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Comparison of physical and practical properties of vacuum mixing systems for acrylic bone cement

Diploma Thesis

Jasmin Jelečević

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Univ. Prof. Dr. Klaus-Dieter Kühn

ao. Univ. Prof. Dr. Andreas Leithner

Graz, am 15. April 2012 *jasmin.jelecevic@stud.medunigraz.at*

Affidavit

Hereby I declare that I wrote the following diploma thesis independently and without any assistance from third parties. Furthermore, I confirm that I used no sources except for those I indicated.

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Graz, am 15. April 2012 *Jasmin Jelečević*

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Abstract (German)

Einleitung Knochenzemente auf Basis von Polymethylmethacrylat (PMMA) werden seit Jahrzehnten erfolgreich in der Orthopädie und Unfallchirurgie eingesetzt. Nur einige wenige Studien berichten über Monomerdämpfe beim Herstellen von PMMA Knochenzementen. MMA ist bekannt für seine allergisierenden und toxischen Eigenschaften. Aus diesem Grund wurden für eine großtechnische Nutzung bzw. Verwendung von MMA strenge gesetzlich vorgeschriebene Arbeitsplatzgrenzwerte (MAK) festgelegt. Eine Verwendung von Vakuummischsystemen für PMMA-Zemente im Operationssaal im Vergleich zur klassischen Schalen-methode führte bereits zu einer signifikanten Reduzierung von MMA Konzentrationen. Ziel dieser Arbeit war, zwei bislang nicht gegeneinander getestete handelsübliche Mischsysteme vergleichend auf MMA Dichtigkeit während des Anmischvorgangs und nach der Austreibung des Zementes zu testen und zusätzlich Faktoren zu erfassen, die die MMA Konzentration im OP beeinflussen können. **Methoden** Es wurden zwei aktuelle Mischsysteme getestet (Palamix® und Optivac®). Als PMMA-Zement wurde handelsüblicher Palacos®R verwendet. Standardisierte Anmischversuche erfolgten sowohl im Labor (in vitro) als auch im OP Saal (in-vivo). Knochenzementzubereitung wurde von einem erfahrenen Anwender beider in der Studie verwendeten Mischsysteme durchgeführt. Es wurden dabei analog anderer Untersuchungen auf ein in-vivo ähnliches Model zurückgegriffen, wobei das Messgerät mit seinem Saugschlauch in Kinnhöhe des Anwenders positioniert war. Freigesetztes, in der Umgebungsluft vorhandenes MMA wurde mittels Photo-Ionisation Detektor Gerät (MiniRAE® 3000) jede Sekunde für die Dauer von 3 Minuten quantifiziert. **Ergebnisse** Signifikante Unterschiede in Hinsicht auf MMA Konzentration wurden in Abhängigkeit vom Lüftungssystem bzw. Luftstrom beobachtet. Dabei wurden höchste MMA-Werte in einer unkontrollierten Luftbewegungsumgebung im Labor gemessen, und sehr niedrige Konzentrationen im OP Saal unter aktiven Laminar-airflow Lüftungssystem. Generell konnten keine signifikante Unterschiede zwischen den beiden untersuchten Mischsysteme in Hinsicht auf MMA Dichtigkeit beobachtet werden.

Alle gemessenen MMA-Konzentrationen waren sehr niedrig (0.1 - 20 ppm/3 min) und erreichten nie auch nur annähernd Werte der gesetzlich vorgeschriebenen maximale Arbeitsplatzkonzentration (MAK) von 50 ppm/8h. **Diskussion** Die Verwendung handelsüblicher Mischsysteme bei der Herstellung des PMMA-Zementes unter OP-Bedingungen kann eine MMA-Abgabe in die OP-Luft nicht vollständig verhindern. Den weitaus größeren Einfluss auf die MMA Konzentration in der Atmungsluft hat offenbar das Lüftungssystem und hier die exakte und kontrollierte Luftführung. Empfehlenswert für extrem niedrige MMA-Konzentrationen bzw. dessen Wahrnehmung durch das OP-Personal ist ein Anmischen des PMMA-Zementes unter Laminar-airflow bei gleichzeitiger Positionierung gegenüber der Luftauslässe. Auf diese Weise können MMA-Moleküle direkt über den vom Personal wegführenden Luftstrom abgeführt werden.

Abstract

Introduction Polymethylmethacrylate (PMMA) based bone cements have been successfully used in orthopedic surgery and trauma for decades. A few studies have reported about monomer fumes during preparation of PMMA bone cements. MMA is known for its sensitizing and toxic properties. As a result, strict rules have been set and defined (Maximal Exposure Limit short. MEL) regarding the maximum occupational exposure concentration. It has been shown that vacuum mixing systems significantly reduce the MMA exposure compared to the conventional bowl mixing. Our goal was to test two commonly used vacuum mixing systems regarding MMA fume release and by doing so to investigate possible environmental factors that may have an influence on MMA fume concentration in the breathing air of the operating staff. **Methods** We have tested two vacuum mixing systems (Palamix® and Optivac®) using PalacosR® bone cement, in a series of standardized trials in a laboratory (in vitro) as well as in an OP theatre (in vivo). Well experienced user of both mixing systems performed the cement preparation in an in vivo-like set up 5 times for each mixing system. MMA was quantified every second over a period of 3 minutes using a photo-ionization detector (PID) (MiniRAE® 3000) device positioned in the breathing area of the user. **Results** Significant differences regarding the MMA fume concentration were observed depending on the ventilation system, them being highest in an uncontrolled air flow environment, in a laboratory and very low while performing in an operating theatre under the laminar flow ventilation. Generally we have found that there are no significant differences between the two tested systems Palamix® and Optivac® regarding the MMA fume release. All measured concentrations of MMA were very low (0.1 - 20 ppm/3 min) considering the MEL (50 ppm/8h). **Discussion** Usage of vacuum mixing systems for PMMA bone cement preparation cannot fully prevent MMA leakage into the surrounding. Regardless to the mixing system, the most noticeable MMA concentrations are measured after application. Laminar airflow ventilating system or rather the controlled air pathway has a major influence in sensing the low MMA concentrations in the operating theatre by the staff. It is our opinion that our

findings can help the users of vacuum bone cement mixing systems, to further reduce MMA exposure. Recommendable is mixing of the bone cement under laminar airflow in such manner that allows the MMA fume to be blown out through the ventilation while the user himself remains out of the air pathway.

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Glossary and Abbreviations

BPO - Benzoyl-peroxide

BuMA – Butylmethacrylate

CO2 – Carbon dioxide

DmpT - Dimethyl-para-toluidine

GC - Gas chromatography

H2O – Dihydrogen monoxide (Water)

HQ – Hydroquinone

MAK – Ger. Maximale Arbeitsplatzkonzentration.

MEL – Maximum exposure limit

MMA- Methylmethacrylate

PID – Photo-ionization Detector

PMMA- Polymethylmethacrylate

ppm- parts per million (1 ppm = 0,0001%)

SD – Standard Deviation

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1 Introduction

Having pioneered the method for anchoring the femoral head prostheses into the femur using self-curing bone cement, Sir John Charnley is credited with developing one of the most commonly performed orthopedic procedures in the world today (1, 2). In Germany alone, about 152.000 hip arthroplasties and 136.000 knee arthroplasties are performed annually and approximately half of those are being fixated using polymethylmethacrylate - PMMA bone cement (3); although today cement is more commonly used on knee than hip surgeries.

Due to the ubiquitous presence of PMMA bone cement in orthopedic surgery and the development of mixing systems designed to improve bone cement quality, preparation and application, questions emerge. One the most commonly addressed issues today regarding the PMMA bone cement is the vapor of its liquid component, the methylmethacrylate - MMA. This vapor, a small amount of non bonded MMA, is released into the environment within all stages of bone cement preparation during numerous orthopedic surgical procedures.

1.1 PMMA Bone Cement

PMMA bone cement is a "two component system"; first component being a polymer powder and second component being a monomer liquid.

1.1.1 PMMA Powder

The cement powder component is comprised of a spherical polymer powder made of PMMA or MMA copolymers and the *benzoyl-peroxide (BPO)* initiator, required for initiating the curing of the cement. The powder component also contains a radiopacifier (either *zirconium-dioxide* or *barium-sulfate*) which is required for the cement visibility in the radiographic images. It may also contain an antibiotic or a dye for coloring of the powder (2, 4).

1.1.2 MMA Liquid

The liquid component contains mainly the monomer MMA. Methylmethacrylate (MMA for short) is a colorless, clear, flammable liquid of intense odor. As the odor threshold is very low, even the smallest amounts are detectable by the human sense of smell. According to literature, the threshold for MMA lies at 0.20 ppm at 20°C (5); therefore, although it is perceivable how MMA-vapors over a long period of time can be regarded as stressful, the hazard potential cannot be estimated based solely on the sense of smell (5).

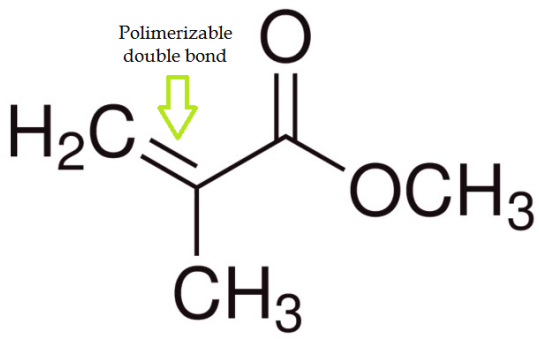

Fig.1 Methylmethacrylate structural formula

Chemically, MMA is an ester of methacrylic acid with a polymerizable double bond. MMA has a melting point at -48°C and boils at 100°C; it has a molecular weight of 100.13 g/mol. At 20°C the vapor pressure is 47 mbar (5). It is only slightly soluble in water. MMA is heavier than air (density 0.944 g/cm³) and should therefore sink to the ground in its vaporized state; however, the concentration of MMA in the immediate breathing zone can vary significantly due to the turbulence and directed airflow in an operating theater, for example (5).

The liquid also contains an activator dimethyl-para-toluidine (DmpT) and is stabilized by small amounts of hydroquinone (HQ) to prevent polymerization during storage. Some commercially available bone cement liquids contain the monomer butyl-methacrylate (BuMA) instead of MMA, which is another ester of methacrylic acid (2, 4).

1.1.3 Polymerization reaction

Combining powder and liquid monomer initiates an exothermic reaction. Peak temperatures in vitro reach 113°C in the anterior cortex of vertebral bodies (6), however, it has been shown that the maximal in vivo temperature measured at the bone-cement interface does not exceed 47°C, and thus it does not exceed the

protein coagulation temperature (2). Methylmethacrylate monomer, the basic building block of PMMA, contains carbon-carbon double bonds which react with the free radical produced by the activator and initiator. The monomer is free to interact with other monomer molecules creating a growing polymer chain. The powder initiates polymerization and creates workable dough (7).

1.1.4 Curing of the bone cement

After adding the PMMA powder into the MMA liquid, curing of the bone cement immediately begins. It is divided into 4 phases (Fig.2). Mixing phase is the initial phase and it ends once a homogenous bone cement dough has been attained. The next phase, the sticky phase or a low viscosity phase, is a waiting phase. The viscosity of the bone cement plays an important role in the duration of this phase. It lasts until the cement dough doesn't fail to separate from a gloved finger (doctor`s finger test acc. to ISO 5833). This is where the working phase begins. In this phase, the cement can be applied and handled without adherence. The fourth and the last phase, the hardening phase, is also a waiting phase. As the bone cement forms a solid, it cannot be manipulated any longer. As a result of the exothermic reaction, highest temperature peaks are reached in this last phase. As the curing of the bone cement is affected by the physical conditions and due to the variety of bone cements available on the market today, there are no specific times for the phases. Working phase as well as the hardening phase especially differ from cement to cement (8–10). The cement we used, Palacos®R, has a working phase of roughly three and a half minutes and a hardening phase of three minutes at 23°C.

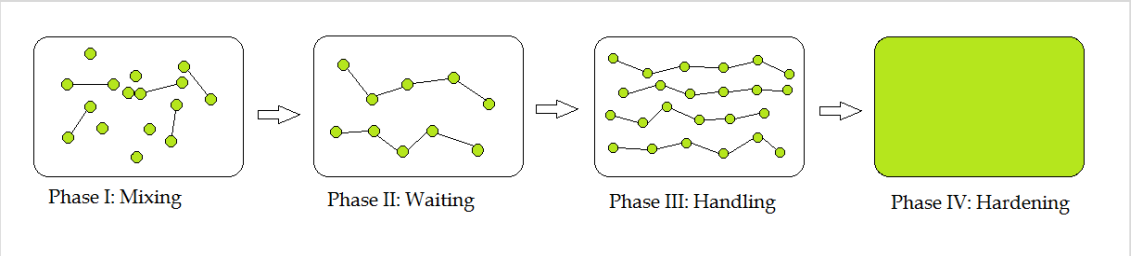

Fig.2 Schematic portrayal of the polymerization reaction (10)

Depending on which phase predominated during the curing process, PMMA bone cements can be divided into low or high viscosity cements. Low viscosity cements generally have a longer sticky phase and a shorter working phase, while the high viscosity cements have a shorter sticky phase and a longer handling phase. Medium viscous cements are in between (7). Radio-pacifier material does not participate in the polymerization reaction, and residual monomer polymerizes over several weeks (11).

1.2 Sensitization to MMA

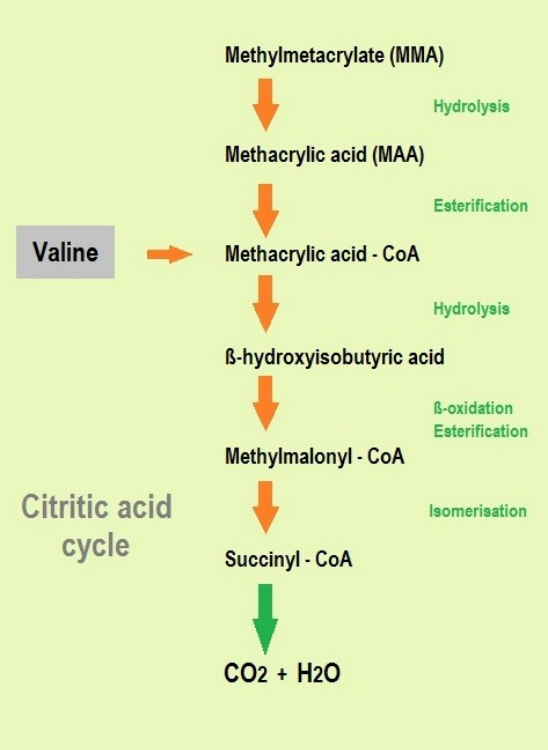

Fig.3 Metabolism of MMA (14)

1.2.1 Metabolism of MMA

There are three modes of MMA absorption in human body: through lungs, skin or gastrointestinal tract. When in contact, MMA absorbs rapidly into the blood stream (12). Most of the MMA is then exhaled through the lungs, while smaller amounts are either secreted out through urine and feces, or oxidatively metabolized to carbon dioxide (CO2) and water (H2O) through the citrate cycle (Fig.3) (13–16). Here, methacrylic acid-CoA arises as an intermediate product which is also a product of decomposition of the natural amino acid valine. Pulmonary elimination of MMA is very fast and takes about 20 minutes (15).

1.2.2 The MEL Value for MMA

On an industrial scale, MMA is used in production of acrylic glass, glues and some kinds of paint. In addition to its use in PMMA bone cement, MMA is also used in dentistry for dental casts and dental prosthesis.

Maximum occupational exposure concentration or maximum exposure limit - MEL is the highest permissible air concentration which is considered safe for

prolonged exposure. In Germany, MEL values are set by the German Senate Commission for examination of harmful occupational substances. MEL value is calculated as an average for an 8 hour work day. As of December 1990, the MEL value for MMA is defined at 50 ppm over 8 hours and maximum 40 hours per week or 100 ppm for short periods of time that are not longer than some minutes per day (5, 17).

1.2.3 The consequence to the MMA long term exposition

In a study with 4324 workers of two United Kingdom factories that produced PMMA sheets, patterns of mortality after long term exposure to MMA were investigated. Mean exposure to MMA was 7,6 years at 13,2 ppm per an 8 hour working day. No evidence was found that employment at the factories or exposure to MMA had adversely affected the mortalities of workers (18).

When considering physiological resistance of the human organism to the MMA, the generally short time exposure of the OP-staff cannot be equated to the continuous exposure of the industry workers (5).

1.2.4 Allergenic and toxic properties of MMA

No persuasive evidence has been provided that exposure to MMA is carcinogenic to human beings (19). Allergic reaction to the MMA may occur through direct contact of the MMA liquid with the skin, as well as through inhalation. In high concentrations, MMA is known to irritate the eyes and the respiratory system mucosa, or to possibly cause contact dermatitis (20–23). It has been reported that, when inhaled in high concentration, MMA may cause symptoms such as shortness of breath or coughing (24, 25).

Reports also exist of MMA diffusion from polymer and sensitization with dental prosthesis carrier, followed by mucosal inflammation (26, 27). Also isolated cases of sensitization caused by surgeon's hand manipulating the PMMA bone cement have been reported (28, 29).

Possible reasons for these cases could be either the improper handling of the MMA, insufficient precaution measures, or extreme MMA fume concentration

levels in the breathing air due to the exothermic polymerization reaction with the PMMA (5).

It should be noted that all of the other PMMA bone cement components such as BPO, HQ or DmpT are known allergens (5, 30) and, therefore, the patch-testing is to be seen as inconclusive (5).

1.3 Usage of the bone cement

1.3.1 Arthroplasty

Arthroplasty is a reconstructive surgical procedure that was shown to improve the management of those joint diseases where the conventional medical therapy was proven to be inefficient. Firm fixation of the prosthetic components to the bone is a key factor for achieving successful results. The fixation can be achieved either by using bone cement or, in more recent cement-free designs, by bony ingrowths into porous coating on the implant which results in so called biologic fixation, or by press-fit. It has been shown that conventional cemented total hip arthroplasty dramatically improves the patient's function and quality of life. The original Charnley low-friction hip arthroplasty, a procedure still considered by many to be the current standard, provided a good to excellent clinical result in 80% to 85% of patients followed for at least 15 to 20 years (31, 32). Since Charnley's original prosthesis was introduced, several variants of the artificial hip joint have been developed. The significant innovations of Charnley's arthroplasty included the combination of a small-diameter femoral head with a high density polyethylene acetabular component to reduce friction and fixation of these prosthetic components to bone with polymethylmethacrylate cement (32).

1.3.2 Infection treatment

Infection following orthopedic surgical procedures such as alloplastic joint replacements also known as arthroplasties or operative stabilization of fractures using intramedular nails or bone plates should primarily be treated surgically. Radical debridement with removal of all necrotic bone fragments and alloplastic implants is obligatory (33, 34).

The PMMA bone cement is an ideal carrier material for the protracted release of the antibiotic substance by diffusion. Local implantation of gentamicin PMMA bead chains or antibiotic loaded PMMA spacer into an infected bone cavity after radical debridement allows local antibiotic therapy in high concentration, with the minimal inhibitory concentration (MIC) far exciding the minimal bactericidal concentration (MBC) of the relevant pathogens, thus being adjuvant therapy to the surgical debridement (35, 36).

A very important feature of vacuum mixing systems for bone cement is that they allow adding antibiotics to the bone cement during bone cement preparation.

1.4 Bone cement mixing systems

Up until the 1980's, composition and preparation of PMMA bone cement had not altered since Charnley first introduced the cementing techniques in the 1959. As it was first used in arthroplasty, the cement was hand-mixed in a bowl and then applied by hand or transferred and injected into the desired spot. Due to the chemical properties of the liquid monomer component of the bone cement, this resulted in high MMA-fume concentration in the operating theater. Furthermore, even when using high viscosity bone cement, a certain amount of cement porosity was preordained in the final material due to the air entrapment. This fact is particularly troublesome given that the porosity has been found to be the major cause of decreased mechanical strength and fatigue life of bone cement (37).

It was in the 1980s when techniques for improving cement strength began to be explored (37). At this time, different vibrating mixing techniques were used with the goal of improving mixing and thus bone cement properties; however, the outcomes were not promising (38). For example, using centrifugation increased the cement´s fatigue life and ultimate tensile strength was reported (39), likely due to the decrease in cement porosity. Another study which investigated several brands of bone cement showed that there is no improvement to cements resistance to fracture when mixing was performed using centrifugation (40). Closed mixing under vacuum was initially developed for environmental reasons; however, it soon became evident that there were numerous advantages to this method, such

as producing homogenous bone cement, enhancing the mechanical properties of the cement with respect to the other mixing techniques used, improving the cementing techniques, as well as significantly reducing the monomer fumes in the operating theatre (37). Today, vacuum mixing is widely accepted as the method of choice for attaining homogenous cement, reducing porosity and increasing the cement strength. Today's vacuum cement mixing results in 0,1-1% porosity compared to the conventional bowl cement mixing technique which caused bone cement porosity in the range of 5-16% (41, 42).

Mixing systems being developed today aim to further reduce MMA-fumes and be as user-friendly as possible, while preserving good mixing performance.

1.5 Motivation

Today, there is a variety of products used for bone cement preparation and application in prosthetic surgery and a number of studies have been published with regard to MMA fume release into the breathing air (43–46). We saw importance in investigating how Palamix® and Optivac®, two of the most commonly used mixing systems in Europe, perform in respect to their MMA-fumes release during the mixing procedure. Moreover, we thought it important to investigate the possible user-dependent and/or environmental factors such as turbulence created due to staff movement or other factors impacting the airflow within the operating theatre which may influence the MMA vapor concentration in the breathing area of the surgical staff.

We designed an experiment that would not only show how these two vacuum mixing systems perform regarding MMA fume release, but also establish a practical relevance of environmental factors, and thus help reduce the exposure of the staff and the patient to MMA during surgery. In our experimental design, we made sure to keep the settings standardized as to ensure the comparability of the recorded data. We have also considered how to keep the experimental setup as similar as possible to the in vivo setting given that this is imperative for the validity of the experiment.

Our primary objective was to measure the concentration of the MMA fumes in the breathing area of the person performing the mixing, as it would be very hard to quantify the total amount of the MMA that escaped during the procedure. In doing so, our intention was to evaluate the acquired values with respect to the MEL value for MMA. As a result of the testing we hoped to acquire the necessary understanding of how and if these values are affected by the PMMA bone cement mixing systems or by the work setting and conditions.

Our secondary goal was to investigate physical properties; for example, residual quantities of the bone cement within systems after cement evacuation, as well as homogeneity of the mixed cement.

2 Materials

2.1 Open vacuum bone cement mixing systems

Bone cement mixing systems

Palamix® (Heraeus Medical, Wehrheim, Germany) is a vacuum mixing and application system for bone cement. It consists of *Palamix*® set (Fig.4), *Palamix*® cement gun and a *Palamix*® vacuum pump. This system is suitable for usage with high or low viscosity bone cements. It is available in multiple cartridge sizes, as well as with different nozzles that vary in length and diameter, depending on application. For organizational reasons we have divided the working steps that were provided by the manufacturer into four phases.

Fig.4 Palamix® bone cement mixing system

A.) Preparation- This phase consists of preparing the cement gun, closing the grip on the mixing rod, attaching the funnel to the top of the cartridge and connecting the vacuum hose to the lid and to the vacuum pump.

B.) Filling and vacuum-First step of the mixing is opening of the MMA ampoule, using the on the funnel, built in ampoule opener, and pouring the liquid through the separate filtered section on the funnel designed to retain any glass splinters from the ampoule. After emptying of the MMA ampoule, the bone cement powder should be poured into the open cartridge using the other, larger section of the funnel. As the MMA liquid and the PMMA powder are found within the cartridge, the funnel has to be removed and the lid attached to the top of the cartridge. After 5-10 sec vacuum buildup, the C.) Mixing phase begins and involves using the mixing rod with steady vertical and rotational movement (1 stroke per second) over a period of approximately 30 sec.

D.) Preparing for application- To proceed, the mixing rod has to be extended to the fullest and the vacuum hose disconnected from the lid. At this point, the grip should be unlocked and the mixing rod removed leaving the cartridge ready to be placed and locked into the cement gun. To evacuate bone cement, the cement gun trigger should be pressed repeatedly.

The Optivac® system (Fig.5) (Biomet, Berlin, Germany) is a vacuum mixing and application system for bone cement. It also contains a vacuum pump and an application cement gun. This system uses a patented mechanism that allows the user to both mix and collect cement under vacuum, thus minimizing the possibility of air entrapment. It is also designed to mix any type of cement regardless of its viscosity. Depending on the application it comes in multiple cartridge sizes and additional nozzles such as slim, revision and right angled nozzle. Working procedure for this system as it was described in the instruction manual provided by the manufacturer can also be divided into four parts.

A.) Preparation- First step is the opening of the *Optivac®* mixing station and attaching the vacuum hose to the foot pump and to the lid. Thereafter, the cartridge should be locked into the package tray.

B.) Filling-Before the funnel is attached to the top, MMA liquid should be poured into the cartridge. The powder should be inserted into the cartridge using the funnel. At this point, the funnel should be removed and the lid attached firmly to the top of the cartridge.

C.) Mixing- The phase begins by starting the vacuum pump using the foot switch. The mixing should be done with cartridge placed in a tilted position and using up and down movements with rotation for 30-45 seconds. To finish, the mixing rod should be rotated at fully extracted state. At this stage the cartridge should be firmly placed onto the releasing

Fig.5 Optivac® bone cement mixing system

knobs of the tray and twisted a quarter of a turn to collect the cement under vacuum. Once the floor of the cartridge has stopped moving, the mixing rod should be snapped off with a firm, quick movement near the cylinder top. To prepare for the next step, the vacuum pump should be stopped and the blue plug should be unscrewed from the top of the cartridge.

D.) Preparing for application- In place of the blue plug on top of the cartridge, desired nozzle should be applied and the cartridge then locked into the cement gun. At this point, the cement should be pressed out in an upward position and applied after having reached the desired viscosity.

Main characteristics summary of both system are shown in Fig.6

Optivac®	Palamix®
Collecting under vacuum: Yes	Collecting under vacuum: No
Vacuum: approx. 120 mbar	Vacuum: approx. 90mbar
Thinner mixing rod, separate application nozzle	Easier to handle due to the combined mixing rod and application nozzle
Cement gun- easier to handle due to collection under vacuum of the bone cement and then locking of the cartridge into the cement gun	Locking of the cartridge into the cement gun followed by manual bone cement collection
Single compartment funnel	Two compartment funnel

Fig.6 Mixing systems characteristics summary

2.2 Bone cement

Palacos®R. (Heraeus Medical, Wehrheim, Germany) is fast-curing, radiopaque, PMMA-based bone cement. The powder contains PMMA, radiopacifier- zirconium dioxide, the initiator- benzoyl peroxide and the colorant chlorophyll (E141). The liquid contains MMA, the activator- N, N-dimethyl-para-toluidine, the stabilizer hydroquinone and the colorant chlorophyll (E141).

The powder is double packed under sterile conditions. The outer non-sterile bag is an aluminum protective bag; whereas the peel-off bag as well as the inner

bag consists of polyethylene/paper containing 40 g of cement powder sterilized using ethylene oxide. The monomer liquid (sterilized by filtration) amber glass ampoule has been packed under sterile conditions, in an individual blister pack sterilized with ethylene oxide.

According to the user manual, working times can vary considerably depending on the ambient temperature when using *Palacos®R* (Fig.7 - Graphic taken from the user manual of Palacos®R bone cement).

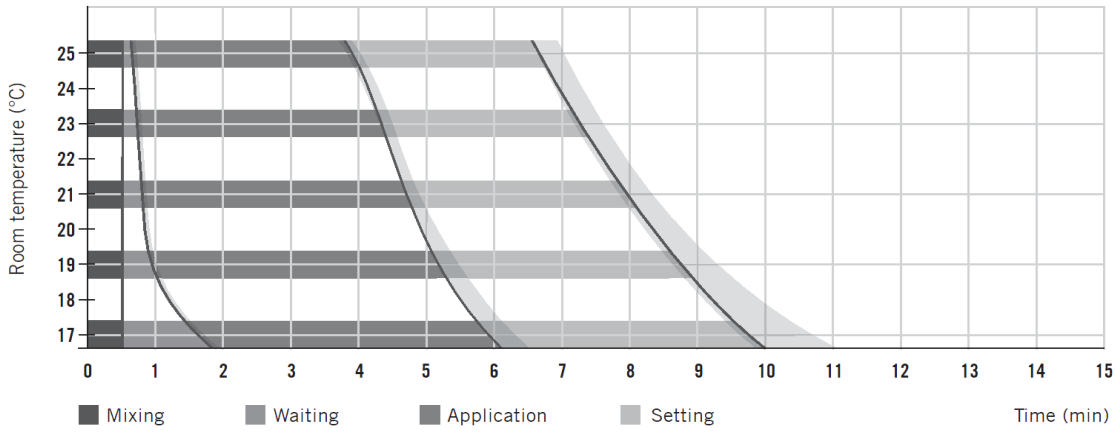

Fig.7 Palacos®R Working times for vacuum mixing (not pre-chilled)

2.3 Measuring devices

2.3.1 MMA measuring devices

Dräger Polytron-7000® (Fig.8) (Drägerwerk, Lübeck, Germany) is an electrochemical diffusion sensor device with a measuring range of 0-100 ppm and sampling pump with airflow rate of 500 cm^3 per minute.

MiniRAE-3000® (Fig.9) (Rae Systems, San Jose, CA, USA) is a photo ionization detector (PID) device with an extended range of 0 - 15,000 ppm and response time of 3 seconds. It has a built in sampling pump with air flow rate of 500 cm^3 per minute (0,5l per min). For MMA detection, the device is calibrated using isobutylene gas with correction factor of 1,5. The lower detection limit for MMA lies at 0,1 ppm. The PID device MiniRAE 3000® is capable of continuous data recording and therefore gives the possibility of analyzing of the working steps and identifying the critical points, where the fume concentration is at its highest.

Fig.8 Dräger Polytron 7000®

Fig.9 MiniRAE-3000® PID-Device

2.3.2 Temperature and Humidity

Temperature and humidity were measured using a GFTH 95 and GTH 175/Pt (Fig.10) (Griesinger Electronic, Regenstauf, Germany) digital hygrometer/thermometer. The Thermometer has a measuring range of -199,9 to +199,9°C and measuring resolution of 0,1°C. The hygrometer has a measuring range of 10 - 95% relative humidity and a measuring resolution of 0,1%.

Fig.10 Digital hygrometer and thermometer

3 Methods

3.1 Bone cement mixing procedure

An experienced user of both tested bone cement mixing systems performed the mixing procedure for total of twelve times for each system. Five times in a laboratory (in vitro), one time in a highly ventilated chamber and six times in an operating theatre (in vivo like). The mixing using Palamix® and Optivac®, was done in a randomized order so that any possible systemic error would be prevented. Mixing was performed according to the manufacturers' instructions. We standardized the mixing procedure by dividing it into a non-timed preparation stage and three timed working stages. Before starting the mixing procedure, we have always performed necessary preparation steps (Fig.11).

Quantifying the MMA would have been pointless during this preparation stage as the MMA ampoule was still sealed; therefore, the measuring start point was set with the breakage of the MMA ampoule. First working stage was filling of the cartridge, sealing it and vacuum build up (30s). Second stage was mixing of the bone cement, collecting it under vacuum with Optivac® and loading the cartage into the application gun or loading the cartridge into the cement gun and collecting the cement mechanically with Palamix® (60s). Third stage consisted of total evacuation of the bone cement onto the working plate creating an approximately 30 cm long bone cement wormlike sample and leaving the cement gun (still loaded with the empty cartridge) on the table next to the working plate for the remainder of the time (90s). Total measuring time was 180 seconds or 3 minutes.

Non-timed necessary preparation steps

1. Unpacking of:
   - Bone cement mixing system
   - PMMA powder bag
2. Taking note of:
   - Temperature
   - Relative air humidity
   - Vacuum pump function
3. Connecting the vacuum lines at both ends
4. Resetting the clock

Fig.11 Non-timed preparation stage

During the experiment in the laboratory (in vitro) set up, two additional steps were undertaken after expiration of the measuring period (see chapters 3.2.3 and 3.2.4).

Following the mixing procedure, all of the materials containing bone cement were removed and the laboratory/ operating theatre was ventilated for at least 15 minutes each time, thus eliminating any residual airborne MMA prior to the next mixing cycle.

3.2 In vitro (laboratory) setting

All laboratory experiments were performed at Palacademy, Wehrheim– Germany, in a laboratory of quality control, a department of Heraeus Medical.

3.2.1 Preliminary test-trials

Test trials were performed using the Dräger Polytron-7000® (Drägerwerk, Lübeck, Germany) device in a laboratory using the same experimental setup as described in chapter 3.2.2.

3.2.2 MMA fumes detection set-up

The first test trials were performed in a laboratory. The total volume of the laboratory room was 150 m^3 (dimensions: L: 10 m/ W: 5 m/H: 3 m). The laboratory was equipped with a standard non-laminar flow ventilation system which was capable of total air exchange rate of 9 times per hour. Ventilation system was set to work at maximum air exchange rate. Temperature and relative humidity were noted in the beginning of every mixing cycle. The measured temperature ranged from 17,9°C to 22°C, with an average of 19,94°C; relative humidity ranged from 63% to 68,3%, with an average of 64,65%.

MMA fumes detection was carried out using the PID deviceMiniRAE-3000® (Rae Systems).

All necessary materials were placed on the working table (dimensions L: 2,5 m/ W: 1 m/ H: 0,9 m). The MMA detecting device was positioned 50 cm above the working surface of the table using a hand-built device holder; thus, at 140 cm, being in an approximate breathing area of the user. All of the mixing took place directly under the suction hose tip of the detecting device at an estimated vertical distance of 15-20 cm.

3.2.3 Residual quantities of the bone cement after evacuation

During our test trials we have noticed that there was always some bone cement left within various parts of the mixing systems. Therefore, we decided to precisely quantify this residual bone cement and investigate if there is any difference between the two systems. Residual bone cement quantification was performed only during the in-vitro testing. This was done by weighing of all relevant system components before the filling stage and after the total evacuation of the bone cement. The residual bone cement weight was then computed simply by subtracting the weight of the empty system from the weight of the system after the mixing procedure.

3.2.4 Homogeneity of the bone cement

Samples of the bone cement were taken to be examined in respect to their homogeneity. This was always done after the expiration of the measuring period as the manipulation of the bone cement could interfere with the measured MMA concentration, thus falsifying the results.

Six samples of bone cement, weighing approximately 1,5 g, were extracted, two from the middle and two at each end of the bone cement worm. These were then packed into marked paper bags and taken out of the laboratory for further testing.

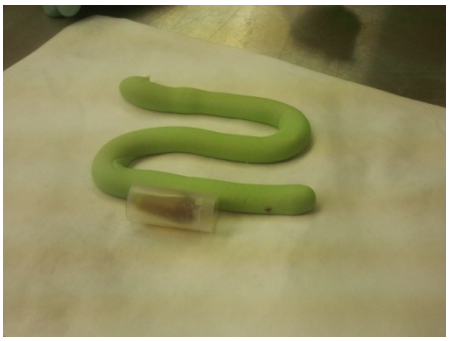

Fig.12 Bone cement worm

Examination of the homogeneity involved incineration of the bone cement samples (over a period of 1 h at 750°C) using muffle furnace, and then comparing the residual weights of the incineration resistant materials such as zirconium-dioxide within each sample. Samples originating from the same bone cement worm were compared amongst themselves as to establish possible differences in homogeneity.

3.2.5 Clean bench

We performed two mixing cycles using each of the mixing systems once. This was done as a test prior to the operating theatre trials and involved using a clean bench to simulate the ventilating conditions within an operating theatre as well as evaluate possible differences compared to the results already obtained in the in vitro setting that could justify supplementary in vivo testing. The volume of the clean bench was 0,72 m^3 with an air exchange rate of maximally 480 m^3 per hour. Within the laboratory room temperature was held constant at 23°C, while the relative air humidity was maintained at 55%. The experimental setting was identical to the in vitro setting.

3.3 In vivo-like (Operating Theater) setting

All in vivo-like experiments were performed in an operating theatre in Graz, Austria, Department of Orthopedic Surgery.

Our second set of test trials was performed in an operating theatre with total volume of 134,68m^3 (dimensions L: 7,3 m/ W: 6,15 m/ H: 3 m). All mixing was performed under laminar airflow ventilation system. Total incoming air volume was 3000 m^3 per hour while the exhaust air volume equated 2700 m^3 per hour, totaling to an air exchange rate of 22 times per hour. Temperature and relative humidity were noted at the beginning of every mixing cycle. Temperature measured in the operating theatre was constant at 23°C and relative humidity ranged from 44,6% to 48,2%, with an average of 46,05%. MMA fumes detection was carried out using the PID device MiniRAE-3000® (Rae Systems).

All necessary materials were placed on the working table (dimensions L: 1,2 m/ W: 0,7 m/ H: 0,9 m). The MMA detection device was positioned 50 cm above the working surface of the table, using a hand-built device holder or a carton, consequently being in an approximate breathing area of the user at 140 cm. All of the mixing took place directly under the suction hose tip of the detection device at an estimated vertical distance of 15-20 cm.

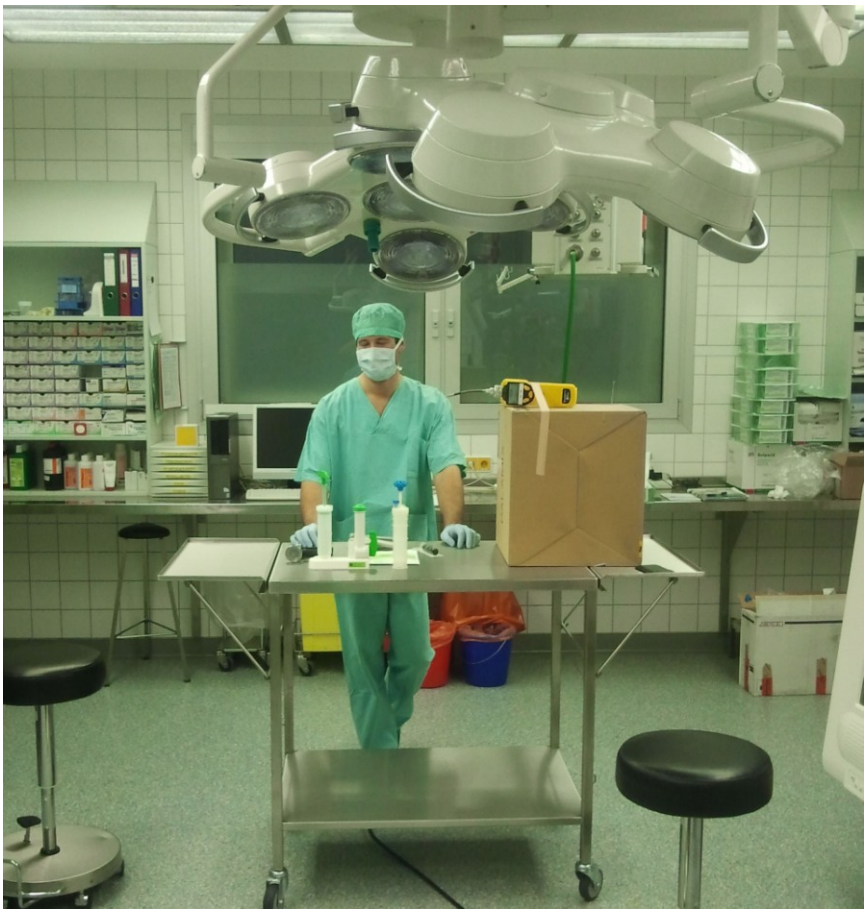

Fig.13 Experiment Setting in the Operating Theatre

In total, we performed six trials using each system, twelve in total. For the first two trials, for each system, we have positioned ourselves directly under the laminar flow. This positioning was somewhat unrealistic given that during an operation, while a surgeon is normally positioned under the laminar flow, the nurse that performs the actual mixing is not. Having realizing this, we changed our positioning so that we would be in a common location, where the actual mixing normally occurs, i.e. not directly under the laminar flow, but, rather, at the edge of air pathway which this ventilation system provides. This is where the remaining ten trials were performed.

3.4 Data collection and statistical analysis

Data was collected continuously at a rate of one second, over a period of 3 minutes. The recording device was capable of storing the collected data. For each recording period, we manually noted the starting time. Once the trials were completed, the raw data was retrieved from the PID device and useful segments

isolated and assigned to their corresponding mixing cycles based on the previously recorded starting times. Data was analyzed using Microsoft® Office Excel 2007 (Microsoft ® Corporation, Redmond, WA, USA). We used the mean value and standard deviation to describe the collected data. Mean concentrations were determined for every stage of each mixing cycle. Additionally, mean exposure was calculated and graphically presented to show measured MMA concentrations over the whole measuring period for each system.

For statistical analysis we used the IBM® SPSS® Statistics 20.0.0 (International Business Machines Corporation, Armonk, NY, USA). For the comparison of two systems, results were tested in a univariate analysis and post-hoc tests were calculated. A P-value of ≤ 0,05 was considered significant.

4 Results

4.1 MMA Fume detection

4.1.1 Laboratory setting (In vitro)

Total mean MMA fume concentration for five mixing cycles over 3 minutes with Palamix® was 7,61 ppm (SD 4,28) and 7,98 ppm (SD 3,39) when using Optivac®. Statistical data analysis showed no significant difference in total concentration between the two systems; however, a significant difference was found in second stage of the mixing procedure – the mixing and collecting stage.

Mixing System	Total Exp. Mean(0-180s)	Exp. Mean Stg. 1 (0-30s)	Exp. Mean Stg. 2 (30-90s)	Exp. Mean Stg. 3 (90-180s)
Palamix®	7,61(SD 4,28)	4,52 (SD 5,22)	2,18 (SD 1,73)	12,26 (SD 7,57)
Optivac®	7,98 (SD 3,39)	11,59 (SD 12,18)	6,55 (SD 3,77)	7,73 (SD 4,08)

Fig.14 Summary of MMA fume concentrations in laboratory setting in ppm

During the first stage (filling and vacuum build-up) highest concentration peak was 27,4 ppm and 10,7 ppm for the Optivac® and Palamix® systems, respectively. During the second stage (mixing and collecting) Optivac® had its highest peak at 12,6 ppm while MMA fume concentration when using Palamix® was no more than 3,1 ppm. During the last stage (loading of the cement gun and evacuating), each system had multiple peaks. For Optivac® the peaks were 12,6 ppm at 120th and 18,2 ppm at 160th second and for Palamix® they were 19,7 ppm at 120th and 24,7 ppm at 170th second.

Timeline of MMA fume concentration over all stages of the mixing procedure is shown in the Fig.15 for Optivac® and Fig.16 for Palamix®.

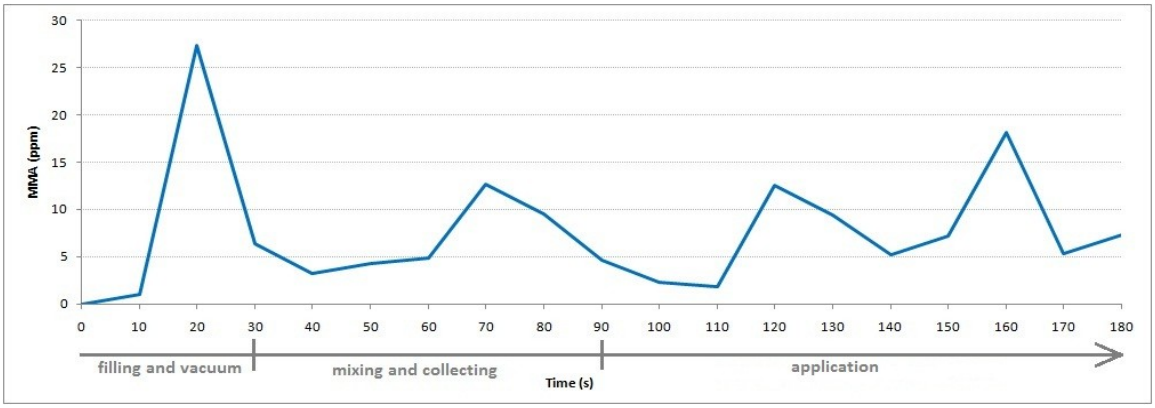

Fig.15 Mean MMA concentration timeline when using Optivac® in a laboratory setting

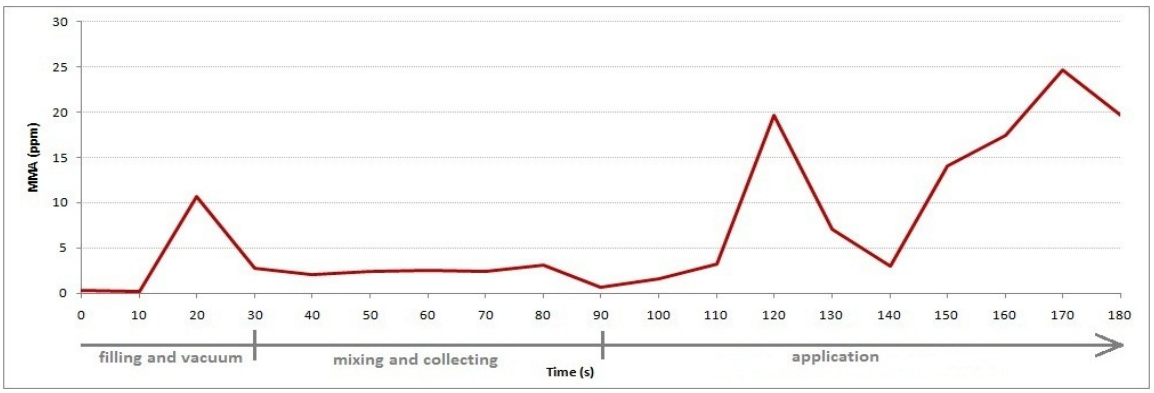

Fig.16 Mean MMA concentration timeline when using Palamix® in a laboratory setting

4.1.2 Operating theatre trials (In-vivo-like settings)

First two mixing cycles produced no measurable MMA fumes in the breathing area of the user for either of the mixing systems. After altering our positioning in the operating theatre to where the nurse is normally positioned during such operations, we have performed ten mixing cycles, five cycles per system.

Total mean MMA fume concentration for five mixing cycles over 3 minutes with Palamix® was 1,06 ppm (SD 0,36) and 1,12 ppm (SD 0,11) when using

Mixing System	Total Exp. Mean(0-180s)	Exp. Mean Stg. 1 (0-30s)	Exp. Mean Stg. 2 (30-90s)	Exp. Mean Stg. 3 (90-180s)
Palamix®	1,06 (SD 0,36)	0,60 (SD 0,11)	1,17 (SD 0,30)	1,14 (SD 0,51)
Optivac®	1,12 (SD 0,11)	0,96 (SD 0,31)	1,38 (SD 0,45)	1,00 (SD 0,25)

Fig.17 Summary of MMA fume concentrations in operating theater setting in ppm

Optivac®. Statistical data analysis showed no significant difference in total concentration between the two systems; however, a significant difference could be found for the first stage of the mixing procedure – filling and vacuum stage.

During the first stage (filling and vacuum build-up) highest concentration peaks were 1,86 ppm and 0,8 ppm for Optivac® and Palamix®, respectively. During the second stage (mixing and collecting) Optivac® had its highest peak at 2,24 ppm, while MMA fume concentration when using Palamix® was no more than 1,57 ppm. During the last stage, for Optivac® the peak was 1,61 ppm at 120th and for Palamix® the peaks were 1,74 ppm at 140th and 1,63 ppm at 160th second.

MMA fume concentration timeline over all stages of the mixing procedure is shown in the Fig.18 for Optivac® and Fig.19 for Palamix®. It is important to note that the measuring device showed a zero value that varied between 0,3 ppm and 0,7 ppm despite the waiting times between individual trials.

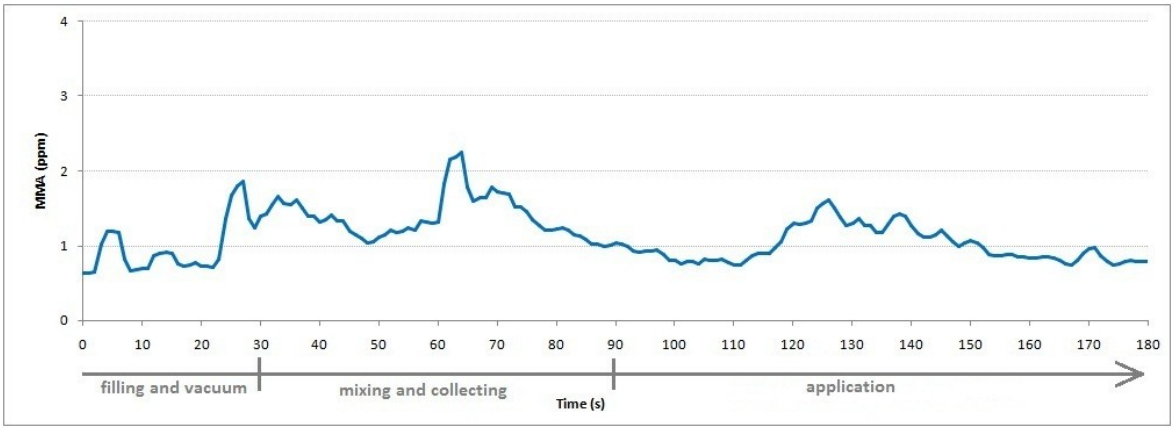

Fig.18 Mean MMA concentration timeline when using Optivac® in an operating theatre

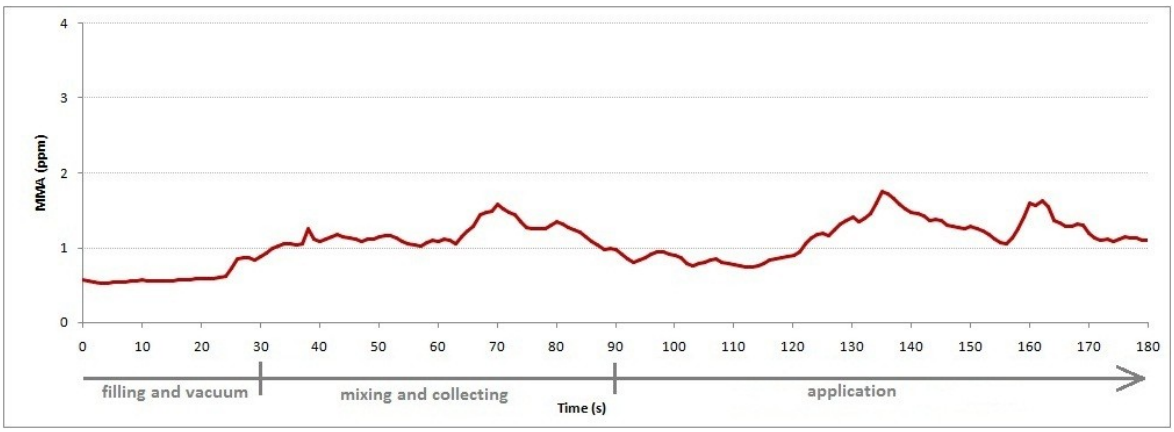

Fig.19 Mean MMA concentration timeline when using Palamix® in an operating theatre

4.2 Residual quantities of bone cement

As described earlier, some of the bone cement always remains within or on various parts of the mixing systems after total evacuation. Mean residual bone cement quantity when using Palamix® was 9,4g (SD 0,64) which equals 15,6% of the bone cement mixed, whereas when using Optivac® mean residual quantity was 16,9 g (SD 0,75) or 28,1%. Statistical analysis has shown that there is a significantly higher residual quantity of bone cement with the Optivac® system.

Optivac®	Palamix®
16,9g (28,1%)	9,4g (15,6%)

Fig.20 Residual bone cement quantities

4.3 Homogeneity of the bone cement

After the bone cement samples have been processed, residual weights of the incineration resistant materials were obtained. Residual weights of incineration resistant materials were expressed in percentages to ensure comparability of the samples.

Bone cement mixed using either system showed no significant difference in the bone cement homogeneity. Results are summarized in the Fig. 21.

Sample origin	Incineration rest-Palamix®	Incineration rest-Optivac®
Beginning	10,78%	10,63%
Middle	10,38%	10,60%
End	10,53%	10,61%

Fig.21 Incineration rest in percentage for Palamix® and Optivac®

5 Discussion

Several studies have shown that vacuum mixing systems significantly reduce MMA fumes in the operating theatre compared to the traditional open bowl hand mixing (43, 44, 46). However, the mixing system cartridges are never completely sealed as the bone cement is being prepared and therefore some MMA fumes are able to escape during the mixing procedure and during application. During our experiments we were able to find evidence to support this.

A variety of systems have been tested in this context, yet to our knowledge there has never been a direct comparison of these two similar bone cement mixing systems that were chosen for our experiment. Schlegel et al. 2004 (44) compared the Optivac system to six other mixing systems in terms of their MMA fume release. Another study compared the Palamix® system with two other systems in 2010 (45). We chose Palamix® and Optivac® because they are two commonly used mixing systems today and to our knowledge there has been no direct comparison of these two systems to date.

In our opinion, there are three main causes for MMA fume leakage into the environment while using the vacuum mixing systems. First is the filling of the cartridge with monomer liquid. Second cause for the MMA leakage is the movement of the mixing paddle while mixing the bone cement. This allows small amounts of MMA to escape through the narrow opening, circumventing the mixing rod. Third cause is the evacuation of the bone cement out of the mixing cartridge and its handling thereafter as the polymerization reaction is still in progress and MMA molecules are freely dispensed into the surrounding air. This occurrence is not mixing system dependant.

It has been suggested that systems using the mechanical collection of the bone cement contribute to the higher MMA evaporation (47). We were not able to support this claim through hour testing, as the MMA fume exposure during the mixing and cement collecting phase was significantly lower when using Palamix® where cement is collected mechanically, compared to the Optivac® which is equipped with a collecting under vacuum mechanism. Schlegel et al. (44) stated

that although expected to reduce the MMA fume release, Mix-OR system equipped with collecting under vacuum mechanism has led to higher MMA fume concentrations compared to the two systems (ACM and Vacu-Mix) which use the mechanical collection of the bone cement. This however, might have been a consequence of the increased monomer loss during the mixing procedure with Mix-OR system, as described by the author.

5.1 Laboratory setting

The two bone mixing systems that were compared, Palamix® and Optivac®, showed no significant difference in MMA fume release within the whole measuring period; however, significantly higher MMA fume concentration was measured when using Optivac® during the bone cement mixing and collection stage. We were not able to define possible reasons for this as the Optivac® systems is equipped with a mechanism for collection of fumes under vacuum mechanism and has a smaller diameter of the mixing rod compared to Palamix®. Therefore, we were not able to support literature claims (45, 47) that these factors have an impact on system dependant MMA leakage.

We have observed peaks during the filling and vacuum stage when using both systems. Palamix® showed a peak of 32,9 ppm during its third measuring cycle and 19,6 ppm during the fourth, while Optivac® showed peaks through three measuring cycles highest being 87,2 ppm, second highest at 27,8 ppm and third at 18,3 ppm. During other cycles none of the systems produced peaks higher than 2,6 ppm. To explain this occurrence of occasional peaks during the filling and vacuum stage we came to conclusion that the cause is most probably some random movement of the user of which we were not aware; however, based on our results, we hypothesize that such random movement is less likely to produce higher peaks when using Palamix®. This is because Palamix® is equipped with separate filtered section on the funnel where the monomer ampoule is placed to empty itself into the cartridge. We see an advantage here, as this section is built under an angle that allows the ampoule to empty itself fully without any further

manipulation, thus reducing the chance of accidentally creating a peak by the user during the filling stage.

After evacuation with Palamix®, two peaks were measured: 19,72 ppm at the 120th second and 24,72 ppm at 170th.Peaks measured after application with Optivac® were somewhat lower with 12,56 ppm at the 120th second and 18,18 ppm at 180th. As this measured stage is not system dependent, it is hard to clarify if the measured peaks correlate with mixing systems, however we hypothesize it is due to the significantly larger quantity of the bone cement that is evacuated out of the Palamix® system (on average 6,2 g, or~10% of the total mixed bone cement quantity). However, we are not able to exclude other possible causes for this, such as movement of the user or the staff or other environmental factors.

5.2 Operating theater setting

In support of our speculations prior to our experiments in the operating theatre, the results have shown a significant reduction of MMA fumes in the breathing area of the user compared to the results from our laboratory trials. Quantified MMA fumes were significantly lower across all mixing procedure stages and with both systems tested.

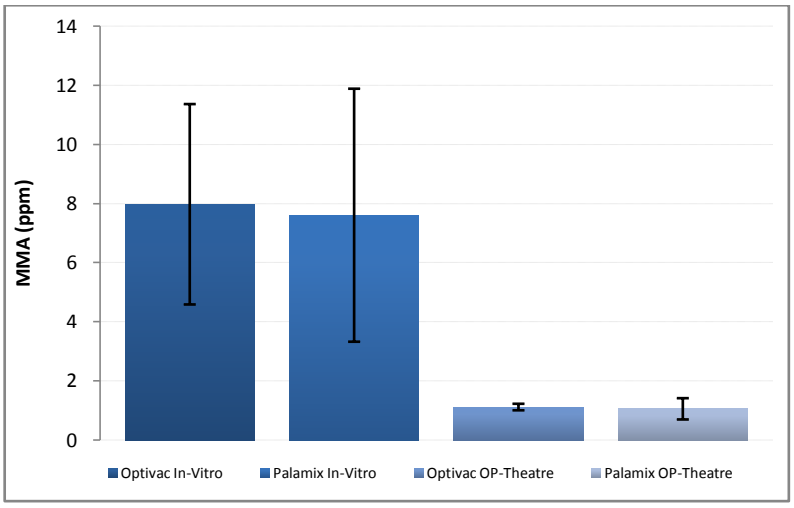

Fig.22 Mean MMA concentrations over the measuring period with both systems

The laminar airflow ventilating system was the key factor in reducing the MMA fumes in the breathing area of the user, as it was the only major deviation to our experiment conditions in laboratory. There were other environmental factors that were slightly different, such as average temperature or relative humidity; however, we do not believe that those have played a deciding role in reducing the MMA fumes in the breathing area. Furthermore, our presumption that the ventilating system may play an important role in reducing the MMA in the breathing area of the user has proven itself true with the first two single shot measuring cycles that took place directly under the laminar airflow ventilation system. There, we were unable to quantify any MMA fumes while using either system. This is by far the most significant result of our investigation as it has a clinical relevance, and it can be applied by the staff to minimize the exposure to MMA. This can be accomplished by simply positioning the user so that the mixing procedure can take place inside the air pathway from the laminar airflow ventilation system, while the user himself stays outside of it (as shown in Fig.23), rather than mixing and standing within air pathway from the laminar airflow ventilation system (as shown in Fig.24).

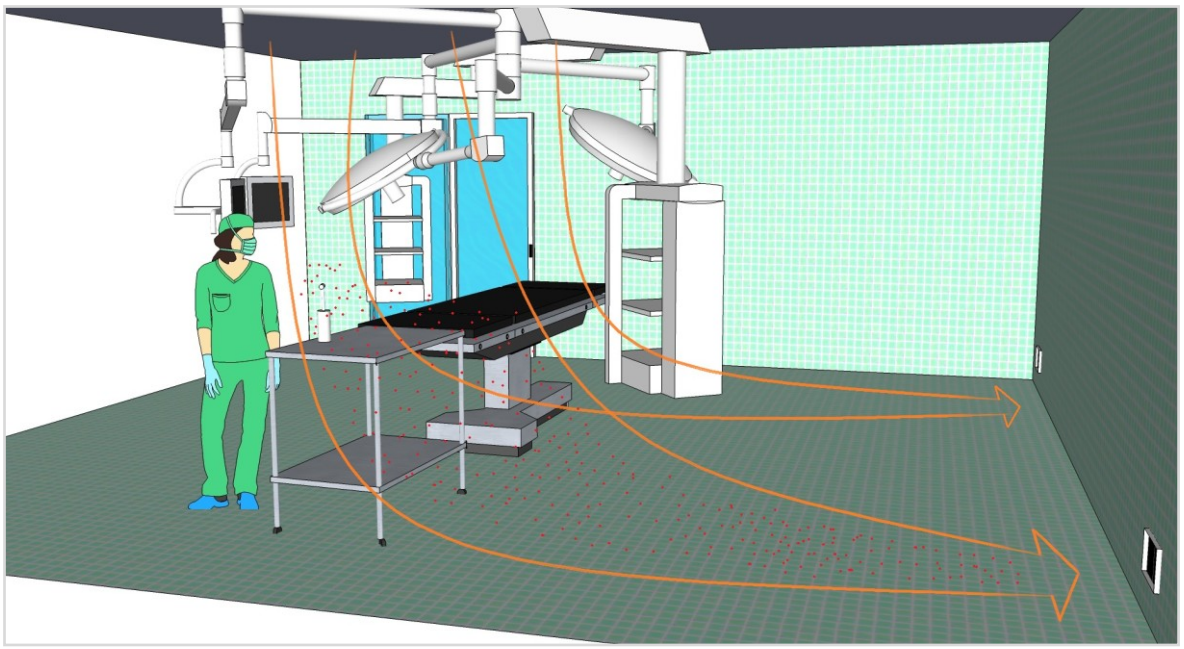

Fig.23 Mixing while staying out of air pathway

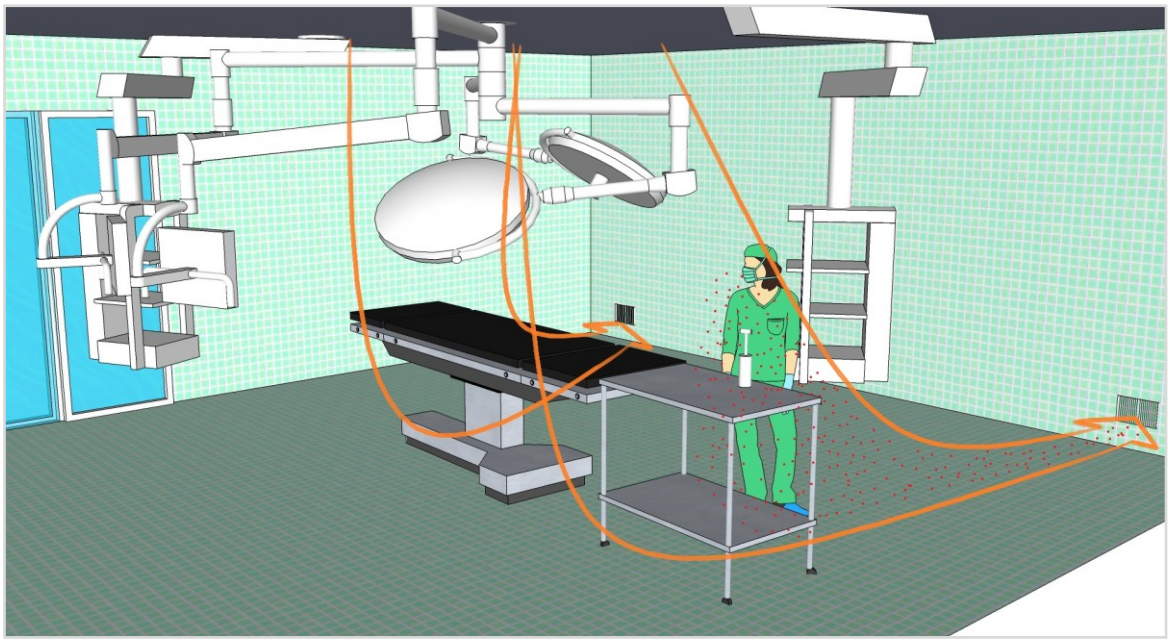

Fig.24 Mixing while staying within the air pathway

During the remainder of our trials, which occurred at the edge of the air pathway created by the ventilating system where the actual mixing takes place during surgery, we were able to detect and quantify MMA fumes while using both systems. Over the whole measuring period no significant differences were found between Palamix® and Optivac® in respect to the mean MMA fume concentration in the breathing area of the user. This correlates well with the results from the laboratory setting.

During the filling and vacuum stage of the mixing procedure in the operating theatre, we have measured significantly lower MMA fume concentration with Palamix® averaged at 0,60 ppm (SD 0,11) compared to the 0,96 ppm average (SD 0,31) of the Optivac® system. As already discussed, we think that the cause for this significantly higher MMA fume concentration in the breathing area of the user when using Optivac® is the separate filtered section on the funnel of the Palamix® system (Fig.25).

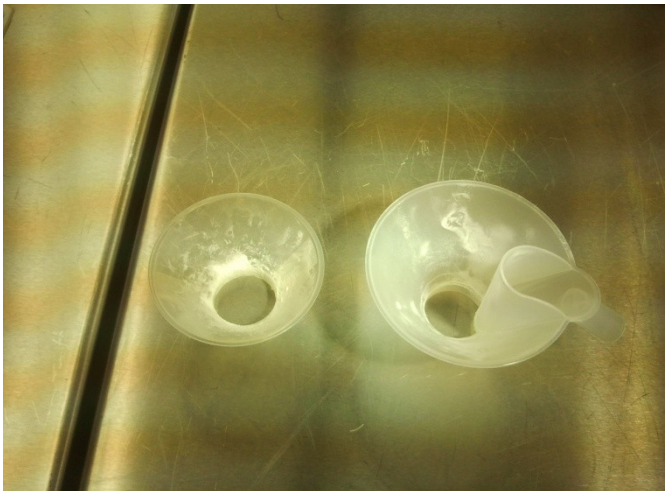

Fig.25 Optivac funnel (left); Palamix funnel (right)

As the MMA fume concentration

during the mixing and collecting stage in our laboratory trials was significantly higher with Optivac®, we were led to conclusion that for the same reason Optivac® system also averaged a slightly higher MMA fume concentration during the operating theater trials.

During the third stage of the mixing procedure, the evacuation of the bone cement out of the mixing cartridge onto a working plate, there was no significant difference between the systems, in respect to the MMA fume concentration in the breathing area of the user; however, we have noticed a slightly higher mean MMA concentration after evacuation with Palamix®. This occurrence also correlates with our results from the laboratory trials. Even though this stage is not system dependent, we find that this may be explained with significantly lower residual bone cement quantity within the Palamix® mixing system.

Our operating theatre results with Optivac® correlate with a similar study (44) where Optivac® was tested regarding MMA fumes using two detection methods (the GC and the PID); however, we were not able to confirm the result of another recent study by the same author (45), that tested Palamix®. In that study, Palamix® averaged 7,4 ppm (SD 2,74), under similar conditions to our operating theatre trials. We obtained a comparable result of 7,61 ppm (SD 4,28) in our laboratory trials, while the MMA concentration in our operating theatre trials was significantly lower at 1,06 ppm (SD 0,36).

Strictly, our result is at odds with the claim that collection under vacuum leads to lower MMA emission into the environment (37), as we saw no significant difference between Palamix® and Optivac® regarding MMA leakage.

5.3 Residual cement quantities within systems

The possibility of obtaining information on residual cement quantities within the systems has presented itself during our first test trials as we have noticed some differences in design of mixing systems used and how it affects quantity of the bone cement that is evacuated after mixing, or rather the quantity of the bone cement that remains on various parts of the mixing system after application.

Significantly higher residual bone cement quantity in Optivac® is, in our opinion, a consequence of the system design.

This can be seen as somewhat problematic, as the user is told to have a certain quantity of the bone cement material at disposal, whereas this amount is reduced by approx. 28,1% when using Optivac® or 15,6% when using Palamix®.

5.4 Measuring device choice

At first, we wanted to have two devices that would simultaneously quantify MMA fumes during our testing in order to achieve a greater accuracy of the collected data.

Earlier studies used mostly gas chromatography as detection method for MMA during similar experiments (43, 48, 49). Even though this method is known for its accuracy, it is the complexity of the process that gives the PID device an advantage. A recent study directly compared the two methods, and has shown that the two correlate good in the lower measuring range; however, the PID tends to underestimate the actual MMA fume concentration with differences between the two methods ranging from 44.51% to 88,16% (3). As all our testing was done using the MiniRAE-3000®, this should be considered; however, even so, measured concentrations of the MMA fume in the breathing area of the user, do not approach the given MAK value.

For our test trials we have used another detecting device, the Dräger Polytron 7000®. Very soon after our first test trials, we have come to conclusion that this device is inadequate for our experiment as the reaction time of the device is very long compared to the PID, and therefore not suited for immediate MMA fume concentration measuring.

6 Conclusion

When working with PMMA bone cement, a certain concentration of MMA in the breathing air is inevitable. Therefore, individuals known to have allergic reactions or irritating sensation to MMA should not work with this material disregarding the working conditions or which mixing system is being used.

We have shown that two of the most commonly used mixing systems Palamix® and Optivac®, have a comparable MMA leakage during the mixing procedure and that total exposition to MMA when using these systems, is far below the MEL value.

We have also shown and described the major role that the laminar airflow ventilating system plays in further reduction of MMA fume in the breathing area of the user. This has practical value as it can be applied to minimize the exposure of the user and the operating staff.

According to our findings, information about how laminar airflow can help to further reduce MMA fume concentration in the breathing area should be provided by the manufacturer in the mixing system user manual, preferably with a sketch similar to the one that we have shown.

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