Decreased migration with locally administered bisphosphonate in cemented cup revisions using impaction bone grafting technique

A randomized, controlled study evaluated with RSA and DXA with a 2-year follow-up

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Background and purpose — Impaction bone grafting (IBG) in revision hip surgery is an established method in restoring bone stock deficiencies. We hypothesized that local treatment of the morsellized allograft with a bisphosphonate in cemented revision would, in addition to increased bone density, also reduce the early migration of the cup as measured by radiostereometry (RSA).

Patients and methods — 20 patients with aseptic cup loosening underwent revision using the IBG technique. The patients were randomized to either clodronate (10 patients) or saline (10 patients, control group) as local adjunct to the morsellized bone. The outcome was evaluated by dual-energy X-ray absorptiometry (DXA) during the first year regarding periacetabular bone density and with radiostereometric analysis (RSA) for the first 2 years regarding cup migration.

Results — 2 patients were lost to follow-up: 9 patients remained in the clodronate and 9 in the control group. Less proximal migration was found in the clodronate group compared with the controls, measured both over time (mixed-models analysis, p = 0.02) as well as at the specified time points up to 2 years (0.22 mm and 0.59 mm respectively, p = 0.02). Both groups seemed to have stabilized at 1 year. We found similar bone mineral density measured by DXA, and similar RSA migration in the other directions. No cups were re-revised.

Interpretation — Local treatment of the allograft bone with clodronate reduced early proximal migration of the revised cup but without any measurable difference in periacetabular bone density.

The most common reason for revision hip surgery is aseptic loosening (Garellick et al. 2015). The loosening process is associated with osteolysis and loss of the acetabular bone stock. Revision surgery using impacted bone graft (IBG) and cement in the acetabulum aims at restoring the bone stock and has been shown to have good outcome with high implant survival rates (Schreurs et al. 2009, Garcia-Cimbrelo et al. 2010, van Egmond et al. 2011, Te Stroet et al. 2015).

The success of revision arthroplasty with IBG is twofold. The short-term success is related to the initial mechanical stability of the construct. The long-term outcome is related to the biological stability and depends on graft incorporation and remodeling into new, vital bone. Thus, manipulation of the graft to improve either initial stability and/or graft incorporation and remodeling may both improve the longevity of this type of socket revision. The impacted bone graft is remodeled and almost completely transformed into a new bone structure in the acetabulum, but to a lesser extent in the femur (Van der Donk et al. 2002, Ullmark and Obrant 2002). It is important that mechanically robust new bone forms, to compensate for the simultaneous graft resorption during remodeling and to maintain stable conditions for the prosthesis. The graft resorption can be reduced pharmacologically. Bisphosphonates are effective inhibitors of bone resorption (Russell et al. 2008) and have been shown to inhibit resorption of the bone next to an implant (Aspenberg 2009), improve prosthetic fixation (Hilding and Aspenberg 2007) and reduce the need for revision surgery (Teng et al. 2015). In a recent randomized study, local bisphosphonate treatment of the acetabular bone bed reduced the migration of primary cemented acetabular components (Schilcher et al. 2017).

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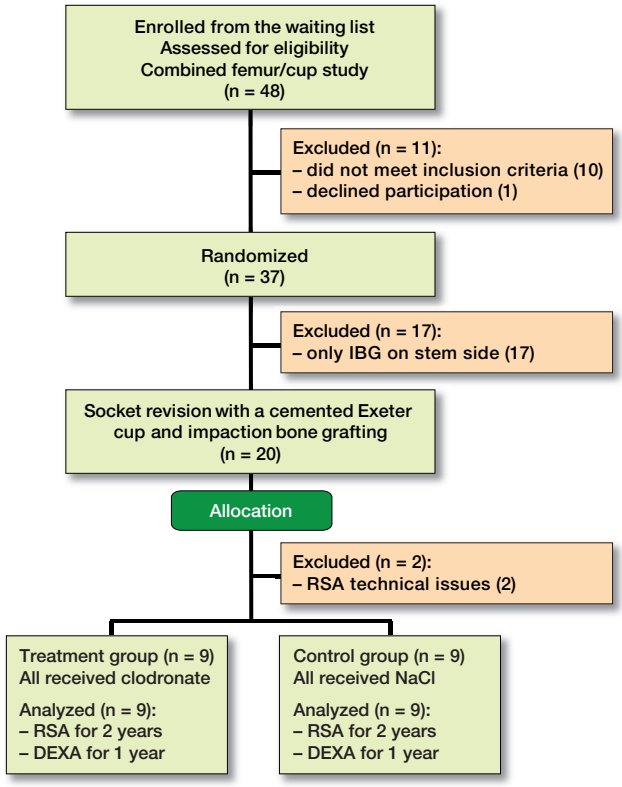

Figure 1. Flow chart diagram: patient recruitment, randomization, and follow-up.

A few studies have been published using local bisphosphonate treatment of IBG. In a randomized double-blinded study in femoral stem revisions, clodronate prevented graft resorption (Kesteris and Aspenberg et al. 2006), whereas in a similar randomized study in acetabular revisions no beneficial effects were noted after oral administration of risedronate regarding fixation, bone mineral density (BMD), or bone remodeling (Saari et al. 2014).

We hypothesized that local treatment of the allograft with clodronate would prevent graft resorption, and in turn reduce the cup migration and improve cup fixation. We used radiostereometric analysis (RSA) to study postoperative implant migration, and dual energy X-ray absorptiometry (DXA) to study bone mineral density (BMD) around the acetabular cup.

Patients and methods

Study design

We enrolled patients scheduled for revision hip surgery with IBG and a cemented stem and/or cup in a randomized, double-blind, controlled study. The stem part of the study is going to be reported on with 5 years' follow-up results.

Inclusion criteria were aseptic loosening following a primary total hip arthroplasty (THA), in patients aged 55–85 years. Exclusion criteria were earlier use of bisphosphonates, kidney disease, calcium disorders, rheumatic arthritis, hyperparathyroidism, dental problems, and malignancy in the last 5 years, mental disorder including dementia, skeletal disorders, and pregnancy. 48 patients were assessed for eligibility between February 2008 and March 2012. 37 patients were included, 17 were operated with a stem revision only and 20 patients had both a stem and cup revision.

Table 1. Patient demographics

	Clodronate (n = 9)	Saline (n = 9)
Age (years) at surgery	72 (64–80)	72 (55–85)
Female/male	2 / 7	5 / 4
Body mass index	27 (22–31)	27 (22–35)
Paprosky classification of bone stock IIa/IIb	4 / 5	5 / 4

Participants

The 20 patients (mean age 72 (55–85) years; 12 men) who underwent acetabular revision only were operated using a cemented Exeter cup (Howmedica International, London, UK) and the IBG technique. After inclusion, 2 patients were excluded because of technical RSA issues. In 1 patient, the number of visible tantalum markers was insufficient for analysis, regarding both the cup and the periacetabular bone. In the other patient, the supporting mesh interfered with the visibility of the tantalum markers.

These 2 patients, although meeting the inclusion criteria, were excluded from the study. Thus, 18 consecutive patients completed the 2-year RSA analysis and the 1-year DXA examination (Figure 1, Table 1).

Surgery and drug delivery

All revisions were performed through a posterolateral approach by 3 experienced orthopedic surgeons. The patients were randomized into 2 groups by closed and pre-numbered envelopes (concealed allocation, ratio 1:1). The envelopes were opened during the preoperative preparations by an assisting scrub nurse, who prepared either clodronate or saline solution for later, mixing with the morsellized graft before the operation started. The scrub nurse involved during the operation, the surgeon, and the patient were all blinded to the result of randomization. Graft treatment on the acetabular side followed the treatment of the femoral side as decided by the randomization procedure, which was not performed separately for the acetabular side. Fresh-frozen femoral heads were thawed in 500 mL saline with 1-gram gentamycin and thereafter morsellized using a bone mill, producing bone chips of approximately 3–8 mm in size. The bone chips were irrigated with saline using a pulse lavage gun for removal of fat and marrow. The experimental solution was prepared by mixing 500 mL of saline (NaCl 9 mg/mL) with either 10 mL of saline (control

group) or 10 mL of clodronate 60 mg/mL (treatment group). The bone chips were soaked for a minimum of 10 minutes in the experimental solution, then rinsed in 500 mL saline and finally compressed in a cotton cloth before implantation. A metal mesh was used with IBG in 1 patient in the clodronate group due to an acetabular rim defect. Systemic cloxacillin and low molecular heparin were given as prophylaxis. Postoperative weight bearing was allowed, as tolerated.

RSA

For later RSA evaluation, 9 tantalum markers (Ø = 0.8 mm) were implanted during surgery into the cup in a pre-defined pattern, by a bead inserter gun. Another 8–9 markers were implanted into the periacetabular bone but not in the allograft. Morsellized allograft was impacted into the acetabulum using a standard technique (Gie et al. 1993). Vacuum-mixed Refobacin Bone Cement (Biomet, Warzaw, IN, USA) was introduced with a cement gun. Exeter cups, for 32 mm femoral heads, were used in all 18 patients.

The reference RSA examination was performed after the patients were mobilized, between 3 and 5 days postoperatively and after 3, 12, and 24 months, using a uniplanar technique, digital radiographs (Ranstam et al. 2000, Valstar et al. 2005), ceiling-mounted X-ray tubes and a calibration cage 41. UmRSA software was used for the RSA analysis (version 6.0, RSA Biomedical, Umeå, Sweden). The upper limit for RSA exclusion was set at a condition number of 150 and a mean error of rigid body fitting of 0.35 (Valstar et al. 2005). Migration results from the RSA analyses were expressed as rotations (degrees) and translations (mm) about and along the 3 axes in an orthogonal coordinate system: longitudinal (Y), transverse (X), and sagittal (Z) axis. The precision of the RSA measurements was assessed by 12 double examinations (Ranstam et al. 2000). The RSA technician was blinded to the result of randomization.

DXA

Areal BMD was measured by DXA by 3 experienced operators who were blinded regarding patients' group allocation, using the GE Lunar Prodigy 600 VA fan-beam densitometer (GE Medical Systems, Madison, WI, USA) with baseline defined as the scan taken postoperatively. The values of bone mineral density (BMD) in g/cm^2, bone mineral content in grams, and the measured area in cm^2 were recorded. Bone density of the remodeling allograft bone was measured as change in BMD (g/cm^2) from postoperatively up to 3 and 12 months. Patients were scanned in supine position (Mortimer et al. 1996) and the area from the lower border of the distal sacroiliac joint to the distal tip of the femoral stem included in the scan. The software paint feature was used to mark and exclude non-osseous structures. BMD was measured in 4 zones as defined by Wilkinson et al. (2001) and subsequently modified by Laursen et al. (2005) (Figure 2). When the ROIs in a patient had been defined, they were copied and pasted into all subsequent scans

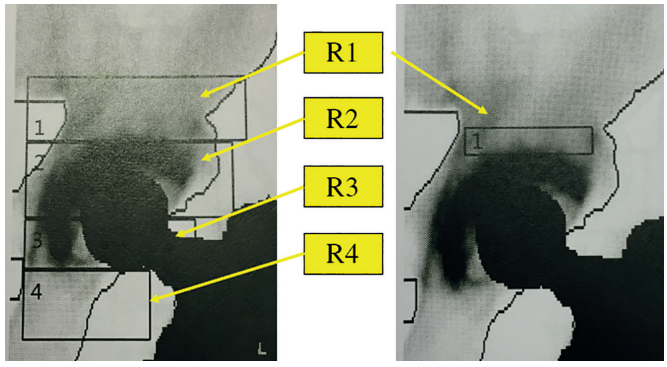

Figure 2. DEXA scan on a hip with a cemented cup with IBG showing the 4-ROI (left) and 1-ROI model (right).

of the same individual. The radiopaque cement mantle was included in the analyses (Wilkinson et al. 2001).

We considered that incorporation between host bone, allograft, and cement involved not more than 1 cm, rather than 2.5 cm as suggested by Wilkinson et al. (2001). We thus redefined and made complementary reanalysis of region 1; the superior limit was defined as a horizontal line lying 1 cm superiorly from the horizontal line touching the top border of the cement and the cup, which defined its lower limit. VZ and OB measured all the ROIs.

Radiography

Preoperative bone loss in the acetabulum assessed on conventional radiographs was classified according to the Paprosky classification (Paprosky et al. 1994). 9 patients were classified as type II-A and 9 as type II-B (see Table 1).

Statistics

We conducted a power analysis for the combined stem and cup study, based on distal stem migration along the y-axis (Ornstein et al. 2004). 16 patients were needed in each group to show a clinically important difference of 1 mm migration with 80% power and the p-value set to 0.05.

The primary outcome, prosthetic migration along the y-axis, was analyzed using the Mann–Whitney U-test for the acetabular revisions. In order to combine migration data from all time points throughout the 2-year follow-up period, we used a mixed-design analysis of variance model to test for differences between groups (clodronate and control). The structure of the repeated covariance matrix was defined as autoregressive (AR-1). As dependent variable, we defined rotation and translation in each axis (X, Y, Z, fixed effect factor). Main effects in the model were time and group (categorical). Interaction between the main effects was tested in separate models. Random intercept for each individual was tested but did not contribute to the model fit. When the trial was designed, micromotion as measured by RSA was set as primary outcome. For the acetabular side the most prominent failure direction is proximal cup migration, i.e. Y-translation, which was therefore considered

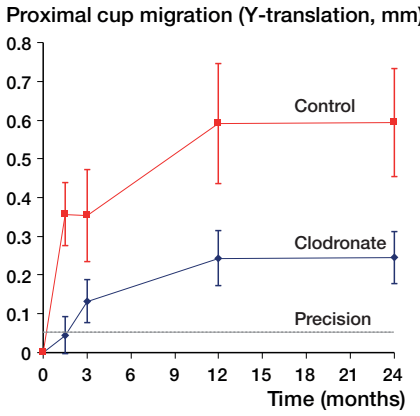

Figure 3. RSA, Y-translation: Mean values at baseline, 6 weeks, 3, 12, and 24 months. Error bars represent the standard error of the mean (SEM).

the primary endpoint for the cup analysis before analysis of the study data started. The choice of primary outcome was not changed by knowledge (or perceived knowledge) of trial data and therefore operational bias was avoided.

The secondary outcome measure, change in proximal bone density in the ROIs, was tested using the Mann–Whitney U-test. All data were analyzed using SPSS® software version 21 for Windows (IBM Corp, Armonk, NY, USA). Statistical significance was 2-sided and set at $p < 0.05$.

Ethics, registration, funding, and potential conflicts of interests

The study was performed in accordance with the CONSORT statement, in compliance with the Helsinki Declaration, and approved by the Regional Ethics Review Board in Lund (2007/60 and 2009/172) and the Swedish Medical Product Agency. All patients gave informed written consent. The study was registered in the EUDRACT database (2006-006439-39) and was externally monitored by a hospital-based but independent organization (RSKC, Skåne University Hospital, Lund University). Stryker, unconditionally, financially supported part of the RSA analysis. No competing interests were declared.

Results

RSA

The primary effect variable was mean proximal migration (i.e. Y-translation after 2 years). There was a statistically significant difference between groups regarding Y-axis translation as shown with both the Mann–Whitney U-test and mixed-model analysis. At 6 weeks, the clodronate group showed less proximal migration (Y-translation = 0.1 mm, p = 0.01) than the control group (Y-translation = 0.35 mm). The effect was seen for the whole 2-year follow-up period (clodronate group: Y-translation = 0.22 mm, p = 0.02, control group: Y-translation = 0.59 mm) (Figure 3). With mixed-model analysis the mean difference between the groups (p = 0.02; 95% CI 0.04–0.55) was statistically significant in the Y-translation (Table 2). In the latter, there was also a statistically significant main effect of time ($p < 0.001$). No statistically significant difference between groups was found regarding translation (mm) along the X and Z axis or any rotation (degrees) (Table 2). The precision of the RSA setup is presented in Table 3.

Table 2. Migration data up to 2 years postoperatively: Values are mean with 95% confidence intervals

Factor Follow-up (months)	Clodronate group	Control group	p-value p [a]	 p [b]
Translations (mm)				
X: medial (+)lateral (–)				0.6
1.5	0.04 (–0.05 to 0.13)	–0.01 (–0.17 to 0.15)	0.2	
3	0.00 (–0.08 to 0.08)	0.10 (–0.19 to 0.41)	0.3	
12	–0.02 (–0.16 to 0.12)	0.13 (–0.34 to 0.60)	0.6	
24	0.00 (–0.09 to 0.01)	0.20 (–0.21 to 0.61)	0.3	
Y: proximal (+)/distal (–)				0.02
1.5	0.10 (–0.00 to 0.19)	0.35 (0.16 to 0.54)	0.01	
3	0.11 (0.00 to 0.23)	0.35 (0.07 to 0.62)	0.2	
12	0.21 (0.06 to 0.37)	0.59 (0.23 to 0.94)	0.03	
24	0.22 (0.07 to 0.36)	0.59 (0.27 to 0.91)	0.02	
Z: anterior (+)/posterior (–)				0.9
1.5	–0.01 (–0.08 to 0.06)	–0.03 (–0.20 to 0.13)	0.4	
3	–0.08 (–0.23 to 0.08)	0.01 (–0.33 to 0.34)	0.4	
12	–0.02 (–0.26 to 0.22)	–0.06 (–0.40 to 0.28)	0.6	
24	–0.10 (–0.35 to 0.14)	–0.14 (–0.55 to 0.27)	0.9	
Rotations (°)				
X: posterior (+)/anterior (–) tilt				0.4
1.5	0.13 (–0.01 to 0.28)	–0.17 (–0.86 to 0.51)	0.3	
3	0.14 (–0.11 to 0.39)	–0.26 (–0.85 to 0.31)	0.1	
12	0.19 (–0.14 to 0.54)	–0.20 (–1.17 to 0.75)	0.3	
24	0.18 (–0.11 to 0.48)	0.01 (–1.05 to 1.08)	0.4	
Y: ante- (+)/retroversion (–)				0.8
1.5	0.04 (–0.05 to 0.13)	0.38 (–0.37 to 1.13)	0.9	
3	–0.01 (–0.07 to 0.04)	–0.33 (–1.99 to 1.32)	0.9	
12	0.01 (–0.11 to 0.14)	–0.50 (–2.19 to 1.18)	0.4	
24	–0.06 (–0.25 to 0.11)	–0.43 (–2.12 to 1.25)	0.6	
Z: decreased (+)/increased (–) inclination				0.4
1.5	0.04 (–0.12 to 0.21)	0.00 (–0.40 to 0.39)	0.8	
3	–0.07 (–0.28 to 0.13)	0.19 (–0.47 to 0.86)	0.4	
12	–0.15 (–0.43 to 0.12)	0.21 (–0.85 to 1.27)	0.8	
24	–0.12 (–0.39 to 0.14)	0.32 (–0.59 to 1.23)	0.05	

[a] Mann–Whitney U-test.
[b] Mixed-models analysis

DXA

No statistically significant differences in the BMD (g/cm^2) over time between the groups could be identified either at the 4-ROI model or at the re-defined R1 model (Tables 4 and 5).

Discussion

We hypothesized that a bisphosphonate added to the morsellized graft would prevent graft resorption, and in turn reduce

Table 3. Precision of the RSA setup measuring translation and rotation in the X-, Y-, and Z- plane obtained from the 12 double investigations: Values represent 95% confidence limits for significant motion

Plane		Precision
Translation (mm)	X	0.15
	Y	0.14
	Z	0.31
Rotation (°)	X	0.50
	Y	0.45
	Z	0.23

Table 4. Results from DXA measurements—difference at 3 and 12 months compared with postoperative measurements: Values are mean (g/cm²) and 95% CI

Gruen region	Follow-up (months)	Clodronate group	Control group	p-value [a]
I	3	–0.02 (–0.12 to 0.08)	–0.09 (–0.21 to 0.02)	0.5
	12	–0.01 (–0.10 to 0.07)	–0.02 (–0.12 to 0.08)	0.7
II	3	0.15 (0.02 to 0.29)	0.35 (0.16 to 0.54)	0.8
	12	0.12 (–0.07 to 0.33)	0.59 (–0.18 to 1.37)	0.3
III	3	0.11 (–0.07 to 0.31)	–0.11 (–0.60 to 0.37)	0.6
	12	0.12 (–0.09 to 0.34)	0.21 (0.02 to 0.39)	0.7
IV	3	0.03 (–0.03 to 0.11)	0.02 (–0.05 to 0.09)	0.7
	12	0.13 (0.04 to 0.21)	1.02 (–1.11 to 3.17)	0.9

[a] Mann–Whitney U-test.

Table 5. Results from modified DXA measurements at Region 1—difference at 3 and 12 months compared with postoperative measurements: Values are mean (g/cm²) and 95% CI

Gruen region	Follow-up (months)	Clodronate group	Control group	p-value [a]
I	3	–0.05 (–0.20 to 0.11)	–0.07 (–0.20 to 0.05)	0.9
	12	–0.04 (–0.19 to 0.11)	–0.02 (–0.08 to 0.07)	0.5

[a] Mann–Whitney U-test.

the cup migration and improve cup fixation. Indeed, we found less proximal translation of the cup in the clodronate group, suggesting that local graft treatment with bisphosphonate can reduce cup migration and potentially the risk of late aseptic loosening. We were unable to show any effect of the study drug in the density of the host and graft bone around the cup component as previously suggested in stem revision using the same drug, and similar procedure and operative technique (Kesteris and Aspenberg 2006).

Early prosthetic migration is an indicator of an increased risk of late loosening (Pijls et al. 2012). An early migration may be related to the load and impaction of the grafted bone and later migration may be due to graft remodeling. Histological analyses of the impacted bone graft have shown a heterogeneous pattern with a mixture of living and necrotic bone (Van der Donk et al. 2002, Ullmark and Obrant 2002). By adding a bisphosphonate, the resorption of the grafted bone is delayed, compared with non-treated bone, and the resulting net volume of new-formed vital bone and avital necrotic graft bone might be larger and denser (Aspenberg and Astrand 2002, Aspenberg 2009). We speculate that this could explain the difference in the first-year migration pattern between our study groups. An early stable construct would influence and also improve the secondary long-term stability. Thus, both primary stability, obtained by adequate impaction, as well as the secondary stability, boosted by the bisphosphonate effect, could be important for a long-lasting stable fixation, which requires a longer follow-up.

To our knowledge, there are only 2 studies in humans using bisphosphonates with allograft bone, either local (Kesteris and Aspenberg 2006) or oral (Saari et al. 2014). These 2 studies have diverging results. In the Kesteris study, with only femoral stem revisions included, the grafts treated with bisphosphonate increased in density postoperatively and remained unchanged for 2 years (Kesteris and Aspenberg 2006). Saari et al. (2014) showed no beneficial effect regarding BMD or bone remodeling around the revised cups at 3-year follow-up, despite using an oral third-generation bisphosphonate. The result of our study cannot be directly compared with previous studies as it involves different revision localizations, surgical alternatives, or different bisphosphonate generations and applications. However, we chose to use clodronate, a first-generation bisphosphonate with an intermediate potency and a low bone affinity (Kanis and McCloskey 1997), since it was successfully used in an earlier study (Kesteris and Aspenberg 2006). Further, we considered that the flu-like side effects of the later generation bisphosphonates were best avoided.

The strength of our study is the randomized, double-blinded design with only 2 dropouts. On the other hand, the study, although the largest randomized study of IBG cup revisions, consists of a small number of patients and, in particular, the power calculation was not conducted separately for the patients that underwent cup revision. Another limitation of our study is that information regarding the volume of morsellized bone used in each patient is not recorded.

To our knowledge, no previous DXA study has been conducted regarding cemented cups with IBG. We found the methodology and interpretation of the BMD measurement in cup revisions difficult. The ROIs used for the BMD analysis on the acetabulum are not standardized. In addition, a good cementing technique in conjunction with IBG resulted in penetration of cement into the interstices of the surrounding bone, making the line of demarcation between cement and bone indistinct. Taken together, we believe this could be the explanation for the lack of significant findings regarding BMD, in spite of the decreased prosthetic migration.

In summary, our study suggests good early results using IBG with allograft treated locally with a bisphosphonate (clodronate) in cemented cup revisions, as shown with RSA. This local allograft treatment seemed to be a safe method and no drug-related side effects or adverse effects were registered. A reduced proximal migration of the cup was seen but no detectable effect on acetabular bone density. Although statistically significant, the effect size was limited and it can be argued whether it is clinically significant. The positive findings, however, call for further studies perhaps using more modern bisphosphonates as local graft adjunct in a larger group of patients and with longer follow-up.

VZ: study conduction, data analysis, writing of the manuscript. OB, MT, MSU, GF: study design and conduction, data analysis, critical revision of the manuscript.

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