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Serum Levels of Methyl Methacrylate Following Inhalational Exposure to Polymethylmethacrylate Bone Cement

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ABSTRACT

Teratogenic effects of polymethylmethacrylate cement at levels used during routine orthopaedic procedures have never been reported, however the hypothetical risk remains a major concern among female surgeons. Our aim was to determine if methyl methacrylate is detectible in the serum during routine cement exposure. Methods: Twenty healthy volunteers were exposed during the mixing of polymethylmethacrylate cement in a simulated operating room environment. Forty serum samples were obtained during the expected peak inhalational exposure and levels of methyl methacrylate were assessed utilizing headspace gas chromatography mass spectrometry. Results: Methyl methacrylate was not detected in any of the forty experimental specimens. Conclusions: With a detection level of 0.5 ppm, methyl methacrylate is undetectable in the serum during routine mixing of polymethylmethacrylate cement.

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Polymethylmethacrylate (PMMA), commonly known as bone cement, is the synthetic polymer of methyl methacrylate (MMA). It has been commercially used since the 1930's in cast acrylic sheet manufacturing. Its use in arthroplasty was popularized in the 1960's by Sir John Charnley [1,2]. Questions continue to arise as to its carcinogenic and teratogenic effects [3]. The American Conference of Governmental Industrial Hygienists (ACGIH) has established a threshold limit value (TLV) for methyl methacrylate of 100 ppm, meaning the time-weighted-average for a normal 8 h workday and a 40 h workweek to which nearly all workers may be repeatedly exposed to methyl methacrylate without adverse effects [4]. Singh et al. in 1972 [5] studied the possible teratogenic effects of methyl methacrylate by exposing pregnant female rats to high levels of methacrylate esters via intraperitoneal injections. Analysis of fetuses showed a dose-related increase in resorptions, gross and skeletal abnormalities, and a reduction in fetal weight. Though the increase in adverse effects was only minor when compared to controls, this landmark article led to the generally accepted practice for pregnant operating room personnel to leave the room during cementation. Even with later animal studies utilizing an inhalational exposure closer to the recommended TLV showing no statistically significant difference in resorptions, fetal weight, or external/visceral/skeletal malformations [6,7], concerns among pregnant operating room personnel still exist [3]. With an increasing number of female surgeons specializing in arthroplasty, leaving the room during cementation is not possible. This growing dilemma is the impetus for this study.

Linehan et al. [8] attempted detection of methacrylic acid (the hydrolyzed form of MMA) in their own serum following routine total joint arthroplasty using headspace gas chromatography. Seven total serum samples were taken from 11 to 23 min from initiation of mixing. No MA was detectable in any of the samples. Based on our review of the literature showing peak concentrations of MMA in the air occurring before two minutes after the initiation of mixing, and peak serum levels of MMA at 30 s following IV administration and 2–3 min in patients following cementation of implants in joint arthroplasty [6,9–14], it is felt that this study was limited by poor timing of blood draws in addition to small sample size. Thus, we aimed to increase the chances of detecting MMA in the serum following routine mixing of PMMA cement by collecting the samples within this expected early peak and increasing the sample size.

Materials and Methods

Following IRB approval, healthy volunteers aged 18–65 were solicited through an email announcement to medical students and residents at our medical center. Participants were excluded if they had any significant medical comorbidity (specifically, a history of pulmonary disease, to include asthma), were pregnant, or had a history of adverse reaction to PMMA. Twenty healthy volunteers (10 male and 10 female) were divided into five groups of four. Informed

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consent was obtained from each participant. Height and weight were recorded for each participant. Each female participant completed a urine dipstick pregnancy test.

The experiment was performed in a standard, non-laminar flow operating room without the use of exhaust hoods and using an open mixing bowl technique. Each volunteer had a 23-gauge butterfly IV placed by a registered nurse after donning routine universal precaution operating room attire (mask, hat, gown, gloves). A group of four participants surrounded a mixing bowl while the study investigators mixed the PMMA cement (two bags of Stryker Simplex P radiopaque bone cement) and timed blood draws (Fig. 1). Two blood samples of 5 mL each were obtained from each participant. The first sample was obtained 30 s after the initiation of mixing and a second sample at the three minute time point. Collecting serum samples within three minutes after the initiation of mixing was chosen based on our review of the literature showing peak concentrations of MMA in the air occurring before two minutes after the initiation of mixing, and peak serum levels of MMA occurring at 30 s following IV administration and 2–3 min in patients following cementation of implants in joint arthroplasty [6,9–14]. Because the peak of MMA following an inhalational exposure is unknown, we chose to draw blood samples at two different points within this 3 min window, hoping to increase our likelihood of detection.

Blood samples were collected in BD Vacutainer tubes (5 mL draw volume, 13×100 mm) and were immediately transported to the lab for processing. The samples were cold centrifuged at 4 °C at 3000 rpm for 10 min. Two mL of serum was then transferred to glass vials designed to have minimal headspace. Each vial was closed with a Teflon septum and secured by a crimped aluminum cap. Care was taken to keep the samples at 4 °C until the very timing of transfer. The vials were then immediately placed in a −57 °C freezer until being shipped on dry ice. Analysis of the serum samples was performed using headspace gas chromatography mass spectrometry by Jordi Labs LLC (Bellingham, MA), a lab with special expertise in this area. The analysis was run using a Tekmar 7000 equilibrium headspace analyzer, Hewlett Packard 5890 Series II gas chromatograph and a VG 70SE magnetic scanning mass spectrometer with electron impact ionization. The protocol for the collection, storage, transport and serum analysis via headspace gas chromatography has been previously well described and accepted to detect MMA and MA [8,10,11,15]. To ensure accuracy of detection of MMA by this protocol, two serum samples from the author prior to the experiment and without any exposure to MMA or other everyday acrylic vapors were collected, stored, and transported according to the study protocol to Jordi Labs LLC, where they were spiked with 1 μg MMA and were re-analyzed, with a detection limit calculated to be 0.5 ppm. Additional controls were created using samples of water spiked with 1 ppm MMA, again analyzed with detection limits calculated to be 0.5 ppm, consistent within ±4%, which is presently considered to be the industry standard.

Results

Both the serum and water control samples yielded the analyte peak of MMA as expected, validating the experimental techniques and ensuring no interference from the serum itself. No MMA was detected in any of the forty samples at the 0.5-ppm detection level. Three of the participants, including one of the authors and two registered nurses involved with the study, were exposed to fumes over the entire six hour study period totaling six rounds of cement mixing. These participants assisted in collecting specimens for the first 5 rounds of mixing and then became participants during the last round of mixing, having their blood drawn at the same 30 s and 3 min time points. These six samples thus effectively represented a cumulative exposure. These samples also had no detectable MMA (Fig. 2).

Discussion

Literature evaluating serum levels in patients and air and serum levels in operating room personnel is limited. MMA has been consistently detected in the serum of patients undergoing total joint replacements with peak levels at 2–3 min after initiation of cementation [10,11]. After intravenous administration of MMA in beagles, peak levels were seen at 30 s and were nondetectable at 5 min [9]. Personal air sampling devices have been used to measure exposure levels of MMA experienced by operating room personnel [6,12,13] with McLaughlin et al. [9] demonstrating concentrations never rising above 280 ppm with levels dropping rapidly to 60 ppm two minutes after mixing and to less than 10 ppm six minutes after mixing. Only one animal study successfully detected MMA in serum following an inhalational exposure [15]. Linehan et al. [8] attempted detection of methacrylic acid (the hydrolyzed form of MMA) in their own serum following routine total joint arthroplasty, but in the seven serum

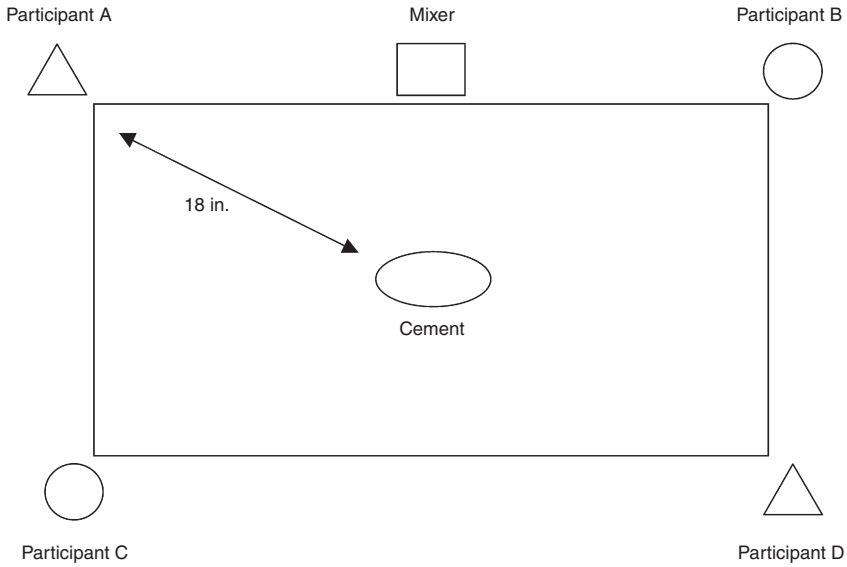

Fig. 1. Schematic of experimental set up. The cement is mixed in the middle of the table by a designated mixer while each participant sits at one corner of the table approximately 18 inches from the cement. A nurse stands next to each participant to draw blood at 30 s and 3 min from the initiation of mixing.