Comparing the use of preformed vs hand-made antibiotic spacer cement in two stages revision of hip periprosthetic infection

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ABSTRACT

Background: The number of periprosthetic joint infections (PJI) is continuously increasing because of the increasing number of arthroplasties performed every year. Two-stage revision, using antibiotic-loaded spacers, remains the gold standard for their treatment. The aim of our study is to compare the use of preformed vs hand-made spacers in hip arthroplasty infections evaluating infection eradication, bone loss and clinical/functional outcomes.

Methods: From January 2010 to December 2017 we performed a prospective nonrandomized study. We pooled 50 patients affected by infected hip joint replacements, and divided them in 2 groups, one receiving commercially preformed spacers and the other receiving hand-made spacers. The study endpoint was set at 12 months. Intra-operative and peri-operative complications, Harris Hip Score (HHS), Short Form 12 Health Survey, intra-operative and radiological evaluation of bone loss were collected. Data were analyzed using descriptive statistics, T-test and Fisher Exact test.

Results: We found a statistically significant differences ($p < 0.05$) between the two groups in favour of the VancogenX group for the following variables: surgical time, first and second stage intraoperative complication rates, infection eradication. Moreover, the preformed-spacers group had better results in the preservation of bone stock, even though the difference was not statistically significant ($p > 0.05$).

Conclusion: Our results support the use of preformed antibiotic spacers, even though more studies are needed.

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1. Introduction

An increasing number of procedures performed around the World characterizes total hip arthroplasty (THA). For this reason, the incidence of septic complications is growing too.¹

Due to the change in the profile of antibiotic resistant bacteria, the prevention and the treatment of primary THA infections has become even more difficult.^{1,2} The incidence of prosthetic joint infections (PJI) varies depending on the joint involved; according to literature the rate of arthroplasties becoming infected is on the one hand 1.7% for primary and 3.2% for non-primary hip arthroplasties²; on the other hand the incidence is 5% of patients under

hip or knee prosthesis.³ Although if a correct and timely microbiological diagnosis of infection is done within 4 weeks, it could be possible to follow a conservative approach on the prosthesis, due to microorganisms are not yet organized in biofilms.¹

A delayed diagnosis (>4 weeks) of early and late infections involves the necessity of prosthesis removal [^{1,4}] due to the production of a structured and mature microbial biofilm. Biofilm is an aggregate of micro colony of microbial cells adherent to a living or nonliving surface embedded in an extracellular polymeric matrix. It allows bacteria to develop a high capacity to survive even through antibiotic therapy.^{1,5} The advantage of a correct and early diagnosis is the possibility to provide the most appropriate therapy that is not otherwise possible; for this reason timing plays a crucial role in these patients but it is not possible only in early screening.^{1,3}

The PJI are treated by debridement, antibiotics, and implant retention (DAIR) and single or two-stage revision procedures.⁶ According to the literature, two-stage revision is the gold

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standard in this field. To perform this procedure surgeons, have to use a bone cement spacer as a replacement for the removed infected prosthesis. In particular the spacer is used in the interim period between the removal of the infected prosthesis and the implant of the new one. Spacers can be made by the surgeon or can be commercially preformed. A spacer has a double function: a) mechanical/functional to maintain space, allow partial joint movement and weight-bearing; b) biological through the antibacterial effect of the antibiotic which protects the device from bacterial adhesion and participate to the eradication of the infection. In addition, spacers should ensure the femoral and acetabular bone stock and ease of removal for prosthetic implantation.

This study aims to compare the use of VancogenX-Space™ Hip (Tecres Spa, Sommacampagna, Verona, Italy) to hand-made spacers in hip arthroplasty infections by evaluation of eradication of infection, bone loss and functional outcomes.

2. Methods

From January 2010 to December 2017, at the Trauma Level I Center Vito Fazzi Hospital (Lecce, Italy) 50 patients with an infected hip joint replacement were treated. Patients were divided into two groups: the first group (VancoX) made by 26 patients received a preformed spacer (Vancogenx-Space Hip – Tecres Spa, Sommacampagna (VR), Italy); the second group (HM) made by 24 patients received a hand-made spacer. The inclusion in either groups was based on patient's choice and surgeon preference. The

demographics of the two groups is reported in Table 1.

The groups were homogeneous in terms of age, gender ratio, reason for primary hip replacement, infection free survival of the implants, as well as infection type according to Tsukuyama classification⁷ and Cierny-Mader classification⁸.

Patients were evaluated using clinical and radiological criteria: hip complication after spacer placement (blood loss, periprosthetic fracture, device dislocation/loosening, limb shortening); intra-operative data; Harris Hip Score (HHS) and Short Form 12 Health Survey (SF-12)⁹; acetabular and femoral bone loss^{10,11}; spacer stability¹²; post-operative complications.

The evaluation endpoint was set at 12 months.

All patients were informed in a clear and comprehensive way of the two types of treatment and other possible surgical and conservative alternatives. Patients were treated according to the ethical standards of the Helsinki Declaration and were invited to read, understand, and sign the informed consent form.

All patients underwent the same post-operative rehabilitation protocol.

2.1. Statistical analysis

Descriptive statistics were used to summarize the characteristics of the study group and subgroups, including means and standard deviations of all continuous variables. The *t*-test was used to compare continuous outcomes. The Fisher exact test was used to compare categorical variables, since the contingency tables had

Table 1
Patient demographics.

Description of population	VancoX	HM
Number of Patients	26	24
Mean of ages (SD)	76.84 (±7.10)	79.66 (±7.11)
Range of age	62–89	63–87
Gender Ratio (M:F)	0.44(8:18)	0.41(7:17)
Reason for Primary Hip Replacement implant	Trauma: 11(42.31%) Degenerative Joint Disease: 15(57.69%)	Trauma: 10(41.67%) Degenerative Joint Disease: 14(58.33%)
Type of Implant	Uncemented Hemiarthroplasty 4 (15.38%) Cemented Hemiarthroplasty 2(7.69%) Uncemented Hip Arthroplasty: 16(61.54%) Cemented Hip Arthroplasty: 4(15.39%)	Uncemented Hemiarthroplasty 4 (16.67%) Cemented Hemiarthroplasty 2(8.33%) Uncemented Hip Arthroplasty: 15(62.50%) Cemented Hip Arthroplasty: 3(12.50%)
Average implant time before periprosthetic infection in years(SD; range)	6.2(±4.75; 0.8–12)	6.4(±4.77; 0.6–13)
Widmer's Classification	II(Late Chronic): 4(15.38%) III(Hematogenous): 22(84.62%)	II(Late Chronic): 4(16.67%) III (Hematogenous): 20(83.33%)
Tsukuyama classification	II (late chronic): 4 III (hematogenous): 22	II (late chronic): 4 III (hematogenous): 20
Type Cierny Mader Osteomyelitis's Classification	Stage 1A: 3(11.54%) Stage 1B: 3(11.54%) Stage 2A: 4(15.38%) Stage 2B: 3(11.54%) Stage 3A: 3(11.54%) Stage 3B: 3(11.54%) Stage 4A: 4(15.38%) Stage 4B: 3(11.54%)	Stage 1A: 3(12.5%) Stage 1B: 3(12.5%) Stage 2A: 3(12.5%) Stage 2B: 3(12.5%) Stage 3A: 3(12.5%) Stage 3B: 3(12.5%) Stage 4A: 3(12.5%) Stage 4B: 3(12.5%)

values smaller than 10 patients. The statistical significance was defined as $p < 0.05$. We used Pearson correlation coefficient (r) to compare the predictive score of outcomes and quality of life. Statistical analyses were performed with SPSS v.15.0 (SPSS Inc., an IBM Company, Chicago, IL, USA).

Mean ages of patients (and their standard deviations) were rounded at the closest year. The predictive score of outcomes and quality of life and their standard deviations were approximated at the first decimal while Pearson correlation coefficient (r) was approximated at the second decimal. The reliability and validity of the correlation between functional acetabular stability and cup osteo-integration were determined by the Cohen's kappa (k). To calculate the agreement between acetabular or femoral bone loss. We have made a simple relationship between perfection that is 1 and the percentage of bone loss using the Paprosky's criteria.¹⁰

2.2. Surgical approach

All patients received short-term Cefazolin for antibiotic prophylaxis (2 g before the surgery) and 1 g 3 times a day for five days after surgery.

2.2.1. First stage

The first stage of the surgical procedure (infection control) involved the following steps: prosthesis removal, debridement, spacer implantation. All surgeries were performed with the patient in the lateral position. The approach was preferably made via the previous surgical scar. In cases of fistula, gentian violet was injected via the fistula to mark the surgical site, the fistula was then resected. Joint fluid samples were collected for bacterial culture. Synovial membrane and periarticular tissue samples were collected for bacterial culture and pathological examination. In cases of a stable stem or difficulty in removing the bone cement, extended trochanteric osteotomy with preservation of the attachments of the gluteus Medius and vastus lateralis muscles onto the femur was performed. Contaminated tissues on the acetabulum, around the femoral neck, and in the femoral marrow cavity were thoroughly curetted and sampled for bacterial culture and pathological examination. Granulation tissue that appeared on visual inspection to be caused by infection was curetted completely, whereas bone, except for free sequestrum, was preserved as much as possible. After curettage, the lesion was washed with a large volume (more than 10 L) of saline solution by using pulsed irrigation.

Then the spacer was implanted: the first group received a commercially preformed spacer (Vancogenx-Space Hip), loaded with gentamicin and vancomycin; the second group received a hand-made spacer prepared during the first surgical stage or a day earlier in the same operating room (in the latter case, it was then wrapped in a sterile sheet and drape and refrigerated). The hand-made spacer was prepared using Cemex RX bone cement (Tecres Spa, Sommacampagna (VR), Italy) with the addition of gentamicin in liquid form (GM): 1200 mg of GM (60 mg/ampoule) were mixed with 40 g of cement, placed in a sterile pack, and dried with hot air before use. In cases of infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA), the spacer was prepared using 2 g of vancomycin (VCM) per 40 g of a cement. If the pathogen had not been identified 2 g VCM and 1200 mg GM were mixed with 40 g cement. To prevent breakage, the spacer was reinforced with a modeled Steinmann pin in its core.

2.2.2. Interim stage

Antibiotics effective against the causative organisms of infection were chosen and administered until the patient's C-reactive protein (CRP) level returned within normal limits.

In case of complications such as persistent infection by the

causative organism, the antibiotic treatment strategy was reviewed and modified in collaboration with the infection control team of our institute. When the infection was effectively controlled, CRP level normalized after approximately 3 weeks. In such case, the second surgical stage was planned after a waiting period of 6–8 weeks.

2.2.3. Second stage (revision surgery)

The spacer was removed and the synovial membrane of the pseudo-synovial cavity formed around the spacer was curetted and sampled for bacterial culture; a joint fluid sample was also obtained for bacterial culture. Infection control was evaluated based on the presence or absence of bacteria by performing immediate pathological examination of a Gram-stained smear and a polymorphonuclear leukocyte count. In case of bone defect, a bone allograft was used for reconstruction and the hip prosthesis was then implanted.

2.3. Rehabilitation protocol

After the first stage partial weight-bearing was allowed on an individual basis in relation to the anatomic condition, bone and muscular trophism, and clinical conditions of the patient during rehabilitation stages. The patients carried out isometric and bed exercises, deep breathing; circulatory exercises - ankle pumps; static quads; gluteal squeeze; hip flexion/heel slide; long arc quadriceps; hip flexion; hip extension; hip abduction; hip hitching.

After the second stage a touch down weight-bearing with walker for 6–8 weeks was allowed, followed using a cane in the contra-lateral hand for 6 months. Patients were informed that a wheelchair should be used for long distances with careful avoidance of excessive hip flexion greater than 80° while in wheelchair. This can be achieved by placing a cushion in the wheelchair seat, with the higher cushion point posterior. Patients were permitted to do isometric and bed exercise.

3. Results

3.1. 1st stage

Mean surgical time and antibiotic systemic treatment were shorter in the VancoX group ($p < 0.05$), and intra-op blood loss was lower in the VancoX group ($p < 0.05$). Site of infection, acetabular and femoral bone defect were similar in the two groups, as well as intra-op complications. Pathogens were similar in the two groups, with a large proportion of Gram positive. CRP and labeled leukocytes scintigraphy normalization as well as the length of antibiotic therapy was shorter in the VancoX group ($p < 0.05$).

Data are reported in [Table 2](#).

3.2. 2nd stage

Mean surgical time was shorter in the VancoX group ($p < 0.05$). Intra-op blood loss was similar. A higher rate of complications (intra-op fractures) was found in HM group ($p < 0.05$). The type of revision implant used was different between the two groups: in most cases uncemented implant were used. In the VancoX group a revision cup was used in 10 cases and a long stem in 15 patients, in the HM group a revision cup was used in 16 cases and a long stem in 6.

At a mean follow-up of 26.3 months (VancoX) and 26.8 months (HM) all patients were infection free. Results are shown in [Table 3](#).

3.3. HHS and SF-12 trend

In [Table 4](#) the Harris Hip score (HHS) and the SF-12 trends are

Table 2

First stage results. *p < 0.05 (statistical significance); °loosening/dislocation.

	VancoX	HM
Mean surgical time (SD; range)	63.2* (±12.4; 28–96) mins	86.7 (±9.8; 52–112) mins
Site of infection	Cup: 14 Stem: 3 Cup & Stem: 9	Cup: 13 Stem: 3 Cup & Stem: 8
Pathogens	Gram p.ve MSSA: 8 MRSA: 1 S.epidermidis: 2 E.faecalis: 1 β-hem Streptococci: 2 S.hominis: 2 S.agalactiae: 1 E.faecium: 1 Gram n.ve E.coli: 4 P.aeruginosa: 2 S.algae: 1 Fungi C.albicans: 1	Gram p.ve MSSA: 8 MRSA: 1 S.epidermidis: 2 E.faecalis: 1 β-hem Streptococci: 1 S.hominis: 2 S.agalactiae: 1 E.faecium: 1 S.anginosus: 1 Gram n.ve E.coli: 4 P.aeruginosa: 2 P.mirabilis: 1
Acetabular bone defect (Paproski)	I: 16 II: 2 (A); 2 (B); 2 (C)	I: 15 II: 2 (A); 2 (B); 2 (C)
Femoral bone defect (Paproski)	I: 4 II: 4 III: 1 (A); 1 (B) IV: 2	I: 4 II: 3 III: 1 (A); 1 (B) IV: 2
Complications during/after 1st stage		
Intra-op blood loss	438 ± 59 mL	432 ± 57 mL
Intra-op fracture	1	2
Implant migration°	2	0
Limb shortening (1–2.9 cm)	3	3
Limb shortening (>2.9 cm)	2	2
Post-op fracture	0	0
CRP normalization (SD; range)	123* (±23; 67–169) days	164 (±29; 90–193) days
Labeled leukocytes scintigraphy normalization (SD; range)	169* (±22; 77–186) days	190 (±32; 103–210) days
Mean antibiotic therapy (SD; range)	139* (±26; 93–197) days	171 (±32; 89–213) days

Table 3

The table shows how the VancoX spacers had a better ability to preserve the acetabular background having statistically significant a lower bone wear in Second stage results.

*p < 0.05. Instead, we saw that the Vanco X Spacers had statistically significant bone wear, greater due to stem shield stress than HM.

	VancoX	HM
Mean spacer implantation (SD; range)	5.28 months (±0.56; range 3–6)	5.87 months (±0.56; range 3–6)
Mean surgical time (SD; range)	92.2* (±9.4; 28–96)*	120.7 (±12.7; 52–112)
Type of revision implant	Normal cup: 14* Normal stem: 9* Revision cup: 10* Long stem: 15* Cemented cup: 2 Cemented stem: 2	Normal cup: 6 Normal stem: 16 Revision cup: 16 Long stem: 6 Cemented cup: 2 Cemented stem: 2
Acetabular Paprosky Bone Defect's Classification After the cemented spacer remotion	I: 12(46.15%) IIA: 4(15.38%) IIB: 4(15.38%) IIC: 3(11.54%) IIIA: 2(7.69%) IIIB: 1(3.85%)	I: 5(20.83%) IIA: 5(20.83%) IIB: 5(20.83%) IIC: 4(16.67%) IIIA: 3(12.50%) IIIB: 2(8.33%)
Femoral Paprosky Bone Defect's Classification After the cemented spacer remotion	I: 8(30.77%) II: 6(23.07%) IIIA: 4(15.38%) IIIB: 4(15.38%) IV: 4(15.38%)	I: 12(50%) II: 3(12.50%) IIIA: 3(12.50%) IIIB: 2(8.33%) IV: 4(16.67%)
Complications		
Intra-op blood loss	765 ± 124 mL	768 ± 122 mL
Intra-op fracture	2*	6
Implant migration	0	0
Limb shortening (1–2.9 cm)	6	6
Limb shortening (>2.9 cm)	1	1
Post-op fracture	0	0
Infection recurrence	0	0
Mean follow-up (SD; range)	26.3 (±3.9; 12–48)	26.8 (±4.2; 12–50)

Table 4
HHS and SF-12 trend.

	VancoX		HM	
	HHS	SF-12	HHS	SF-12
After index operation	94.7 (82–100)	94.7 (86–100)	92.6 (82–100)	94.6 (86–100)
Before PJI	88.7 (74–96)	93.2 (78–100)	88.8 (74–96)	93.5 (78–100)
At PJI	32.6 (26–62)	44.6 (28–74)	33.8 (26–62)	44.8 (28–72)
After 1st stage	48.6 (24–68)	52.1 (24–68)	48.8 (24–68)	51.6 (24–72)
Before 2nd stage	56.8 (36–72)	61.8 (40–84)	56.8 (36–72)	62.8 (40–84)
12 months after 2nd stage	83.1 (64–92)	86.1 (64–94)	82.9 (64–90)	86.9 (64–100)

Table 5
X-rays agreement for bone loss.

	VancoX	HM
X-rays agreement for bone loss - acetabulum	0.68 ± 0.12	0.79 ± 0.11
X-rays agreement for bone loss - femur	0.79 ± 0.09	0.71 ± 0.08

reported: it is evident that before the value decreases dramatically at the time of PJI and slightly increases after 1st stage revision getting better before the 2nd stage revision surgery to go back to values similar to the ones recorded after the index operation, even though on average lower of about 10 points.

The statistical intercorrelation score between bone loss and pre-spacer radiographs does not show a high degree correlation of both groups for both the acetabulum and the femoral shaft. [Table 5](#).

4. Discussion

Due to the increasing number of arthroprostheses performed worldwide, the number of PJI is continuously increasing. In the management of PJI the gold standard is two-stage revision with the use of a cement spacer that can be hand-made by the surgeon or commercially preformed. Preformed spacers are characterized by a high mechanical resistance¹³ predictable antibiotic release^{14,15} and its use reduced surgical time.¹⁶

This study aims to compare, in a homogeneous population of patients, the use of a preformed and hand-made spacer in terms of clinical and functional performances.

According to D'Angelo, who found a surgical time reduction of 37 min in the 1st stage and 40 min in the 2nd stage using a preformed spacer [17]; this study shows a reduction of surgical time, compared to HM group, of the 1st stage and 2nd stage for the VancoX group of 23 and 28 min ($p < 0.05$).

No difference was found between groups in intra-op blood loss during 1st and 2nd stage.

No difference was found between groups as regards complications during or after 1st stage (30.8% vs 29.2%). As regarding to the complications during or after 2nd stage a significative difference was found between the two groups (26.9% vs 54.2%, $p < 0.05$).

The results shown in this study are coherent with the results of D'Angelo, in particular the HHS scores at PJI (32.6 vs 33.8, respectively for VancoX and HM) and follow-up at 12 months (83.1 vs 82.9) are comparable with the scores reported by the Author (43.4 vs 35.4 at PJI, 76 vs 75.5 at FU of 40 months).¹⁷

It is important to note that the dislocation rate was exceptionally low: two cases in the preformed spacer group ($2/26 = 7.7\%$), no case in the hand-made group. In contrast to this, Gil Gonzalez reported a global rate of dislocation of 20%, in patients with proximal neck cementation the rate was 12.5%, in patients without proximal neck cementation the rate was 26.3%.¹⁸

Due to HM spacers are moulded respecting patients' individual variables such as physiological neck varus/valgus and off-set it is

possible to have a better articular congruence. As result this can explain the low dislocation rate observed in the HM group, in agreement with the results of Citak M et al.¹⁹

In the 2nd stage we implanted 15 long femoral stem prostheses in the VancoX group vs 6 in the HM group. The use of long femoral stem can be explained by the biomechanics of the VancoX spacer stems, that act as fully dynamic endomedullary nails, generating stress shielding. Furthermore, we implanted only 10 revision acetabular cups in the VancoX group vs 16 in the HM group. The better spherical shape of VancoX spacers preserved acetabular bone stock reducing the need for revision cups.

As regards CRP and labeled leukocyte scintigraphy normalization time this was shorter in the VancoX group (123.5 days vs 164.5 and 168.8 days vs 189.7, respectively). These results can be explained by better antimicrobial and anti-biofilm properties of the preformed spacer; in fact, VancogenX spacers are loaded with both Vancomycin and Gentamicin and have better anti-adhesive and elution properties.²⁰ In contrast to handmade spacers, preformed ones have a more stable composition and antibiotic concentration, allowing a constant and predictable elution. This may allow a faster and more efficient eradication of the infection. Due to this result, it was possible to observe shorter time between first and second surgical stage and shorter antibiotic therapy, therefore less systemic damages.

According to the review paper which compared preformed hip spacers and hand-made hip spacers,¹⁹ no difference was found in terms of infection eradication.

In conclusion, we can assert the efficiency of VancogenX spacers in the two-stage surgical revision of the arthroprostheses for periprosthetic infections; this study confirms better outcomes in terms of eradication time of the infection and intraoperative complications. We obtained better results in terms of bone defect using VancogenX Spacers even if this difference is not statistically significant compared to the other group; however, our results should encourage more studies about this treatment in order to create more specific and correct indications ([Fig. 1](#), [Fig. 2](#)).

4.1. Limitations

The limits of the current study are the limited number of patients, the non-probability sample of convenience, due to few centric sample, Level 1 Trauma Center.

Another limit is the retrospective design of this study.

Disadvantages of retrospective studies: inferior level of evidence compared with prospective studies; subject to confounding (other risk factors may be present and not measured); cannot determine cause-effect correlation, just association; some key statistics cannot be measured.

Selection of patients may be biased, making generalization of the results difficult. It may be unclear whether the confluence of findings is merely a chance occurrence or is truly characteristic of a new disease or syndrome.

Another limitation was that the measurements and intervention

Fig. 1. Patient of 58 years, male, operated 3 years earlier for arthritis left hip on outcomes of congenital hip dysplasia. Comes under control for formation of a formation on the lateral side face of the thigh near the great trochanter. The patient complained of a 6-month-old fever, hip pain and lameness. The X-ray showed osteolysis peri femoral stem (A). Fistulography (B) proves the existence of an advanced fistula formation from the proximal femoral meta-epiphysis due to Staph. Aureus infection. Removal of the prosthetic implant and implantation of VancogenX Long Antibiotic Spacer (C). X-rays shows the demolition of the great trochanter to remove or stem (C). 3 month X-ray follow up (D). 6-month X-rays of control (E) and the three phase scintigraphy (F) performed at 6 months showing the presence of uptake due to stress spacing of the antibiotic spacer. Tumor total hip prosthesis implant due by the proximal femur for bone stock loosening of the proximal third of femur (G). 1-year X-rays control showing no acetabular or femoral loosening (H).

Fig. 2. 38 year old woman operated 7 years earlier in another hospital by left metal-metal THA, in aseptic necrosis of the femoral head (A). The patient complained, hip pain and fever. The exams showed high phlogosis indices, and the elevated markers of chromium (Cr) and cobalt (Co) without neurological signs and symptoms. Removal of the prosthetic implant and an antibiotic spacer implant and cementing the inside of the acetabulum after having effected buffers, positive for E. Coli. After 6 months the patient performs three phase scintigraphy with the labeled leukocytes (C) which showed remission of inflammatory and inflammatory pathology. During the revision surgery, the loss of the bone stock at the acetabular level (D) was noted. In addition, a long stem type Wagner (E) was chosen for the focal osteolysis of the great trochanter. 1-year X-rays control showing no acetabular or femoral loosening (F).

were made without randomization of the researcher to the experimental groups, which have potential for bias. Finally, other limiting factors of the study acknowledged by the authors can be the potential for regression to the mean, the presence of temporal confounders and the mention of subjective score.

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Human and animal right

For this type of study is not required any statement relating to studies on humans and animals. All patients gave the informed consent prior being included into the study. All procedures involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments.

Declaration of competing interest

All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest

include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

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