Review Article

Local and Systemic Effects of Unpolymerised Monomers

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ABSTRACT

Methyl methacrylate (MMA), a widely used monomer in dentistry and medicine has been reported to cause abnormalities or lesions in several organs. Experimental and clinical studies have documented that monomers may cause a wide range of adverse health effects such as irritation to skin, eyes, and mucous membranes, allergic dermatitis, stomatitis, asthma, neuropathy, disturbances of the central nervous system, liver toxicity, and fertility disturbances.

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Introduction

A material may be said to be *biocompatible* when it has the quality of being non-destructive in the biological environment. It is important to appreciate that this interaction works in both ways such as the effect of the material on the biologic environment and the effects of the biologic environment on the material.[1] All dental biomaterials release substances into the oral and working environment to a varying degree. The biological reactions can take place either at a local level or far removed from the site of contact (i.e., systemically). The latter is a very important consideration. Because it may not always be readily apparent that clinical symptoms such as dermatological, rheumatic or neural reactions could be associated with a biomaterial. Both patients and the dental personnel are exposed to these interactions and the potential risks, with the patient being the recipient of the restorative materials and the dental personnel handing many of the materials on a daily basis. Resin-based dental materials are extensively used today in dentistry. Methyl methacrylate (MMA), a widely used monomer in dentistry and medicine, has been reported to cause abnormalities or lesions in several organs. Experimental and clinical studies have documented that monomers may cause a wide range of adverse health effects such as irritation to skin, eyes, and mucous membranes, allergic dermatitis, stomatitis, asthma, neuropathy, disturbances of the central nervous system, liver toxicity, and fertility disturbances.[2-7] Monomer is highly used in the factory, reconstructive surgeries and dentistry. In dentistry, more than 98% of the restorations are done by the polymers and monomers. The dental staff is at higher risk of adverse reactions to monomers than the patients. The aims of this article are to focus on the toxic effects of different unpolymerized monomers on different systems of body. It will also concern about the prevention of the exposure of different monomers to the patients and the operators in the working field.

Applications of biopolymers in dentistry

General dental applications dentures (bases, liners, tissue conditioners, artificial teeth, temporary restoration in FPD, etc.), cavity restorative materials (composites self cure/light cure), sealants (pulpal, cavity and margin sealants), impression materials (alginate, agar, elastomers, waxes, etc.), cements (resin based cements), dentin bonding agents, orthodontic appliances, habit breaking appliances (nail biting, thumb sucking, etc.), oral and maxil-

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lofacial appliances, cleft palate plates, and maxillary supports, etc., are the examples of Applications of biopolymers in dentistry.

Genetic and Cellular Damage

Several studies have investigated and identified the cytotoxicity and genotoxicity of some of these methacrylates during the last decade. Many dental resins contain a co-monomer such as triethylene glycol dimethacrylate (TEGDMA), which causes gene mutations *in vitro*. The formation of micronuclei is indicative of chromosomal damage and the induction of DNA strand breaks detected with monomers like TEGDMA and 2-hydroxyethyl methacrylate (HEMA). As a consequence of DNA damage, the mammalian cell cycle was delayed in both G1 and G2/M phases, depending on the concentrations of the monomers. Studies demonstrated that monomers reduced the levels of the natural radical scavenger glutathione (GSH), which protects cell structures from damage caused by reactive oxygen species (ROS). Depletion of the intracellular GSH pool may then significantly contribute to cytotoxicity, because a related increase in ROS levels can activate pathways leading to apoptosis. Complementary, cytotoxic, and genotoxic effects of TEGDMA, HEMA and Methacrylate are inhibited in the presence of ROS scavengers like N-acetylcysteine (NAC), ascorbate, and Trolox (vitamin E).[8-13]

In an in vitro study, Bereznowski reported that MMA exerts its toxic effects by interacting with the cell membrane. Additionally, mitochondria are intercellular target organelles and interaction of MMA with the mitochondrial membrane leads to structural and functional damage. The outer membrane was ruptured and the matrix structure was disorganized.[14] Drozdz et al.[15] studied the toxicity of BisGMA and found it genotoxic for human lymphocytes. One study indicated that dentin adhesives were inducers of toxic-genetic events, with the mitotic recombination being the main mechanism of action.[16]

1) Nose

The monomers used in dental resin-based materials are volatile and it is usually possible to smell them in dental clinics. MMA is highly volatile with a vapor pressure of 36-47 hPa at 20°C. MMA is used as a basic material for different resins and plastics, either as a monomer or as a polymer (poly-methyl methacrylate). MMA is an irritating and corrosive substance. The nasal olfactory epithelium is the first target tissue and mucosal degeneration and necrosis are reported at low concentrations. The MMA metabolite methacrylic acid causes lesions of olfactory epithelium. These metabolites are formed enzymatically by carboxylesterase.[17-19]

2) Respiratory systems

Monomer vapor is irritating to the respiratory system. Repeated inhalation may be harmful; lung irritation and serious central nervous system disorders may result.[20] In an animal study, Sokmen and Oktemer showed that when rats were exposed to low concentrations (0.45 ppm) of methylmethacrylate monomer vapor, histopathological manifestations of lungs and trachea were observed. The statistically significant pathologic changes were loss of cilia of trachea and bronchial respiratory epithelium, hyperplasia of peribronchial lymphoid follicles, and respiratory capillary hyperemia. At (sub) lethal concentrations, pulmonary lesions were seen including emphysema, edema, and collapsed lungs. These results demonstrated the importance of ventilation in working places for people who use methylmethacrylate.[21] Lozewicz et al. reported a case of asthmatic reaction immediately occurring following provocation by MMA. After several years of this work, he developed chest tightness, dyspnea, and cough which persisted for several hours after exposure to even small amounts of MMA.[22]

3) Irritant contact dermatitis

Depending on the concentration and exposure time, the reaction can vary from erythema to necrosis. The monomer may exert a direct cytotoxic effect on the cells in the superficial skin or mucosa, most often corresponding exactly with the site of application. Repeated contact with low doses of primary irritants over extended time periods can develop cumulative insult dermatitis, and is caused by a gradual deterioration of the natural barriers. Such exposure conditions are mainly seen in occupational settings.[23,24]

One example is the 'three-finger syndrome'; this type of reaction is often seen on the first three fingers of the left hand, in right-handed persons. These three fingers are exposed to spray from bonding resins when used to reflect the patients' lips during treatment and may also have been in

contact with the remnants of spills on the outside of squeeze-bottles containing the liquid monomers.[25-27] Gloves used for prevention of microbial contamination do not protect from exposure to monomers in dental materials. The monomers penetrate vinyl and latex gloves within a few minutes, and may therefore be in contact with the skin for an extended time period.[28-31]

4) Allergic contact dermatitis

Most components of dental materials are of low molecular weight. By acting as haptens and combining with body proteins, they may form complete antigens capable of inducing sensitization of immune-competent cells. The risk of sensitization depends on various factors such as the type and concentration of the substance and the type and condition of the contacting tissues.[32] The actual contact site with the allergen is usually the first place where clinical symptoms develop. However, contact-sensitized individuals may develop a number of symptoms when exposed to the allergen systemically, either orally or by inhalation, infusion, transcutaneous or transmucosal absorption.[28,33-36]

5) Neuropathy

A direct neurotoxic action is possible in dental technicians, who handle monomeric methylmethacrylate resin with bare fingers. Methyl methacrylate is absorbed through the skin and is known to affect the myelinated nerve function.[37] Methylmethacrylate is a cutaneous irritant and penetrates skin effectively. Sensory conduction velocities in the finger nerves were slowed in conjunction with the reported numbness. The neurological complaints were more common among those with a longer career and heavier exposure. Biopsies from a dental laboratory technician who had been preparing dental prostheses for more than 30 years have shown direct pathological effects of methyl methacrylate on nerve fibers, resulting in a sensorimotor peripheral neuropathy.[38,39]

Sadoh DR reported a case of occupational exposure of monomer in which a dental technician, who was in the profession for 14 years, developed a generalized neuropathy.[40]

6) Contact stomatitis

Contact allergy results from a delayed hypersensitivity reaction that occurs when antigens of low molecular weight penetrate the skin or mucosa of susceptible individuals. When allergic reactions were noted, they were described as white, necrotic lesions on the mucosa; either as small, multiple lesions or as large ulcers mimicking aphthous stomatitis.

Although allergic responses to the methacrylate in general are rare, mostly, auto-polymerizing (self-cure) resins cause these reactions more often rather than by the heat-cured ones.[41] These antigens combine with epithelial-derived proteins to form haptens that bind to Langerhan's cells, migrate to the regional lymph nodes and present the antigen to T lymphocytes, which become sensitized and undergo clonal expansion. After re-exposure to the antigen, sensitized individual develop an inflammatory reaction confined to the site of contact.[42] Contact stomatitis is unknown, but it is believed to be significantly less common than contact dermatitis for the following reasons:

a. Saliva quickly dilutes potential antigens and physically washes them away and digests them before they can penetrate the oral mucosa.

b. Since the oral mucosa is more vascular than the skin, potential antigens that do penetrate the mucosa are rapidly removed before an allergic reaction can be established.[43]

Direct application of relining materials in the oral cavity and subsequent release of high concentrations of monomers from the initially cured resins may severely irritate the mucosa.[44,45] By immersion of acrylic resin dentures in hot water (50°C) for one hour before insertion into the oral cavity can minimize the possible risk of sensitization or allergic reactions by acrylic dentures. This procedure is particularly important with the auto-polymerized resins used either for rebasing or as a denture base material.[43]

7) Effects on bone

The effects on bone includes inhibition of proliferation, alkaline phosphatase (ALP) activities, the expression of osteocalcin, and mineralized tissue formation at 200 microgm/L or more with HEMA. These results indicate that HEMA at the concentrations similar to that observed in elution tests affected osteoblastic proliferation, differentiation, and mineralization, suggesting that elution of unreacted HEMA could be the main component of the adverse effects of resin-modified glass-ionomer (RMGIC) on osteoblast-like cells and influences of resin restoratives on the osteoblasts are possibly

dependant on release characteristics of unpolymerised monomers.[46]

8) Gastrointestinal system

Tansy et al. observed an inhibition of gastrointestinal motility by breathing the methylmethacrylate monomer.[47] They assumed that this effect might be occurring due to the cardiopulmonary mechanism. Ingestion can cause gastrointestinal irritation, nausea, vomiting and diarrhea. Ingestion of this product may also result in adverse central nervous system effects including headache, sleepiness, dizziness, slurred speech and blurred vision.

9) Genital tissue

It is believed that the liver couldn't metabolize the MMA at both high (32%) and low (4%) concentration by its nonspecific carboxylesterase enzyme. The MMA that circulates in the blood is associated to the seminal vesicle atrophy either through its direct action on testosterone secretion or its possible indirect action on testosterone through the hypophysis. This hypothesis is still to be demonstrated by further studies which will address the concomitant effects of MMA on the pituitary gland, the testis and the seminal vesicle.[2]

10) Effect on embryo

Exposure of pregnant women to a working environment containing these esters is always a potential health threat, since these monomers have been found to act as embryotoxic and teratogenic agents.[48] Clinically there have been no reports indicating that dental monomer directly affects the fetus. However, judging from the fact that BISGA-MA and MTYA have been shown to exhibit some degrees of cytotoxicity, appropriate consideration need to be taken while developing the product using this monomer.[3,9,49-51]

Ways of reducing exposure[31,45,52]

1. In dental laboratories and operating room, monomers vapors shall not exceed 100 ppm, and exhausting systems should be used following Occupational Safety and Health rules.
2. Wear protective work clothing, laboratory coat or apron, safety glasses and wear impervious gloves.
3. Containers should be tightly covered, to prevent evaporation.
4. Exposure indication batches should be made to indicate the amount of monomer exposure in the working area.
5. Wash thoroughly immediately after exposure to monomer and at the end of the work shift.
6. Flush away with running water immediately after contact with them through eye or skin contact.
7. Remove contact lenses if it can be done safely and immediately flush eyes with water for at least 15 minutes, while holding eyelids open.
8. Move affected individual to non-contaminated air. Loosen tight clothing such as collar, tie, belt or waistband to facilitate breathing.
9. In case of spill, clean up spill using appropriate sorbent materials.
10. Resin-based materials should be adequately cured.
11. Vacuum mixing system for monomer should be used as compared to handmixing, to reduce the monomer fumes.[52]
12. Posthazard and warning information in the work area should be install.
13- Seek medical attention when any symptom develops and persists.

Conclusion

Resin-based dental restorative materials are extensively used today in dentistry. However, significant concerns still remain regarding their biocompatibility. In spite of their good physical and mechanical properties and excellent esthetic characteristics, may, in turn, cause some side effects. The side effects may lead to severe lesions in oral cavity or far from the application place of the materials. Techniques should be employed to reduce patients, doctors, nurses and other medical staff contact with monomer exposure during dental procedures in order to reduce the risks of possible complications.

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