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Nasal mucosa inflammation induced by inhalation of methyl methacrylate acrylic prostheses: In Vivo study

Inflamação da mucosa nasal induzida pela inalação de metil metacrilato em próteses acrílicas: estudo *In Vivo*

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ABSTRACT

Objective: The aim of this study was to determine, through histological analysis, the inflammatory effects of inhalation exposure to MMA on the nasal mucosa of mice. **Material and Methods:** This study involved an in vivo experiment using fifteen white mice (Mus musculus), which were randomly assigned to three groups. Group 1 served as the negative control, Group 2 was exposed to MMA for one week, and Group 3 was exposed to MMA for three weeks. Mice were exposed to MMA via inhalation for one and three weeks, six hours every day, five days a week. A semi-quantitative scoring system was used to evaluate the histology of the nasal mucosa, and the thickness of the nasal mucosa was also measured. The evaluation was conducted in five different fields of view, and the average score was documented. Data were analyzed statistically. The Shapiro–Wilk test was used to assess normality. Depending on distribution, group comparisons were performed using one-way ANOVA followed by LSD post hoc test or Kruskal–Wallis followed by Mann–Whitney post hoc test. A p-value <0.05 was considered statistically significant. **Results:** Group 1's mucosal histology evaluation was within normal bounds. Group 2 showed nasal mucosa with mild histological damage. Group 3 showed nasal mucosa with moderate histological damage. Measurement of the thickness of the nasal mucosa of mice exposed to MMA showed an increase in mucosal thickness in both groups 2 and 3. In group 3, the thickness of the nasal mucosa increased more significantly. There was a significant difference between the three groups. **Conclusion:** Inhalation exposure to MMA leads to nasal mucosal inflammation that correlates with the duration of exposure, with mild inflammation observed after one week of exposure and moderate inflammation after three weeks.

KEYWORDS

Histology; Inhalation; Methyl methacrylate; Nasal mucosa; Toxicity.

RESUMO

Objetivo: O objetivo deste estudo foi determinar, por meio de análise histológica, os efeitos inflamatórios da exposição por inalação ao metil metacrilato (MMA) na mucosa nasal de camundongos. **Material e Métodos:** Este estudo envolveu um experimento *in vivo* com quinze camundongos brancos (*Mus musculus*), distribuídos aleatoriamente em três grupos. O Grupo 1 serviu como controle negativo; o Grupo 2 foi exposto ao MMA por uma semana; e o Grupo 3 foi exposto ao MMA por três semanas. Os camundongos foram expostos ao MMA por inalação durante uma e três semanas, seis horas por dia, cinco dias por semana. Um sistema de pontuação semiquantitativa foi utilizado para avaliar a histologia da mucosa nasal, e a espessura da mucosa nasal também foi medida. A avaliação foi realizada em cinco campos de visão diferentes, e a média das pontuações foi registrada. Os dados foram analisados estatisticamente. O teste de Shapiro–Wilk foi utilizado para avaliar a normalidade. Dependendo da distribuição, as comparações entre grupos foram realizadas utilizando ANOVA de uma via seguida pelo teste post hoc LSD ou Kruskal–Wallis seguido pelo teste post hoc de Mann–Whitney. Um valor de $p < 0,05$ foi considerado estatisticamente significativo. **Resultados:** A avaliação histológica da mucosa do Grupo 1 estava dentro dos padrões normais. O Grupo 2 apresentou mucosa nasal com leve dano histológico. O Grupo 3 apresentou mucosa nasal com dano histológico moderado. A medição da espessura da mucosa nasal dos camundongos expostos ao MMA mostrou aumento da espessura mucosa nos Grupos 2 e 3. No Grupo 3, o aumento da espessura da mucosa nasal foi significativo. Houve diferença significativa entre os três grupos. **Conclusão:** A exposição por inalação ao MMA provoca inflamação da mucosa nasal que se correlaciona com a duração da exposição, com inflamação leve observada após uma semana de exposição e inflamação moderada após três semanas.

PALAVRAS-CHAVE

Histologia; Inalação; Metil metacrilato; Mucosa nasal; Toxicidade.

INTRODUCTION

Currently, the use of Polymethyl methacrylate (PMMA)-based materials offers significant advantages in the fields of dentistry and orthopedic prosthetics, as well as in ophthalmology and maxillofacial surgery. In dentistry, MMA is the main ingredient in many dental resins, including those found in dental composites, dentures, and temporary crowns. Inhaling highly volatile MMA vapor is the primary way that people are exposed to MMA monomers at work, especially dental professionals and laboratory staff [1-3].

Methyl methacrylate (MMA) monomer is a liquid component of PMMA that is colorless, volatile, and has a pungent odor [4,5]. When handling acrylic resins, the MMA monomer can evaporate, leading to potential harmful effects from inhalation. Exposure to MMA inhalation can irritate lung tissues and the respiratory tract, leading to symptoms such as coughing, sore throat, and headaches, while also affecting the central nervous system (CNS), causing confusion, dizziness, and, in severe cases, loss of consciousness [6,7].

As the initial line of defense, airway cells—including bronchial epithelial cells—protect the host from harmful inhalants. Permeability of the epithelium is essential for tissue homeostasis [8]. After entering the body, MMA molecules interact with nucleophilic targets in the cell, including proteins, DNA, and glutathione, because of the electrophilic carbon atoms in their chemical structure. Production of reactive oxygen species may occur, varying based on the level of exposure to MMA during this interaction. When the levels of these species surpass the body's antioxidant defenses, oxidative stress occurs. Oxidative stress can damage all cellular components, including DNA and the cell membrane, and the propagation of this damage may lead to harmful consequences for the organism. For instance, malondialdehyde (MDA), a byproduct of lipid peroxidation in cell membranes, possesses mutagenic and carcinogenic properties [1].

A study found that rats exposed to 100 ppm of methyl methacrylate for two years showed inflammatory changes, degeneration, and atrophy in the olfactory epithelium, while no adverse effects were noted at 25 ppm. However, the respiratory nasal epithelium did not show any changes at the 100 ppm level. In contrast, exposure to 400 ppm of methyl methacrylate led to inflammation in the respiratory nasal epithelium, as observed through microscopy. In a different study, rats exposed to 110 ppm of methyl methacrylate for 6 hours experienced slight degeneration and necrosis in the olfactory epithelium, but this was subsequently followed by epithelial regeneration. Meanwhile, no lesions were detected in the respiratory nasal epithelium [9]. Only a few studies have investigated the potential effects of MMA exposure, particularly on the nasal mucosa. This study aimed to determine the histological effects of MMA inhalation exposure on nasal mucosal inflammation in mice.

MATERIAL AND METHODS

This study was an experimental laboratory investigation that used a post-test only group design. Fifteen healthy male white mice (Mus musculus, DDY strain, Deutsch Danken and Yoken, Japan), aged three months and weighing approximately 20–30 g, were used as experimental subjects in this study. The sample size was determined using the following formula: $Min(Nt)=Min(n)\times k=k(10/k+1)$ and $Max(Nt)=Max(n)\times k=k(20/k+1)$, where Nt is the total number of samples, n is the number of samples per group, and k is the number of experimental groups. In this study, k=3 gorups, the samples sizes per group are as follows: $Min(n)=10/3+1=4.3=rounded\ down\ to\ 4$, $Max(n)=20/3+1=7.7=rounded\ up\ to\ 8$. Then, $Min(Nt)=Min(n)xk=4x3=12$, $Max(Nt)=Max(n)xk=8x3=24$. Based on this study, a sample size of 4 to 8 animals per group is recommended, yielding a total of 12 to 24 animals across all groups [10]. To minimize selection bias, mice were allocated to experimental groups through simple random sampling, where assignments were determined by randomly drawing from a container, giving each animal an equal chance of selection. Mice were inhaled with MMA for six hours every day, five days a week. Characteristics of mice aged 3 months with a body weight of ±20-30 g and healthy. Before the experiment started, the mice were acclimated for a week. Every participant received a regular diet consisting of 67.2% carbs, 12.7% protein, and 5.3% fat, or 10% of their body weight, along with unrestricted access to water. As much food and water as possible were supplied.

The nasal mucosa in mice was examined through histological assessment using a semi-quantitative scoring system, and its thickness

was measured. Although histological scoring was blinded, the study was not fully blinded, as group allocation and treatment were unblinded, and the statistician was aware of group identities. This lack of blinding in certain stages may introduce bias. The assessment was carried out with the aid of an Olympus CX33 microscope, a Sony Beta 3.1 MP Sony Exmor CMOS sensor microscope camera, and the BetaViewInk program. Assessment was performed at 40x objective magnification (400x magnification) in 5 different fields of view and reported as an average score. The assessment is based on a histopathological image scoring system for the nasal mucosa, as presented in Table I [11].

To assess whether the data met the assumption of normality required for ANOVA, we conducted the Shapiro-Wilk test on each group. Based on the results, we proceeded with either a one-way ANOVA (for normally distributed data) or a Kruskal-Wallis test (for non-normally distributed data). The Compare Group with LSD and Mann Whitney post hoc tests were then conducted were then conducted. All statistical analyses were performed using SPSS version 26, and significance was set at $p < 0.05$. Table I displays the nasal mucosa damage scoring system.

This study was carried out in the Anatomical Pathology Laboratory, Faculty of Medicine, Andalas University, Padang, Indonesia, and the Pharmacology Laboratory, Faculty of Pharmacy, Andalas University.

RESULTS

This study was conducted in order to determine the effects of MMA inhalation on the nasal mucosa of mice. MMA inhalation exposure was conducted for one and three weeks, six hours a day, five days a week. To calculate the MMA exposure dose, the MMA weight was measured daily before and after treatment. The average exposure to MMA per day per mouse was ±23.9 ppm.

Nasal mucosa damage in mice exposed to methyl methacrylate monomer was assessed based on histological scores across five different fields of view. The average score was reported. Group 1 exhibited normal nasal mucosal histology, while Group 2 showed mild, and Group 3 moderate, histological damage. Significant differences were observed between the three groups with $p<0.05$ (Table II).

Histological analysis of nasal mucosa following methyl methacrylate exposure revealed progressive tissue damage across experimental groups, as shown in Figure 1. Group 1 showed normal pseudostratified ciliated epithelium, while Group 2 exhibited epithelial thickening and signs

Table I - Nasal mucosa damage scoring system

Score	Parameters of the level of nasal mucosa damage	Level
0	No leukocyte infiltration was seen, no epithelial hyperplasia or goblet cells were seen, and no cell degeneration was seen.	Normal
1	Mild leukocyte infiltration, mild hyperplasia of epithelium and goblet cells, slight degeneration of cells.	Slight inflammation
2	Moderate infiltration of leukocytes, moderate hyperplasia of epithelium and goblet cells—some cells undergo cell degeneration.	Moderate inflammation
3	Dense infiltration of leukocytes, marked hyperplasia of the epithelium and goblet cells—some cells appear to have undergone cell degeneration.	Severe inflammation

Table II - Histological damage assessment of the nasal mucosa of mice exposed to methyl methacrylate monomer

No	Group/Treatment	Nasal mucosa histological damage score		Statistical analysis		
		Group mean±sd	Level of damage	Kruskal-wallis	Compare Group	Mann-Whitney
1	Group 1 (control)	0.12±0.11	Normal	p = 0.002	Group 1 & 2	p= 0.008*
2	Group 2 (1 week treatment)	0.80±0.24	Slight inflammation		Group 2 & 3	p= 0.007*
3	Group 3 (3 weeks treatment)	2.04±0.26	Moderate inflammation		Group 3 & 1	p= 0.008*

*indicates that the difference is statistically significant $p < 0.05$.

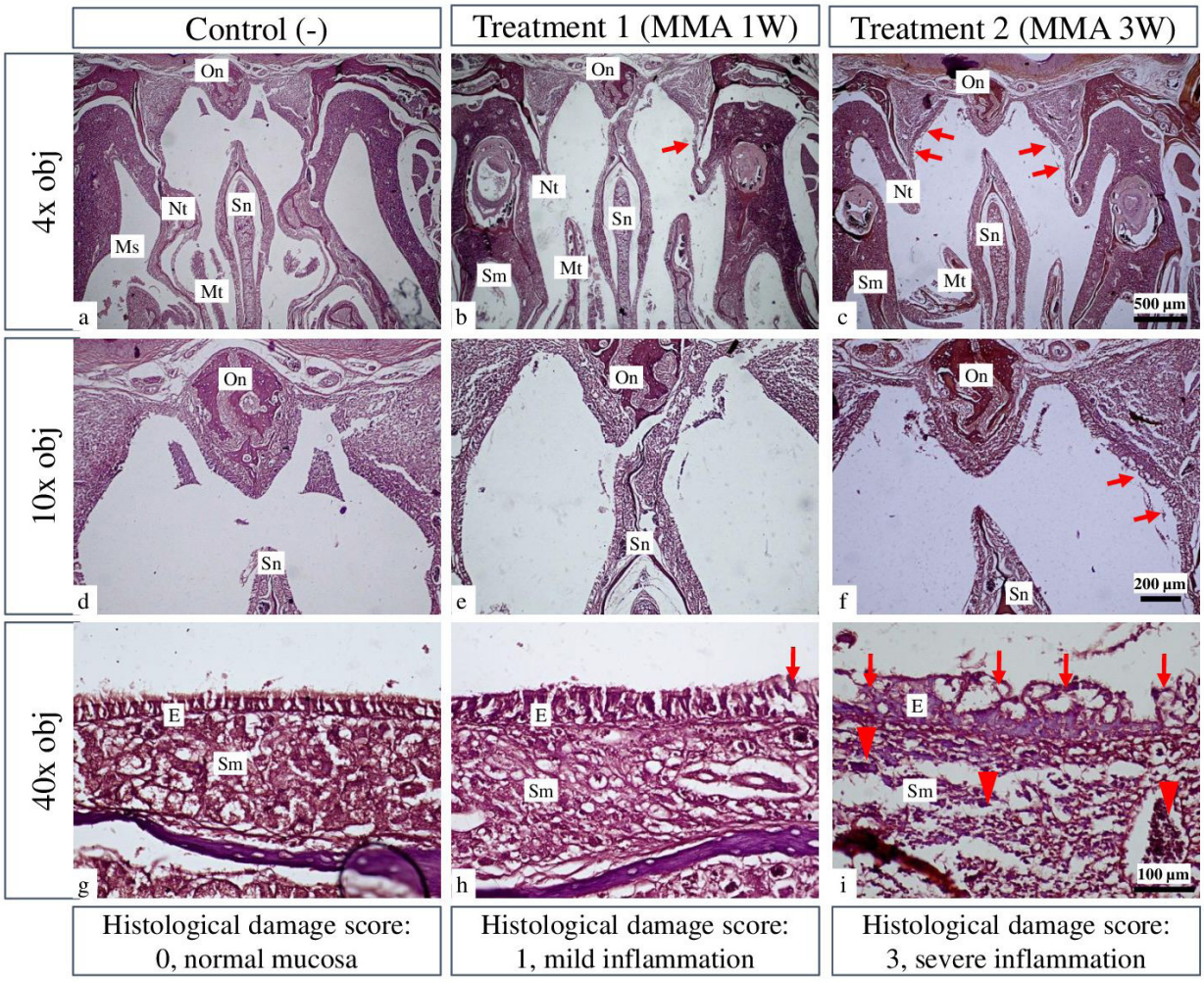

Figure 1 - Histological changes in the nasal mucosa following inhalation exposure to methyl methacrylate monomer. Coronal section of mouse nasal tissue at level II naso-maxillo turbinate. Showing nasal septum (Sn), ossea nasalis (On), nasal turbinate (Nt), maxillary turbinate (Mt), and maxillary sinus (Ms). Group 1 (a, d, g) shows the nasal mucosa lined with pseudostratified ciliated epithelium (E) and underneath it is submucosal tissue (Sm). Group 2 (b, e, h) shows mucosal changes with increased epithelial thickness due to cell hyperplasia, as well as areas of mucosal damage with degeneration and death of epithelial cells (↓). Sub mucosa with distribution and clusters of inflammatory cells (▼). Group 3 (c, f, i) showed more significant mucosal damage. Hematoxylin eosin, top panel original magnification 40x, middle panel original magnification 100x, bottom panel original magnification 400x.

of cell degeneration. In Group 3, mucosal damage was more extensive, with widespread epithelial necrosis and intense inflammatory infiltration in the submucosa.

Measurement of nasal mucosa thickness in mice exposed to MMA showed an increase in mucosal thickness in both group 2 and group 3. The increase in nasal mucosal thickness was more significant in group 3. Statistical tests showed significant differences between the three groups, $p = 0.001$ (<0.05) (Table III).

As illustrated in Figure 2, there was a progressive increase in the thickness of the nasal mucosal epithelium across the exposure groups. Group 1 exhibited normal pseudostratified ciliated epithelium, whereas Group 2 displayed epithelial hyperplasia and areas of mucosal disruption. The most severe thickening was observed in Group 3, indicating a dose-dependent response to MMA inhalation exposure.

DISCUSSION

Normal respiratory function is essential for a healthy life free from morbidity, yet the work environment is often filled with various pollutants, whose effects can vary significantly based on their concentration, duration of exposure, and specific circumstances. Methyl methacrylate, a highly toxic vapor, is particularly prevalent in dental practices [12].

Inhalation represents a significant pathway for exposure to chemicals found in the workplace

Table III - Measurement of the thickness of the nasal mucosa of mice exposed to methyl methacrylate monomer

No	Group/Treatment	Thickness of the nasal mucosa (µm)			
		Group mean ± sd	One-way ANOVA	Compare Group	LSD
1	Group 1 (control)	21.91±1.45	p = 0.001	Group 1 & 2	p = 0.187
2	Group 2 (1 week treatment)	27.05±7.35		Group 2 & 3	p = 0.002*
3	Group 3 (3 weeks treatment)	41.47±6.73		Group 1 & 3	p = 0.000*

*indicates that the difference is statistically significant p < 0.05.

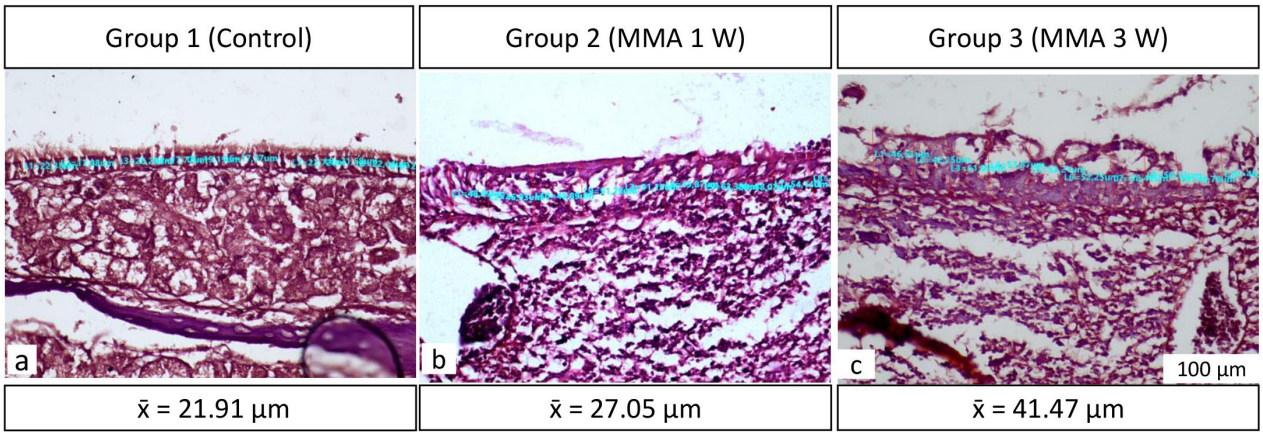

Figure 2 - Measurement of the thickness of the nasal mucosal epithelium of mice exposed to MMA by inhalation. In Group 1, the nasal mucosa is lined by pseudostratified ciliated epithelium (E). Group 2 showed increased epithelial thickness due to cell hyperplasia, accompanied by areas of mucosal damage. Group 3 showed a more significant increase in mucosal epithelial thickness. Hematoxylin eosin, original magnification 400x.

environment [13]. Inflammation that occurs in the nasal mucosa can be caused by infection or the action of toxic, allergic, immunological, or irritant factors [14]. Chemical interaction with the airway lining influences site-specific deposition and damage in rodents that breathe via their noses [15].

We have conducted research on the histological damage to the nasal mucosa resulting from inhalation exposure to MMA. This study showed mild nasal mucosal damage after 1 week of MMA exposure (group 2). Mucosal changes, including cellular hyperplasia and degeneration, as well as epithelial cell death, have been observed (Figure 1). In group 2, there was also an increase in epithelial thickness due to cell hyperplasia accompanied by areas of mucosal damage. Group 3 exhibited more pronounced nasal mucosal damage, accompanied by moderate levels of inflammatory changes. There was also a significant increase in mucosal epithelial thickness. This study is in line with a previous study [16], which reported that group A mice (exposed to MMA in a tightly closed glass room without ventilation) and group B mice (in a ventilated glass room) experienced degeneration and inflammation of the olfactory epithelium. The study was conducted for 6 hours a day, 5 days per week, for 4 weeks at a concentration of 1000 ppm.

Several studies evaluating damage to the respiratory tract, particularly the nasal cavity, have reported findings such as inflammation, glandular atrophy, focal basal cell hyperplasia, and squamous metaplasia of the nasal epithelium. In contrast, the study conducted by Parizi et al. (2005) [17] showed that the thickness of the tracheal epithelium of mice exposed to MMA was similar to that of control mice, and cell adaptations such as atrophy and hypertrophy were not observed. The absence of observed differences in tracheal epithelium compared to nasal findings could be related to the distinct routes of exposure (tracheal vs. nasal), as anatomical and physiological variations may influence tissue susceptibility and response. A mixed inflammatory infiltrate, predominantly composed of lymphocytes, was observed in the tracheal epithelium of both exposed and control mice. However, this finding was not statistically significant when analyzed in relation to inflammation and MMA exposure [17].

The acute oral median lethal dose of MMA in rats is reported to be between 8.4 and 9 g/kg of body weight, suggesting that it has very low acute systemic toxicity. MMA is rapidly hydrolyzed by enzymes and then converted into harmful compounds [3].

The first line of defense for the nasal mucosa is the epithelium [18]. The nasal mucosa's epithelial barrier assists in preserving its functions and homeostasis [19]. Chronic chemical inhalation can lead to disease through a number of mechanisms, including damage of the airway epithelial barrier. The presence of tight junctions between epithelial cells, adherens junctions (AJs), desmosomes, and other compositions facilitate the solid barrier that lines normal airways. The chemical barrier, which consists of cilia and mucus, captures allergies, infections, etc., and stops them from invading the body [8,19]. Damage to the epithelial barrier causes a significant change in appearance, from an inert physical barrier to an active, functional organ that can secrete a wide range of bioactive substances, including complement proteins and cytokines, which help to recruit and regulate various immune cells. Epithelial permeability can actually rise when the integrity of the epithelium is compromised. Thus, immune cells can be activated by invasive exogenous irritants, which will start an immunological response [19]. The production of some inflammatory cytokines during this immune response also compromises the integrity of the epithelial barrier, hence intensifying inflammation [19].

The extent to which the olfactory mucosa lines the nasal cavity varies significantly between species. Less than 5% of the nasal cavities of macaques and humans are lined with olfactory mucosa, compared to over 50% of the nasal cavities of rodents. When compared to primates, rodents are more susceptible to olfactory lesions because of the larger relative size of their olfactory mucosa, which can lead to greater transport of inhaled chemicals to this epithelial subtype. Both the dorsal meatus and the olfactory recess are absent from the less complicated human nasal canal, and the airflow in the human nose differs from that of rats and other species with strong senses of smell (i.e., microsmatic). The fact that rats are obligatory nosebreathers is another significant species difference between humans and rodents that is frequently employed in toxicological research. Rodents may be more susceptible to nasal (portal of entry) effects after inhaling chemicals due to this anatomical restriction [20]. Chemical absorption is influenced by the inspiratory flow rate and vapor solubility (measured by the blood: air partition coefficient). Furthermore, inspiratory flow velocity and particle size affect nasal particle delivery [20].

Although regulatory assessments of acute inhalation toxicity typically rely on in vivo testing, significant anatomical and physiological differences between rodent and human respiratory systems, such as variations in breathing patterns and chemical deposition, complicate the translation of rodent results to predict human inhalation effects [13]. Dental technicians are the healthcare professionals who work most intensively with MMA on a daily basis. As a result, they face a high risk of occupational exposure to MMA vapors [1].

This study has several limitations that should be considered when interpreting the results. First, the duration of MMA exposure in this experiment was relatively short, with the longest exposure period being three weeks. Long-term effects of prolonged MMA inhalation, particularly chronic inflammation or potential tissue damage, were not evaluated and warrant further investigation. Second, the study was conducted in a controlled laboratory setting, and the findings may not fully reflect real-world exposure scenarios, where factors such as environmental conditions, individual susceptibility, and co-exposure to other chemicals may influence the outcomes. Additionally, the study did not explore the potential reversibility of the observed inflammation after cessation of exposure, which is an important aspect of understanding the long-term health risks. Third, the sample size and the use of a single animal model may limit the generalizability of the findings to humans or other species. Future studies should address these limitations by extending the exposure duration, evaluating broader health outcomes, and considering more diverse experimental models. Fourth, this study was not fully blinded, as group allocation and treatment administration were unblinded, and the statistician knew group identities. While histological scoring was blinded, the lack of blinding in other stages may introduce bias.

CONCLUSION

In conclusion, this study demonstrates that MMA inhalation induces nasal mucosal inflammation in a duration-dependent manner in

a rodent model, with mild inflammation observed after one week, moderate inflammation after three weeks, and progressively severe histological damage, including epithelial thickening, associated with prolonged exposure. These effects were statistically significant across all treatment groups, indicating potential health risks in settings with sustained MMA vapor exposure. However, due to anatomical and physiological differences that exist between rodent and human nasal structures, these findings should not be directly extrapolated to human populations. Further research is needed to evaluate the long-term effects of MMA exposure and to inform appropriate occupational safety measures.

Author's Contributions

DA: Conceptualization, Methodology, Investigation, Writing – Original Draft Preparation, Writing – Review & Editing, Supervision, Project Administration, Funding Acquisition. AT: Software, Validation, Formal Analysis, Investigation, Resources, Data Curation, Visualization, Writing – Review & Editing. HA: Investigation, Resources, Data Curation.

Conflict of Interest

No conflicts of interest declared concerning the publication of this article.

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Regulatory Statement

This study has been authorized by the Andalas University Faculty of Pharmacy's research ethics committee under the number 48/UN16.10.D.KEPK-FF/2024.

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