

Review

Surgical Applications of Methyl Methacrylate: A Review of Toxicity

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ABSTRACT. Methyl methacrylate (MMA) is a monomer of acrylic resin widely used in a variety of medical, dental, and industrial applications. Its extensive use in surgery, particularly for arthroplasties, has often raised concerns regarding potential human toxicity for orthopaedic surgeons, surgical nurses, and other operating-room staff who are occupationally exposed to the compound. The main toxic effects of MMA exposure appear to involve the cardiovascular system. When exposed to MMA in the work environment, surgical staff have been reported to suffer from hypersensitivity, asthmatic reactions, local neurological symptoms, irritations and local dermatological reactions. The integrity of latex gloves may also be compromised following exposure to MMA during surgical procedures. At present, MMA is not thought to be carcinogenic to humans under normal conditions of use. Nevertheless, sound occupational hygiene practices should still be used to help reduce workplace exposure to MMA during orthopaedic and other medical procedures. Surgical staff should avoid direct contact with MMA mixtures wherever possible, and room ventilation and adequate airflow should also be optimized. In the present article, the authors review studies relating to MMA toxicity in surgical practice, updating in part a previous literature review and expanding on the toxicity of MMA within the surgical setting.

KEYWORDS: arthroplasties, medical, methyl methacrylate, occupational, surgery, toxic effects

Methyl methacrylate (MMA) is a monomer of acrylic resin with a wide variety of medical, dental, and industrial applications.¹⁻⁵ It has long been used as an acrylic resin cement for orthopaedic surgery and denture bases, as well as for numerous other medical, dental, and industrial products. At a molecular level, MMA, methacrylic acid, and other methacrylates readily polymerize to form long-chain homo-polymers and copolymers, such as organic glass. The MMA monomer [$\text{CH}_2 = \text{C}(\text{CH}_3)\text{COOH}_3$] is the most important ester of methacrylic acid commercially in use at the present time.⁴⁻⁶ Despite its widespread applications in surgical settings, long-term toxicity of the MMA monomer is not well known. Given this dearth of information, the present article reviews studies relating to MMA toxicity

in surgical practice, updating in part a previous literature review¹ and focusing on expanding the toxicity of MMA in the surgical setting.

Biochemistry of MMA

Table 1 describes the chemical formula of MMA and its physical properties. Briefly, MMA (Chemical formula: $\text{C}_5\text{H}_8\text{O}_2$) is a colorless, volatile liquid with an acrid fruity odor and a boiling point of 100–101°C.²⁻⁴ A Concise International Chemical Assessment of MMA was undertaken and published by the World Health Organization in 1998.⁴ MMA, methacrylic acid, and other methacrylates readily polymerise

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Table 1.—Chemical and Physical Properties of Methyl Methacrylate (MMA)

Property and reference number	Description
Chemical name ²	2-Methyl-2-propenoic acid, methyl ester
IUPAC systematic name ²	Methacrylic acid, methyl ester
Synonyms ²	2-(Methoxycarbonyl)-1-propene, methyl 2-methacrylate, methyl 2-methyl-2-propenoate
Abbreviation ²	MMA
Structural and molecular formula ²	$\begin{array}{c} \text{O} \\ \\ \text{H}_2\text{C}=\text{C}-\text{C}-\text{O}-\text{CH}_3 \\ \\ \text{CH}_3 \end{array}$
Chemical formula ²	C ₅ H ₈ O ₂
Boiling point ^{3, 4}	100–101°C
Melting point ^{3, 4}	–48°C
Flash point ⁴	10°C
Appearance ⁴	Colorless, volatile liquid with an acrid fruity odor

to resins by light and heat to form long-chain homo-polymers and copolymers. The MMA monomer is the most commercially important ester of methacrylic acid currently in use as a clear, resistant, durable, and relatively inert plastic material.

Surgical applications

Table 2 presents some examples of the numerous surgical and medical applications for MMA and its homologues. The properties of MMA make it particularly attractive for use as surgical bone cements in arthroplasties, leaded acrylic radiation shields, and dental prostheses. Poly methyl methacrylate (PMMA) is used in rigid intraocular lens implants.⁸

Table 2.—Examples of Surgical and Medical Applications of Methyl Methacrylate (MMA) Homologues

Specialty area	Past, present, and potential applications, with reference number
Orthopaedic surgery	Arthroplasties: bone cement ^{4,7}
Ophthalmology	Intraocular lens; hard contact lens ⁸
Maxillofacial surgery	Craniofacial reconstruction: prostheses ⁹
Plastic and reconstructive surgery	Reconstructive survey: prostheses ¹⁰
Dental surgery	Dental prostheses ⁴
Radiology	Leaded acrylic radiation shields ⁴
Podiatry	Orthotics ⁴
Anatomical pathology	Vascular corrosion casting ¹¹

In total hip and knee joint replacements, most arthroplasties are anchored to the contiguous cancellous bone in an acrylic bone cement bed. There are more than 30 commercially available plain acrylic bone cements in the United States of America alone.¹² With few exceptions, the powder comprises beads of PMMA or a PMMA-based polymer, a radiopacifier of BaSO₄ or ZrO₂ particles, and benzoyl peroxide as the initiator of the polymerization reaction.¹² The liquid monomer comprises MMA monomer, *N,N*-dimethyl-*p*-toluidine (DMPT), as the accelerator of polymerization reaction and hydroquinone as an inhibitor of that reaction.¹² There are some alternate plain acrylic bone cements, which have been developed to overcome various perceived drawbacks of the plain acrylic bone cement formulation, and these have been described elsewhere.¹²

General applications

Outside the medical and dental environment, MMA polymers and co-polymers are used in water-based, solvent-based, and undissolved coatings. Outside the medical environment, exterior latex paint, based on an emulsion containing MMA, is the surface coating in which the monomer is used most widely. Solvent-reducible polymers containing methacrylates are used widely in industrial finishes, metal, and foil coatings.⁵ Polymer concretes, based on MMA and Portland cement, are used to patch highways and bridges, and MMA is also used in the production of polymers that are added to lubricating oil.⁵ In domestic situations, MMA is also used for the preparation of synthetic fingernails and orthotic shoe inserts.⁴

Toxicity and sensitivity to MMA

Studies describing the general toxicity and sensitivity to MMA have been reported since the 1940s.⁶ In medical and surgical settings, postoperative complications are known to occur following the use of acrylic cement in reconstructive orthopaedic surgery, such as hip or knee joint replacements. These associated complications have often involved cardiovascular dysfunction, resulting in mild to moderate hypotension, cardiovascular collapse, and postoperative deep vein thrombosis, particularly at the site of cemented area.^{13–16} Many studies have attempted to explain the pathophysiology of these complications, which seem to include both activation of coagulation and the direct harmful effect of MMA—which may, in turn, cause damage to blood cells and endothelial cells.¹ During total hip arthroplasty, MMA plasma levels have been found to be higher after acetabulum cement implantation—compared with femoral cement implantation—with plasma MMA levels peaking above 1 µg/mL in some cases, although the half-life of MMA is relatively short.¹⁷

An in vitro study revealed that MMA produced direct relaxation of the rabbit aortic ring, constricted with either potassium or noradrenaline in calcium-deficient media and inhibited subsequent calcium-induced constriction.¹⁷ This

suggested that MMA may interfere with intracellular and extracellular calcium mobilisation, including excitation and contraction coupling in vascular smooth muscle, which may, in turn, play some role in producing the hypotension observed to occur when acrylic bone cement is used during orthopaedic procedures.¹⁸ Moreover, *in vitro* studies using MMA concentrations of 0.1–1 $\mu\text{g/mL}$, alone or combined with thrombin, have been shown to effect coagulation via activating tissue factor, indicating that MMA in concentrations found in the central venous blood *in vivo* can probably contribute to the activation of coagulation.¹⁹

In addition, there may be toxic effects from the mixing of various components of the cement in orthopedic settings. Polymerization of the acrylic bone cement is exothermic, with a maximum polymerization temperature around 70–110°C.¹² This is potentially high enough to cause thermal necrosis of the periprosthetic tissue.¹² There may also be toxicity due to the residual DMPT, BaSO_4 , and ZrO_2 in the PMMA matrix, which have been discussed elsewhere.¹² The toxicity of MMA in dental settings has been reviewed elsewhere as well.²⁰

Occupational exposure and toxicity

MMA has long been used in various industries, most of which have involved monomer and polymer production, and/or plastics manufacture. The toxicity of MMA in workers occupationally exposed to MMA at varying doses in these factories is discussed elsewhere.¹ Research on MMA toxicity continues to show conflicting results. A Bulgarian study by Prakova,²¹ for example, revealed that acid-base disruption in humans may be associated with overexposure to airborne MMA in PMMA production operations. Respiratory acidosis was also indicated by increased pCO_2 in some groups of workers, suggesting that the clinical response to MMA exposure may involve both a metabolic and respiratory acidosis component.²¹ However, a recent investigation of two worker cohorts occupationally exposed to MMA in acrylic sheet production did not indicate any increased mortality.²²

Aside from industrial settings, the MMA monomer also appears to be toxic in the medical workplace. Several body systems are probably affected in this occupational environment, including the skin, respiratory tract, and the neurological system. MMA is a mild skin irritant and has the potential to induce skin sensitisation in susceptible individuals.⁴ Orthopaedic surgeons, surgical nurses, and other operating room staff who work with this material may be exposed when they occasionally contact the MMA monomer directly, such as when using acrylic cement during the insertion of prostheses. Medical personnel may also be exposed to a certain amount of MMA fumes during the ultrasonic removal of MMA cement as part of revision hip surgery, although research suggests that these actual levels may be safe.²³ The preparation of prostheses and appliances by theater technicians and other medical staff also involves a certain degree of manual handling and dermal exposure to MMA products.

This was also observed in dental technicians, who were found to have significantly slower distal sensory nerve conduction velocities on the hands exposed to MMA.²⁴ It was thought that this may be due to axonal degeneration in the nerves closest to the MMA dermal exposure.²⁴

Medical staff may also be exposed to a volatilised MMA monomer, which may contaminate the operating theater, medical clinic, or laboratory environment.²⁵ Occupational concentrations of MMA in air have been shown to vary depending on the facility, production volume, and type of ventilation used.²⁶ It should be noted that the MMA monomer is, by nature, a very volatile and highly flammable compound.⁴ Although occupational asthma associated with MMA use has been reported previously, there is still no conclusive evidence that MMA is a respiratory sensitizer.⁴ Parizi and colleagues,²⁷ for example, were unable to find any tracheal inflammatory process or thickening during short-term MMA exposure in animal models. Although an allergy has not been specifically described in the surgical setting, it has been described in the dental setting, especially amongst dental technicians.²⁸

Reducing occupational exposure

To date, there has been no systemic review published on the safety of MMA in the surgical setting. Nonetheless, various methods have been proposed to help reduce the occupational burden of both acute and chronic MMA exposure, as summarized in Figure 1. Surgical staff using MMA, for example, should be informed of the compound's inherent hazards and take appropriate measures to control exposure by using relevant occupational hygiene protocols. These can include, but should not be limited to the following: First, surgical and medical staff should avoid direct contact with MMA and should only use MMA compounds in a well-ventilated area; second, personal protective equipment used as part of occupational hygiene control measures, such as face shields and protective eyewear,²⁹ is important when using standard occupational safety protocols from the broader workplace experience; and third, from an environmental control perspective, recirculating room air filters with gas absorbents of acid carbon for MMA vapour collection may be useful in controlling exposure, as this has been found to be the case with certain other chemicals, such as cyanoacrylate.³⁰ The universal installation of such devices in surgical suites and operating theaters is therefore recommended.

Additional measures to reduce occupational exposures to MMA in the medical workplace have been described elsewhere.⁴ However, the use of vacuum mixing of cement to remove fumes from the operating theater environment could have a considerable impact on the costs of arthroplasties. From a substitution point of view, alternative materials, such as a butyl methacrylate (BMA) monomer used in poly (ethyl methacrylate) n-butyl methacrylate (PEMBMA), have also been developed in recent years. Indeed, the BMA monomer used in PEMBMA is believed to be slightly less toxic than

General measures to reduce exposure

- Increase awareness of MMA's inherent hazards
- Provide appropriate training in the use of MMA in surgery, including safety information for staff

Personal measures to reduce exposure

- Avoid direct contact with MMA compounds
- Wear appropriate personal protective equipment consistent with infection control guidelines

Environmental control measures to reduce exposure

- Use MMA compounds in a well-ventilated area
- Install recirculating room air filters with gas absorbents of acid carbon
- Avoidance of exposure of MMA monomer to any flame or spark
- Appropriate storage of the chemicals

Fig. 1. Summary of possible measures to reduce occupational exposure to Methyl Methacrylate (MMA). Adapted from World Health Organization. Concise International Chemical Assessment Document 4: Methyl Methacrylate. Geneva, Switzerland: World Health Organization; 1998.

the MMA monomer used in PMMA. Biological studies of BMA have been reviewed elsewhere.³¹

Cytotoxicity

Many researchers have previously examined the possible cytotoxic effects of the MMA monomer, as well as the polymer PMMA. However, not all results are consistent. Dahl et al,³² for example, investigated the influence of MMA in the cellular integrity of monocytes, granulocytes, and endothelial cells, finding that all cells treated with 10 µg/mL showed marked signs of cytotoxicity after 1-minute incubation. Following 30-minutes incubation, the majority of cells were totally disintegrated.³² In animal studies, MMA was also found to affect mitochondria function and structure as an uncoupler of oxidative phosphorylation in isolated mitochondria experimentally in rat liver cells.³³ However, animal experiments have revealed no toxic effects of orally-administered MMA to the major organs of rats, with MMA rapidly hydrolysed by serum nonspecific carboxylesterase.³⁴ MMA has also been shown to be toxic in experimental studies using a human neuron-enriched primary culture, derived from embryonic brain tissue.³⁵ The physical and chemical properties of MMA appear to have some effect on the lipid bilayer in biological membranes when cytotoxicity testing has been carried out against primary human gingival fibroblasts, human submandibular gland adenocarcinoma cell line, and human erythrocytes.³⁶ Nonetheless, MMA typically exhibits minimal cytotoxicity and only small changes in dipalmitoylphosphatidylcholine liposomes.³⁶

Carcinogenicity

In addition to in vivo and in vitro experimental studies of acute toxicity, there have also been a number of epidemiological studies that examined the possible mutagenicity related to MMA exposure.¹ In a cohort study from the United States,³⁷ researchers investigated 2,671 men who had worked in 2 plants from the plants' inception (1951 and 1957, respectively) until 1974. Cumulative exposures to MMA were calculated for each worker, with the cohort being divided into groups of MMA-exposed and MMA-unexposed workers. The exposed cohort showed a significantly decreased mortality from all causes assessed, as well as a nonsignificant trend toward increased mortality from all cancers assessed. None of the cancer sites were shown to have a significantly increased risk with increasing dose.³⁷ In another case-control study conducted in Montreal, Canada, an exposure to 0.4% MMA was 1 of the exposures assessed.³⁸ The only cancer site for which there was a significantly increased risk was cancer of the lung.³⁸ A more recent epidemiological investigation examining oncological mortality among workers exposed to some acryl monomers specifically estimated the oncologic risk for individuals exposed to acryl nitrile, MMA, methyl and butyl acrylate, and methacrylic acid.³⁹ In this study, the occurrence of malignancies appeared to depend on the dose of MMA to which a worker had been previously exposed.³⁹

Researchers have also undertaken studies at a chromosomal level. For example, a study of 38 male workers who were exposed to MMA at concentrations of between 0.9 ppm to 71.9 ppm examined chromosome aberration rates and sister chromatid exchange frequency in peripheral lymphocytes.⁴⁰ Results suggested that occupational MMA exposure, under the conditions studied, was not associated with genotoxicity.⁴⁰ These results corresponded with another experimental study that examined the effect of MMA using a TA98 strain of the bacterium *Salmonella typhimurium*. This bacterium was exposed to the mutagens 1-nitropyrene and benzo(a)pyrene, and it was suggested that MMA was probably acting as an inhibitor of chemical carcinogenesis.⁴¹ Monomer components of resin materials, such as triethyleneglycol dimethacrylate, 2-hydroxyethyl methacrylate, and glycidyl methacrylate, were also found to be responsible for the induction of micronuclei from rat liver, indicating clastogenic activity of these chemicals in vitro.⁴² Additionally, no mutagenic effects resulting from MMA were found during in vitro studies using different *Salmonella typhimurium* strains (TA97a, TA98, TA100, and TA102) and in V79 cells in the presence and absence of a metabolically active microsomal fraction derived from rat livers (S9).⁴³ Previous animal experiments have suggested that MMA was not carcinogenic after lifetime inhalation exposures to concentrations of up to 500 to 1,000 ppm in rats and mice, respectively.⁴⁴ MMA was also not revealed to be carcinogenic in hamsters following lifetime inhalation exposures of up to 400 ppm.⁴⁵ Furthermore, exposure to MMA by inhalation of concentrations up to 2,028 ppm resulted in no embryo or foetal toxicity or malformations,

even at exposure levels that were high enough to illicit maternal toxicity.⁴⁶

Given these studies, the International Agency for Research of Cancer (IARC) concluded that there is inadequate evidence for the carcinogenicity of MMA in humans.² Furthermore, there is also evidence suggesting a lack of carcinogenicity of MMA in experimental animals.² The IARC's overall evaluation concluded that MMA should not be classified according to its carcinogenicity. A more recent review by Tomenson et al.⁴⁷ also suggested that although there was an unexplained excess of colorectal cancer in 1 group of workers exposed to high levels of MMA in the 1930s and 1940s, there was no consistent evidence from human or animal studies that MMA is a human carcinogen.⁴⁷ Although further studies are needed in vivo, it appears that, at least for the present time, there is no evidence of any permanent toxic or carcinogenic effects from the MMA monomer under normal conditions of use. Even so, MMA compounds should still continue to be considered a theoretical risk.

Biological and epidemiological monitoring

Despite the occasionally conflicting reports of MMA toxicity and carcinogenicity, the biological monitoring of workers occupationally exposed to MMA remains an important consideration for health professionals. Although certain techniques for the biological detection of MMA, such as blood and urine analysis for methanol,⁴⁸ are known to be appropriate even at low-exposure levels, studies of analytical methods that have been previously used suggest that underreporting may have occurred, particularly among those studies that have relied on detector tube technology.⁴⁹ As MMA continues to be used in a variety of medical, surgical, dental, and other workplaces,^{9,50} additional research into its toxic effects following occupational exposure should be considered from both an analytical and an epidemiological perspective.

Conclusion

MMA's long history and widespread use in surgical settings has made it a regular topic of concern for occupational health. As such, its potential adverse effects suggest that MMA should be used with care and that environmental measures should also be taken, particularly in the operating environment, to extract MMA. The surgical technique used and the condition or formula of acrylic cement preparation should be considered to limit the levels of MMA in plasma in patients. Although there is not enough evidence to prove that MMA is carcinogenic to humans, it is certain to have some toxic effects to neuronal cells and on the respiratory system, and it is also known to cause various skin irritations. These effects are harmful enough that surgical staff should be sure to take steps to avoid direct contact with the monomer. In addition to adequate ventilation in the workplace, the adoption

of other sound occupational hygiene principles can help reduce occupational exposures to MMA among surgical staff.

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