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ORIGINAL STUDY

No effect of PMMA bone cement on thrombocyte levels after total hip arthroplasty

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Thrombocytopenia has been reported to occur after total hip arthroplasty (THA). Several *in vitro* studies have investigated whether polymethylmethacrylate (PMMA) bone cement could be a possible origin for toxic agents that interfere with platelet function and survival. The aim of this study was to screen patient data for postoperative thrombocytopenia and the level of platelet concentrations in relation with the fixation method of THA.

A consecutive series of 499 THAs was studied (24.6% fully cemented, 45.5% hybrid and 29.9% uncemented). Pre- and postoperative thrombocyte levels were recorded. Patient data were reviewed for age, indication, BMI, blood cell count, and thromboembolic events. Patients in the noncemented group were significantly younger and their thrombocyte levels were higher. There were no statistically significant differences in platelet loss between groups at any point in time following THA. Platelet concentrations had fully recovered at the time of discharge from hospital. Power analysis revealed that the cohort was large enough to show even small effect sizes. The use of PMMA cement in THA does not appear to affect postoperative platelet concentrations to any significant extent.

Keywords : bone cement ; platelets ; thrombocyte levels ; THA ; total hip arthroplasty ; thrombocytopenia ; PMMA.

INTRODUCTION

Polymethylmethacrylate (PMMA) is widely used in orthopaedic surgery with good clinical results. It was introduced in total hip replacement (THA) by Charnley in 1958 (*4*). Although the fixation of implants using PMMA has been very successful for several decades, some side-effects have been observed. These include intra-operative cardiovascular reactions like hypotension (*14*), arrhythmia (*11, 16*) and even cardiac arrest (*14*) and sudden death (*12*) have been reported. There are several different theories about the cause of such reactions including air, fat or bone embolism (*7,9*), release of histamine (*10*) and release of methylmethacrylate monomer (*6*) into the vascular system (*15*).

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Postoperative drops in platelet levels in peripheral blood are usually attributed to the intervention itself or to low molecular weight heparin, which is largely used for prevention of deep vein thrombosis in THA. Heparin-induced thrombocytopenia (HIT) type I reaction is a well-known adverse effect of this regimen (*13*). However, PMMA bone cement has been suspected to interfere with platelet function and survival in experimental *in vitro* studies. Cenni *et al* found a significant decrease in platelet numbers with some PMMA cements (*2*).

To date there are no clinical studies analysing the effect of PMMA bone cement on perioperative platelet levels in patients undergoing THA. The objective of this study was to elucidate, if PMMA bone cement affects platelet counts to a clinically relevant extent in patients undergoing THA.

PATIENTS AND METHODS

A consecutive series of 499 THAs was included into this retrospective study. Only patients with a primary total hip arthroplasty (THA) for osteoarthritis (OA) were included. Of these, 123 (24.6%) patients received a fully cemented, 227 (45.5%) a hybrid (stem cemented, cup uncemented) and 149 (29.9 %) a fully uncemented prosthesis. An anterior transgluteal approach according to Bauer in supine position was used in all cases. The Polarstem (Smith&Nephew Orthopaedics AG, Rotkreuz, Switzerland) was used for all patients. It is a tapered straight stem with an identical geometry for the cemented and non-cemented version. The cemented version is polished while the non-cemented version is hydroxyapatite-coated. An EP-Fit Plus cup (Smith&Nephew Orthopaedics AG, Rotkreuz, Switzerland) was used in the non-cemented and hybrid cases. It consists of a press-fit titanium shell and a 32 mm polyethylene insert. A standard Müller PE cup (Smith&Nephew Orthopaedics AG, Rotkreuz, Switzerland) was used in the fully cemented cases. Palacos R + G bone cement was used in all cemented procedures (Heraeus Kulzer, Wehrheim, Germany). The study was approved by the local ethics committee and was performed in accordance with the Helsinki Declaration of 1975.

The following data were collected from medical records : gender, age at time of operation, patients' height and weight, body mass index (BMI), type of component fixation (cemented or uncemented), indication and duration of the operation.

The cohort was divided into two different subgroups : uncemented and cemented. Patients with a hybrid THA (stem cemented and cup uncemented) were included into the cemented group. This appeared justified, as the amount of cement necessary for the cup (approximately 5 g) is small in comparison with the amount needed for stem fixation (40-60 g).

Blood samples were taken on the day prior to surgery, the evening after THA, on the first postoperative day and the day before discharge and were analyzed for sodium, potassium, calcium, alkaline phosphatase, lactate dehydrogenase, protein, leucocytes, erythrocytes, haemoglobin, haematocrit, MCH, MCV, MCHC, platelets, CRP, PT, aPTT, and fibrin levels. Blood or fresh frozen plasma transfusions were recorded as well as anticoagulation regimens prior to THA.

The data acquisition was conducted with Excel 2007 (Microsoft, Redmond, USA). For statistical analysis, graphic and tabular demonstrations, the software Winstat for Excel (R. Fitch Software) was used. A two-sided t-test for independent samples was performed to analyse differences in platelet levels between cemented and uncemented patients. The null hypothesis was that there is no difference in platelet levels after THA between patients with cemented or uncemented technique at the day of operation. The level of significance was defined as $p = 0.05$. To describe the influence of age on thrombocyte levels at baseline, a univariate analysis was performed. A power analysis was performed to determine the power (1-ß) using the software G*Power (*8*). For comparing pre- and post-operative differences in thrombocyte counts [$10^3/\mu l$] box and whisker plots were used. The box height is the interquartile range which represents half of all values ; 25% of values are higher and 25% of values are lower than the box. The median is displayed as a horizontal line across each box. The minimum and maximum values are represented with the vertical lines (fig 2).

RESULTS

Data of 499 patients were included (266 women (53.3%) and 233 men (46.7%)). Mean age was 67 years (women 69 years, men 64.6 years). The mean body mass index was 28.5 kg/m^2. The mean operation time was 98 ± 32 minutes.

Analysis of demographics at index procedure showed significant differences between the two subgroups (table I). Patients receiving an uncemented prosthesis were significantly younger, with significantly higher platelet counts. Correlation analysis revealed a significant connection between patient age and platelet count ($r = -0.103$, $p < 0.027$), which means that thrombocyte levels tend to be lower with higher age.

Table II shows the postoperative results for the two subgroups for thrombocyte and haemoglobin levels. There were no differences between groups regarding the drop in postoperative platelet level as recorded on the evening after THA (fig 1). Thrombocyte levels in both groups remained stable on the first postoperative day. At the time of discharge, thrombocyte levels in both groups had fully recovered. Student´s t-tests for independent variables showed no statistically significant differences for platelet concentrations between groups at any point in time. Figure 2 shows a box-and-whisker plot comparing the difference between platelet levels before and after operation for uncemented and cemented groups with an almost identical distribution.

The percentage of patients with relative postoperative thrombocytopenia (< 150,000 thrombocytes/μl) was slightly higher in the cemented group, and thrombopenia was mainly found in patients with relatively low preoperative thrombocyte levels (tables I & II). These differences were not statistically significant. Of the patients that met the criteria for thrombocytopenia, none had clinical signs of impaired haemostasis.

The drop in haemoglobin level on the first postoperative day compared to the preoperative level was more pronounced in the uncemented group (-41 g/l) than in the cemented group (-37 g/l). Although this difference was statistically significant ($p = 0.002$) it was not clinically relevant. At time of discharge haemoglobin levels were almost identical between both groups.

Figure 1 shows the thrombocyte counts and haemoglobin levels over time in the two subgroups. Obviously, the graphs for thrombocyte levels are almost parallel with each other. Patients in the cemented group start at lower thrombocyte levels, but their later evolution otherwise appears essentially similar.

Clinical apparent deep vein thrombosis occurred in two patients despite adequate prophylaxis with low molecular weight heparin. Both patients had received a cemented THA. After surgery, 79 patients (15.8%) needed transfusion of erythrocyte concentrate. In the uncemented group 12.6% and in the cemented group 17.1% of the patients received postoperative transfusions.

A power analysis (fig 3) showed that the given number of patients of 499 and an α error probability of 0.05 in a two-tailed t-test has a sufficient power (1-ß) to detect even small effects.

DISCUSSION

From the data presented in this study it can be concluded that PMMA bone cement does not significantly affect platelet counts in patients undergoing THA. No statistically significant effect of PMMA on thrombocyte counts could be found between subgroups, despite a high statistical power to detect even small differences.

There are, however, obvious limitations to retrospective studies. Since the indication for cemented

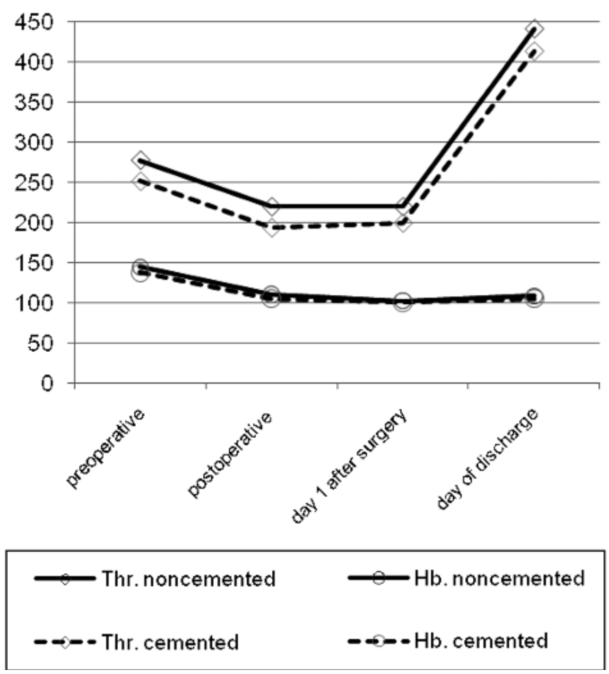

Fig. 1. — Graph showing the evolution of mean thrombocyte (Thr.)[$10^3/\mu$l] and haemoglobin levels (Hb.) [g/l] over time for both subgroups (noncemented vs. cemented).

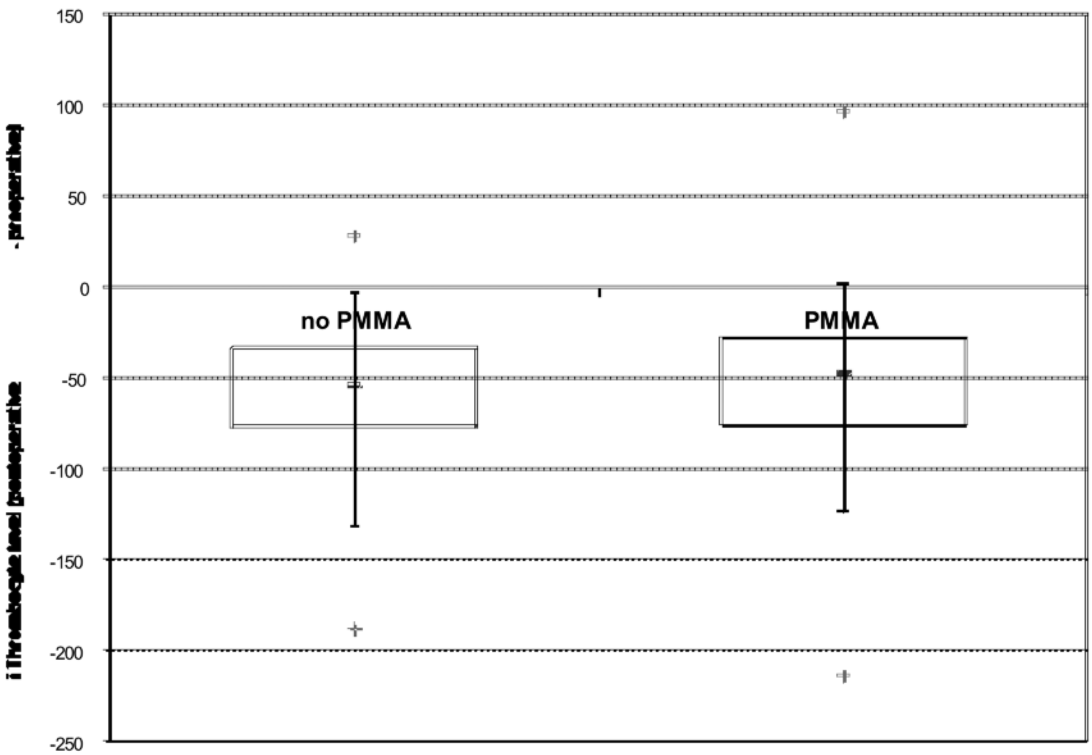

Fig. 2. — Box-and-whisker plot for the difference (Δ) in thrombocyte level [$10^3/\mu l$] (post-operative minus pre-operative). The boxes represent the 25% to 75% percentile. The crosses show the minimum and maximum values of the sample. The short lines in the middle of the boxes show the median value.

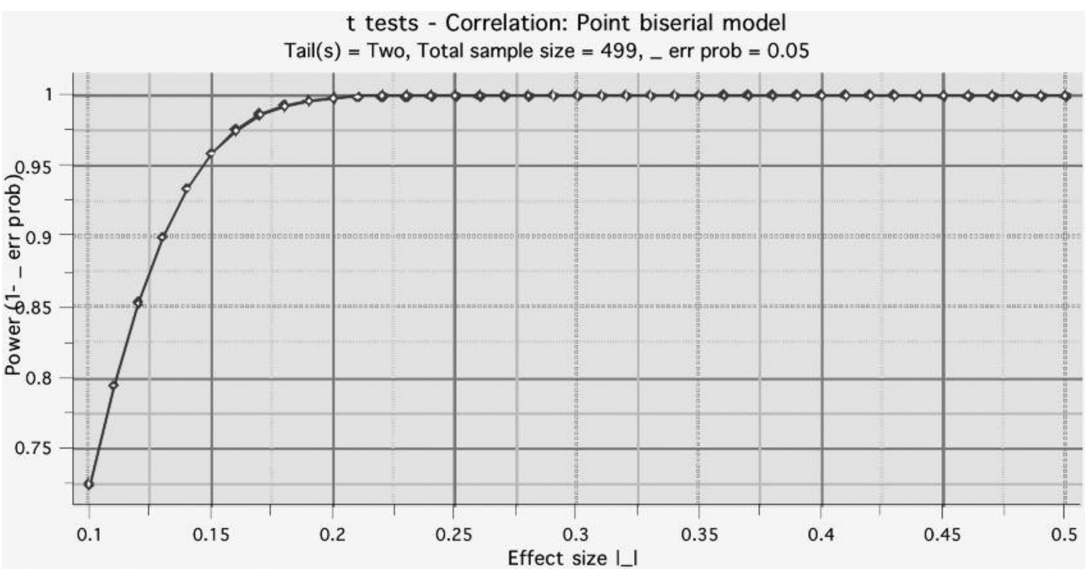

Fig. 3. — Power-analysis for the given sample size of 499, α=0.05 ranging from Effect size small (0.1) to medium (0.5) according to Cohen *(5)*.

Table I. — Patients'data at time of index procedure (Mean ± SD). Statistical analysis was done with Student's t-test. The number of patients with thrombocytopenia was compared using the χ^2 test.

	uncemented (n=149)	cemented (n=350)	p
Age [yrs]	57 (± 11.4)	71 (± 7.9)	< 0.001
Weight [kg]	85 (± 16.4)	80 (± 13.5)	< 0.001
Height [cm]	172 (± 9.3)	168 (± 8.9)	< 0.001
BMI [kg/m²]	29 (± 4.9)	28 (± 4.2)	0.120
Platelet concentration [10³/µl]	277 (± 77.2)	251 (± 64.6)	< 0.001
Haemoglobin level [g/l]	144 (± 14.9)	137 (± 14.5)	< 0.001
Pat. with thrombocytopenia (platelet level< 150,000 / µl)	2 (1.3 %)	9 (2.6%)	0.693 chi²
Operation time [min]	95 (± 32.5)	100 (± 31.2)	0.082
Hospital stay [days]	14 (± 2.7)	15 (± 3.1)	< 0.001

Table II. — Postoperative platelet and haemoglobin levels (Mean± SD). Statistical analysis was done with Student's t-test. The number of patients with thrombocytopenia was compared using the χ^2 test.

	uncemented (n=149)	cemented (n=350)	p
Evening of Operation (postop) Platelet concentration [10³/µl]	219 (± 63.5)	193 (± 52.7)	< 0.001**Δ**
platelet (op – preoperative) [10³/µl]	-57 (± 33.5)	-59 (± 38.8)	0.525
Haemoglobin level [g/l]	110 (± 15.3)	105 (± 13.5)	< 0.001**Δ**
Hb (op – preoperative) [g/l]	-34 (± 14.3)	-32 (± 13.8)	0.190
Patients with thrombocytopenia	15 (10,0%)	61 (17,4%)	0.111
1st postoperative Day			
Platelet concentration [10³/µl]	219 (± 58.1)	199 (± 52.6)	< 0.001**Δ**
platelet (postop – preoperative) [10³/µl]	-58 (± 38,7)	-53 (± 38.6)	0.190
Haemoglobin level [g/l]	102 (± 13.7)	100 (± 13.1)	0.045**Δ**
Hb (postop – preoperative) [g/l]	-41 (± 13.3)	-37 (± 13.0)	0.002
Patients with thrombocytopenia	14 (9.4%)	53 (15.1%)	0.227
Day of discharge			
Platelet concentration [10³/µl]	441 (± 119.6)	413 (± 116.7)	0.018**Δ**
platelet (discharge – preoperative) [10³/µl]	163 (± 98,0)	161 (± 92.1)	0.827
Haemoglobin level [g/l]	108 (± 14.2)	105 (± 11.5)	0.007**Δ**
Hb (discharge – preoperative) [g/l]	-35 (± 14.5)	-31 (± 14.7)	0.020
Patients with thrombocytopenia	1 (0,7 %)	4 (1,14%)	0.889

THA is usually advanced patient age with poor bone quality that makes a stable primary uncemented fixation unlikely, the average patient age was significantly younger in the uncemented group. This leads to a number of related demographic differences at baseline as shown in table I. The ideal study design would have been a randomised clinical trial. Of course, it would neither be ethically justified to treat young patients with a cemented prosthesis nor to treat older patients with impaired bone quality with noncemented prostheses for study reasons. The chosen retrospective approach of a large patient cohort seems to be sensitive enough to reveal even small effect sizes and is appropriate to answer the hypothesis of this study.

There were significant differences between subgroups in thrombocyte and haemoglobin levels at baseline. Consequently, the absolute thrombocyte and haemoglobin loss were used for the comparison between subgroups. To control for blood dilution effects, haemoglobin levels were recorded along with the thrombocyte levels. Expectedly, the blood loss was a little higher in noncemented prosthesis, as the inner bone surfaces were not sealed by bone cement.

While a large number of studies are available to investigate the intraoperative clinical side-effects of the use of PMMA bone cement (*7,9,10*) there are no clinical studies available that analyze the influence of PMMA cement on postoperative thrombocyte levels. Some *in vitro* studies investigated the influence of PMMA on thrombocyte levels and function. Cenni *et al* (*2*) examined the influence of PMMA cement on thrombocyte concentration in platelet-rich plasma 15 minutes after polymerization. They found a significant decrease in platelet count compared to the control with two of seven different PMMA cements tested, including the one used in the current study. In another study by the same authors (*3*) completely cured and polymerised PMMA-cement was incubated in phosphate buffered saline for 72 h at 37°. There was no effect on partial thromboplastine time and haemolysis. Some authors attribute the negative clinical effects of PMMA to the free monomer that is released during polymerization. Eggert *et al* (*6*) showed a maximum release of monomer during the first three minutes of the polymerization. Schoenfeld *et al* (*15*) described a monomer release during the first 15 minutes. Therefore in both studies by Cenni *et al* (*2,3*) the possible influence of toxic monomer could not be analysed.

Blinc *et al* (*1*) analysed the effect of PMMA on platelet aggregation and partial thromboplastin time (PTT). They could not find an influence of fresh PMMA cement, PMMA cement after 24 hours or the liquid component of the bone cement on either platelet aggregation or PTT.

In summary, there is scarce *in vitro* data on platelet toxicity of PMMA bone cement, and results from different studies are partially contradictory. However, this current study shows no clinical impact of PMMA bone cement on postoperative thrombocyte levels in a large retrospective consecutive series of patients undergoing THA.

There was a significant reduction in thrombocyte levels after total hip arthroplasty on the day of operation and on the following day. Thrombocyte levels had fully recovered ten days after operation. No differences could be found in thrombocyte levels between cemented and non-cemented fixation.

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