588±448 N/mm group intervention, with no significant difference between them (p=0.076).

Stem subsidence increased significantly over the increasing load levels in each separate group (p≤0.002) and remained not significantly different between the groups (p=0.609) (figure 2).

The antibiotic-loaded hydrogel was associated with a homogenous distribution around the canal of the stem, with a higher increase in amount around the greater trochanter, just above the prosthesis shoulder (figure 3).

DISCUSSION

To our knowledge, the present biomechanical study is the first one to assess primary stability of uncemented stems with or without the use of this adjuvant antibiotic-loaded hydrogel. No significant effect in primary uncemented femoral stem stability was detected, irrespectively of whether the hydrogel was used or not. Although not significant, the antibiotic-loaded hydrogel addition was associated with decreased subsidence, when compared with the control group. This may have occurred due to the use of artificial rather than real femora and further studies using anatomic bone specimens are required to confirm this finding.

In the current study, the specimens were tested in an extreme scenario, with the maximum applied load exceeding an average human body weight by a factor of 3. Hip joint reaction forces amount to approximately 250% body weight during normal walking but can exceed 800% body weight during stumbling as measured in telemetrized implanted THAs.[20–22 24]

An uncemented collarless stem was used in this study as a worst-case scenario in terms of subsidence and to avoid calcar fractures. Current literature demonstrates better results with the collared design in cadaveric

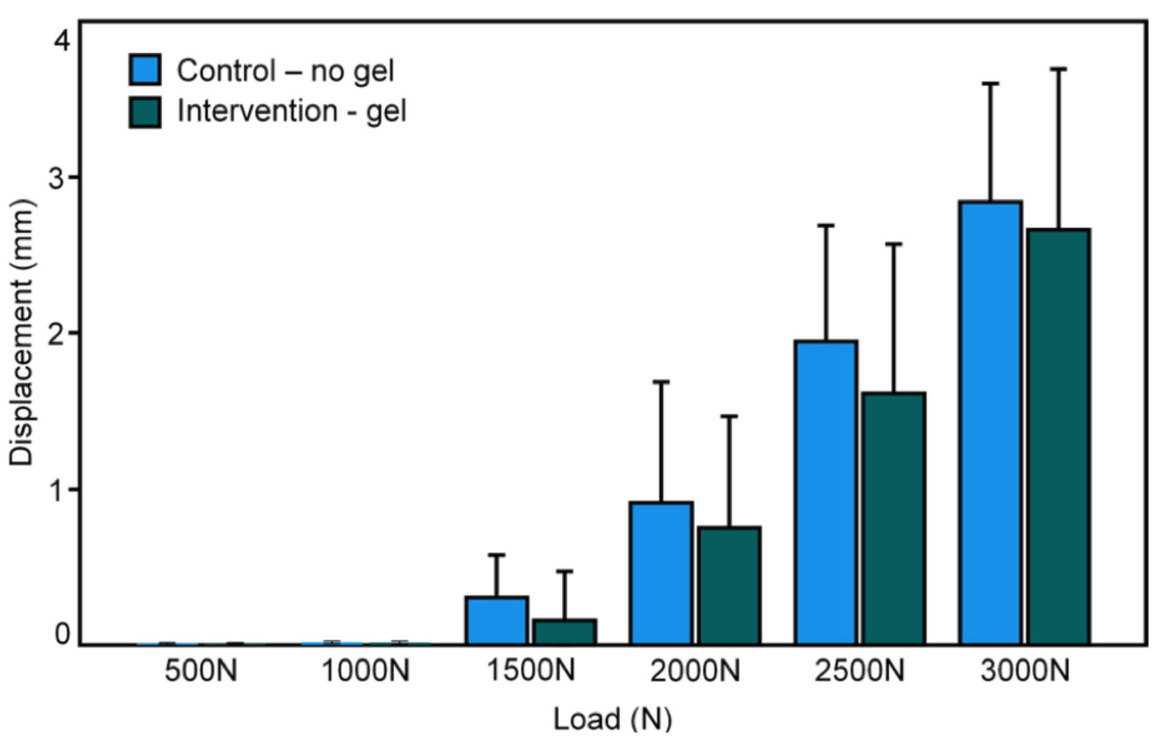

Figure 2 Stem subsidence over the gradually increasing load levels, presented in terms of mean value and standard deviation for each group separately.

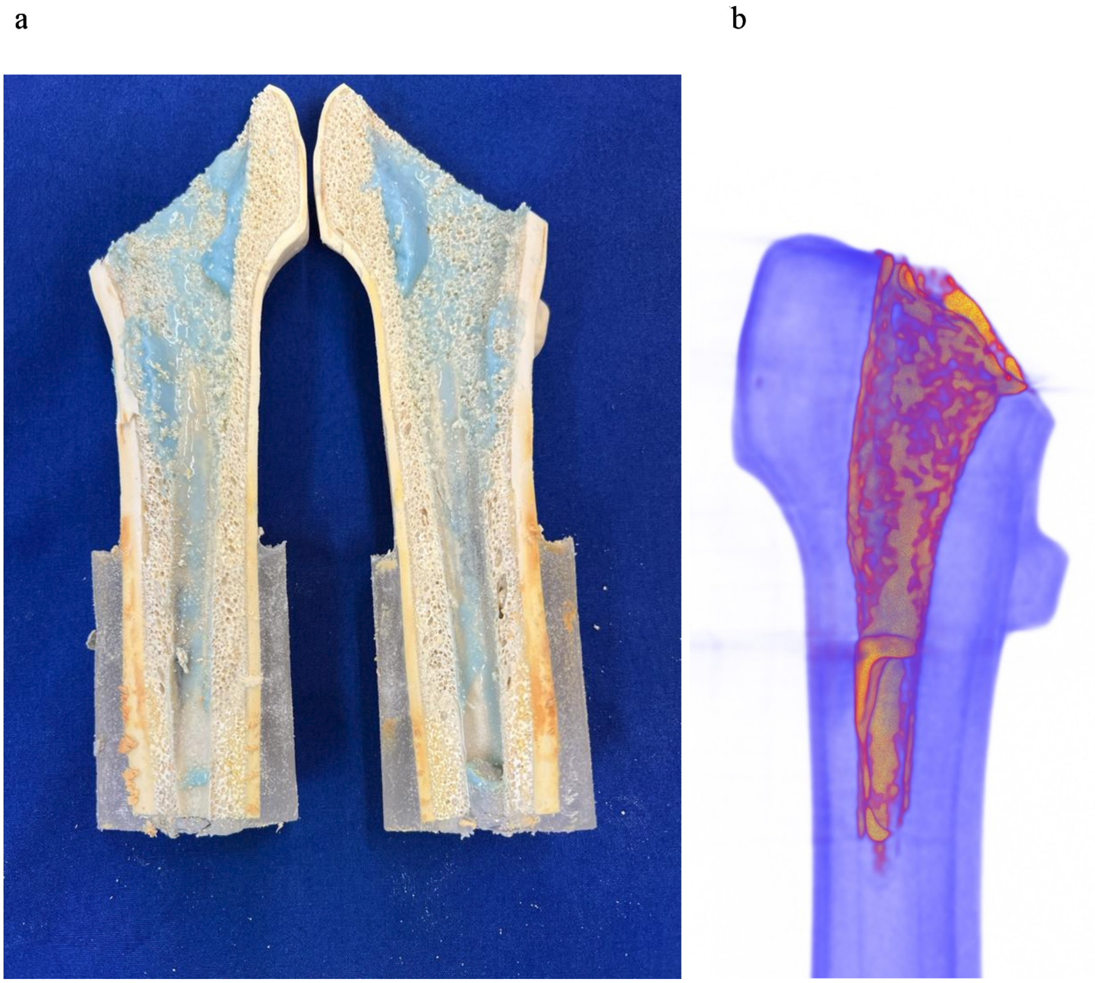

Figure 3 Osteotomized specimen (**a**) and radiograph (**b**) post-testing demonstrating hydrogel penetration.

biomechanical studies.[25 26] Hence, this can be used for added stability in real-life situations.

Furthermore, stem loosening is an important factor in periprosthetic fractures and is considered an appropriate reason to use a collared prosthesis in the early phases of THA, where the stem has not osseointegrated.[26] The effects on osseointegration with the use of the antibiotic-loaded hydrogel on the uncemented stem are not assessed in this study. The antibiotic-loaded hydrogel has shown no effect in fracture healing when used in an in vivo model.[17] This is encouraging in terms of the effect it could have in osseointegration, but further in vivo work would be required to evaluate this. Furthermore, in implanting an uncemented prosthesis, the most optimum conditions for implant longevity should be used, such as using a collar, getting the largest size possible to achieve good stability and minimizing micromotion.

Local antibiotic delivery is part of routine practice in infective THA management.[14] The addition of antibiotics to bone cement reduces infection and aseptic loosening rates.[27] Unfortunately, the commonly used cements are not resorbable, which limits their application for prophylaxis. Therefore, they are rather used for multiple operations. Currently, there is a lack in versatility that would allow for local antibiotics to be administered in primary and revision surgery, regardless of location and device used.[4] The gentamicin-loaded hydrogel has been demonstrated to be an alternative to routine use of an uncemented stem in prevention and treatment of infection. Furthermore, it is a biodegradable material with higher antibiotic concentrations found in antibiotic-loaded cement.[4 6 17 18]

When treating an infected THA, the burden to the patient is significant and a single-stage approach is preferred in appropriate cases.[14 28] In single-stage surgery, antibiotic-loaded hydrogels offer multiple advantages over antibiotic-loaded bone cements.[4 6 7] The more obvious advantage is the high local antibiotic administration without a reoperation or lingering material. Systemic toxicity is a potential cause of concern, although this has been proven to be not an issue with gentamicin-loaded hydrogel, or with a vancomycin and gentamicin mixture.[4 6]

The limitations of this study include the use of artificial bone specimens, as they lack the normal bone response to the antibiotic-loaded hydrogel, despite providing a consistency in anatomical variation. The study focuses on the stem, without looking into the differences when using a cup and stem prosthesis together. Next, whereas the study tested the specimens with a quasi-static loading protocol, that is easily reproducible, cyclic loading would have represented a more physiological scenario, as well as looking into rotational stability and should be used in future investigations. Furthermore, the gentamicin-loaded hydrogel was tested at 1% concentration, which may raise concerns regarding the effect of using different concentrations or different types of antibiotics. The effect of the antibiotic-loaded hydrogel is not tested in regards to the osseointegration, due to the artificial nature of the project. In addition, a limited number of specimens have been used. Finally, the absorption time for the gentamicin-loaded hydrogel could not be simulated given the in vitro nature of the study and the novel medication, allowing restricted data interpretation for time zero immediately after the gel application.

CONCLUSION

From a biomechanical perspective, the adjuvant application of antibiotic-loaded hydrogel during implantation of an uncemented hip stem was associated with non-inferior performance, in terms of primary stability—when compared with implantation of the uncemented stem without use of the hydrogel in synthetic femora. Although being based on a setting under quasi-static loading, this finding makes the prospect of adjuvant antibiotic-loaded hydrogel application potentially feasible; however, it requires further investigations prior to its translation in the clinical practice.

Contributors All authors have been involved in the conception and design of the study, acquisition of data, analysis and interpretation of data. The paper has been reviewed multiple times by all authors and it is believed to be accurate and up to date. GO is the guarantor.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. This was a biomechanical study and data are displayed as part of the paper in figure 2.

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