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Whole blood metal ion measurement reproducibility between different laboratories

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ABSTRACT

Monitoring patients' metal ion blood concentrations can be useful in cases of problematic metal on metal hip implants. Our objective was to evaluate the reproducibility of metal ion level values measured by two different laboratories. Whole blood samples were collected in 46 patients with metal on metal hip arthroplasty. For each patients, two whole blood samples were collected and analyzed by two laboratories. Laboratory 1 had higher results than laboratory 2. There was a clinically significant absolute difference between the two laboratories, above the predetermined threshold, 35% of Cr samples and 38% of Co samples. All laboratories do not use the same technologies for their measurements. Therefore, decision to revise a metal on metal hip arthroplasty should rely on metal ion trends and have to be done in the same laboratory.

Total hip arthroplasty (THA) has proven to be a highly effective treatment of hip osteoarthritis in the elderly which is the reason indications were subsequently extended to young and middle-aged adults as well. Increasing demands in these patient groups due to significant physical activity and higher life expectancy resulted in developing improved bearing materials. These bearings are characterized by potential combinations of highly cross-linked polyethylene, ceramic, or metal cup inserts with ceramic or metal heads.

Metal-on-metal (MoM) bearings have been used with conventional THA for several decades with promising results from early applications [1–3]. Low wear potential of mechanically well investigated prostheses, no relevant risk of material fracture, excellent stability and a high design variability seemed to justify the application of MoM bearings in hip resurfacing (HR) and large head hip arthroplasty (LH-THA) [4–6]. Nevertheless, wear and corrosion of these implants may lead to a release of metal products including chromium (Cr) and cobalt (Co) into surrounding tissue and body fluids as well as internal organs. Metal accumulation may result in local "adverse reactions to metal debris" (ARMD) [7] and potentially induce systemic adverse effects (i.e. toxicity, teratogenicity and carcinogenicity) [8–11].

Although the toxicological significance of local and systemic elevations in metal ions has not been definitively established, monitoring patients with MoM bearings for elevated metal ion concentrations in the blood can be useful in determining the performance of the bearing[12–14]. Metal ions from the corresponding alloying element (i.e. cobalt—Co, chromium—Cr, titanium—Ti, nickel—Ni, molybdenum—Mo) can be measured in the joint itself as well as in surrounding tissue and body fluids. Blood concentrations of ions released from well performing metal implants are low, often less than 1 μg/L [15]. Recent guidelines and metal ion level threshold values have been recently recommended to follow patients with metal and metal bearings THA [16]. As example, the UK Medicines and Healthcare products Regulatory Agency has issued a blood cobalt guidance value of 7 μg/L to identify MoM hip implant patients who may require closer surveillance due to an association with excessive implant wear. High-resolution inductively coupled plasma mass spectrometry (HR-ICP-MS) is one of the most sensitive and versatile techniques available for metal ions measurement and most clinicians are relying on results obtained with this analysis method [17,18].

The objective of this study was to evaluate whole blood metal ion levels drawn for the same patient at the same time, but analyzed in two different laboratories. The aim was to see if there was a difference between the laboratories that may be of clinical significance and that could lead to misinterpretation in the results.

Material and Methods

Study Population

From July 2003 and October 2009, we collected whole blood samples in multiple patients with unilateral MoM hip arthroplasty.

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Many of these patients were taking part in structured research protocols with subsequent publications [12,13,19,20]. For the purpose of the present study, patients were eligible when at least two tubes of whole blood from the same collection time were available.

Sample Collection

For each patient, after discarding the first 5 cc of blood, three whole blood samples were collected in individual polypropylene syringes. For all procedures a twenty-two gauge stainless steel needle (BD Vialon Biomaterial IV catheter, 0.9 × 25 mm, 35 cc/min; Beckton Dickinson, Mississauga, Ontario) were used to cannulate the vein and the outer plastic cannula was left in place while the needle was discarded. All samples were transferred to individual polypropylene tubes (Lavander, K_2 EDTA 7.2 mg for laboratory 1 and Royal blue, trace element K_2 EDTA 10.8 mg for laboratory 2) and kept frozen at −20 °C. Patients were asked to not modify their exercises routine or engage in new, strenuous activities, take new medications or undergo other venous sampling 1 week before blood collection. Samples were kept frozen at −20 °C until analysis by the two different laboratories. Samples were analyzed from December 2011 to April 2013 for laboratory 1 and from March to June 2013 for laboratory 2.

Laboratory 1 Analysis, ICP-MS

The concentrations of Cr and Co ions in whole blood samples were measured with a single quadrupole ICP-MS Elan DRCII from PerkinElmer. The detection limits were 0.1 μg/L for Cr and 0.035 μg/L for Co. Blood samples were diluted in diluent containing 0.5% (v/v) NH_4OH and 0.1% (v/v) octylphenol ethoxylate. External calibration curves were prepared by diluting human blood in diluent and spiking with different volumes of 1 mg L^{-1} multi-elements standard solution (SCP Science, PlasmaCal ICP-MS Verification Standard 1, 5% HNO_3, #141-110-011) in order to emulate 0, 4, 20, 80, and 200 μg/L in the standards solutions. The internal standard for calibration standards and blood samples was yttrium 89 for Co59 (standard mode with correction equation) and indium 115 for Cr53 (DRC mode with ammonia as reaction gas). Commercial blood reference materials were used as controls to verify the results.

Laboratory 2 Analysis, HR-ICP-MS

The concentrations of Cr and Co ions in the whole blood samples were measured in an Element 2 High-Resolution, Sector-Field, Inductively Coupled Plasma Mass Spectrophotometer (Thermo Fisher Scientific GmBH, Bremen, Germany). The detection limits were 0.1 μg/L for Cr and 0.02 μg/L for Co. The blood samples were exposed to concentrated nitric acid to digest protein and concentrated hydrogen peroxide to digest lipids. After dilution with water and internal standard yttrium 89, the final sample was introduced into the instrument and compared against aqueous standards with commercial blood controls to verify the results.

Statistical Significance

The detection limit of the HR-ICP-MS is approximately 3 times the background noise of the samples. The limit of quantification, which determines more precisely the sensitivity and accuracy of the device, is approximately 10 times the background noise. The limit of quantification is therefore 3.33 times the limit of detection. For this study, we have used the very specific detection limit of the HR-ICP-MS used in laboratory 2 (0.1 μg/L and 0.02 μg/L for Cr and Co in whole blood) to establish the limit of quantification. Based on these values, we determined that a conservative difference of 3.5 times the detection limit will be considered statistically significant or 0.35 μg/L for Cr and 0.07 μg/L for Co.

Clinical Significance

We defined in a previous study that a variation in concentration above 1 μg/L for Cr and above 0.5 μg/L for Co could be clinically significant. These thresholds were established based on the average concentrations of Cr and Co varying between 0.5 and 3 μg/L in blood when implants are working well. In the event of a malfunction or clinical problem, the concentration of these ions usually increases dramatically from 2 to 20 μg/L. So, according to the authors, a variation in concentration of less than 1 μg/L for Cr and less than 0.5 μg/L for Co between results would not impact the clinical evaluation and patients follow up.

Statistical Analysis

Statistical analysis was performed using SPSS software, version 20.0. All patients with paired results were included in the study. Continuous values were presented as an average ± standard deviation with minimum and maximum values. Differences between pairs of sample were analyzed by a paired t-test with a confidence interval of 95%. Differences between pairs of samples (in absolute values) were analyzed by a simple t-test with a confidence interval of 95%. Proportion tests were performed with a chi-square test. Correlations between results of laboratories were analyzed with Pearson correlation. The difference between the reproducibility (mean difference) of the measure of chromium and cobalt metal ions was analyzed by Student's t-test for independent data. Statistical significance was set at 0.05.

Ethical Considerations

The research project was approved by the Scientific Committee and the Ethics Committee of our Centre. The study was explained to patients and informed consent was obtained.

Results

We have analyzed a total of 46 pairs of whole blood samples. Patient's mean age at the surgery was 50 years (range 28–65) and there were 24 men and 22 women. Thirty-six patients had large diameter femoral head THA, 9 patients a hip resurfacing (HR) and 1 patient a 28 mm THA. Fifty-one percent of hip implants were made by Zimmer, 18% by Biomet, 11% by Depuy and 20% by Smith Nephew. The mean follow-up at the blood collection time was 63 months (range 12–96). Samples were kept frozen for an average of 0.11 months (min 0, max 0.39 months) before analysis at laboratory 1 and 5.33 months (min 0.1, max 16.16) at laboratory 2.

The distributions of Cr and Co concentrations from the two different laboratories are shown in Fig. 1 and Table 1. The concentrations obtained from laboratory 1 are significantly different than from laboratory 2.

Table 2 and Fig. 2 show the distribution of differences between the two laboratories. Laboratory 1 had higher result than laboratory 2 with a CI (95%) of 0.30 to 1.23 for Cr and 0.12 to 0.93 for Co. The results of laboratory 1 were higher than those of laboratory 2 in 70 and 82% for Cr and Co respectively. The mean ratios between laboratory 1 and 2 are 1.30 (range 0.37 to 4.28) and 1.14 (range 0.46 to 2.12) for Cr and Co respectively.

The distribution of absolute difference between the laboratories is shown in Table 3 and Fig. 3. The means absolute difference between the two laboratories was significant for Cr and Co metal ions measured. Thirty-five percent of paired samples for Cr and 38% for Co had an absolute difference above the predetermined threshold of clinical significance.

We found a high statistical correlation between the laboratories for Cr (0.841) and Co (0.965) measured ($P \leq 0.001$ for Cr and Co). The Bland and Altman graph, shown in Figs. 4 and 5, established that the