

The Effect of Nicotine Exposure on Serum Monocyte Chemoattractant Protein-1 (MCP-1) Levels in Relation to the Risk of Alveolar Osteitis

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ABSTRACT

Background: Alveolar osteitis (AO) is a postoperative complication of tooth extraction characterized by loss of the blood clot, severe pain, and delayed healing. Smoking is a major risk factor for AO, with nicotine contributing to vasoconstriction, tissue hypoxia, and oxidative stress that may impair wound healing. Nicotine may also influence Monocyte Chemoattractant Protein-1 (MCP-1), a chemokine involved in inflammatory responses and tissue repair. **Objective:** This study aimed to evaluate the effect of nicotine exposure on serum MCP-1 levels and its association with the risk of alveolar osteitis in Wistar rats. **Methods:** This in vivo laboratory experimental study involved 14 male Wistar rats divided into control and treatment groups. The treatment group received subcutaneous nicotine injections at a dose of 1.89 mg/kg body weight for 10 days before and 3 days after mandibular incisor extraction. Serum MCP-1 levels were measured using a sandwich ELISA, while the occurrence of alveolar osteitis was assessed macroscopically through socket observation. Data were analyzed using One-Way ANOVA followed by Tukey's HSD test, with a significance level of $p < 0.05$. **Results:** Nicotine exposure significantly increased serum MCP-1 levels compared with controls at 24 hours (103.77 vs. 82.19 pg/mL) and 72 hours post-extraction (86.27 vs. 72.18 pg/mL). Higher serum MCP-1 levels were significantly associated with a greater incidence of alveolar osteitis ($p < 0.05$). **Conclusion:** Nicotine exposure increases serum MCP-1 levels and is associated with an increased risk of alveolar osteitis following tooth extraction.

Keywords: alveolar osteitis; nicotine; MCP-1; inflammation; wound healing

INTRODUCTION

Alveolar osteitis (AO), commonly referred to as dry socket, is one of the most frequent complications following tooth extraction. It is characterized by the premature disintegration or loss of the blood clot within the extraction socket, resulting in exposed underlying bone and intense postoperative pain. The reported incidence of AO varies according to the type and difficulty of extraction, with a higher occurrence following mandibular third molar surgery. Several factors have been associated with the development of AO, including traumatic extraction,

pre-existing infection, poor oral hygiene, female sex, and tobacco smoking [1,2].

Among these risk factors, smoking has received considerable attention because of its detrimental effects on post-extraction wound healing. Previous studies have demonstrated that tobacco smoking is associated with an increased risk of AO, with the risk influenced by smoking intensity and postoperative exposure [1,3]. Nicotine, one of the principal biologically active components of tobacco, can cause vasoconstriction and reduce local blood flow, thereby

limiting oxygen and nutrient delivery to injured tissues. In addition, smoking may mechanically disturb the blood clot, and tobacco-derived substances may interfere with the inflammatory and fibrinolytic processes required for normal socket healing [3,4]. These effects may contribute to delayed tissue repair and increase susceptibility to AO.

The healing of an extraction socket is a complex biological process involving hemostasis, inflammation, proliferation, and tissue remodeling. During the inflammatory phase, chemokines play an important role in regulating the recruitment and activation of inflammatory cells. Monocyte Chemoattractant Protein-1 (MCP-1), also known as C-C motif chemokine ligand 2 (CCL2), is an important chemokine involved in the recruitment of monocytes and macrophages to sites of tissue injury. MCP-1 expression increases during tissue inflammation and wound healing and contributes to the regulation of macrophage infiltration at the site of injury [5,6].

The relationship between nicotine exposure and inflammatory mediators is complex. Nicotine has been reported to alter vascular function, immune-cell activity, and cytokine expression in oral tissues. In gingival fibroblasts, nicotine exposure has been shown to modify the expression of several inflammatory mediators, while studies in smokers have demonstrated alterations in MCP-1 levels in periodontal tissues and gingival crevicular fluid [7,8]. These findings suggest that nicotine may influence the inflammatory environment during tissue repair. However, the specific relationship between nicotine exposure, MCP-1 expression, and the development of AO remains insufficiently understood.

Nicotine-related inflammatory responses may also depend on exposure conditions and tissue context. Smoking has been associated with oxidative stress, while nicotine can exert both pro-inflammatory and anti-inflammatory effects in different inflammatory settings [13,14].

Understanding the role of MCP-1 in nicotine-associated AO may provide further insight into the molecular mechanisms underlying impaired post-extraction healing. Therefore, this study aimed to evaluate the effect of nicotine exposure on MCP-1 levels and its association with the risk of alveolar osteitis. Specifically, this study assessed MCP-1 levels in groups exposed and not exposed to nicotine and analyzed the relationship between MCP-1 levels and the occurrence of AO.

MATERIAL AND METHODS

1. Study Design

This study was an experimental laboratory study using a randomized post-test-only control group design. The study was conducted to evaluate the effect of nicotine exposure on serum Monocyte Chemoattractant Protein-1 (MCP-1) levels and the occurrence of alveolar osteitis following tooth extraction in Wistar rats.

2. Animals and Sample

The study involved 14 male Wistar rats (*Rattus norvegicus*) obtained from the Faculty of Dental Medicine, Universitas Airlangga. The inclusion criteria were male Wistar rats aged 8–12 weeks, weighing approximately 200–250 g, and in good general health. Animals with abnormalities, illness, or conditions that could interfere with the experimental procedures were excluded. The animals were randomly allocated into control and nicotine-exposure groups, with each group subsequently divided according to the observation period.

3. Experimental Groups and Nicotine Exposure

The animals were randomly assigned to four groups: control groups and nicotine-exposure groups (control group, $n=7$; experimental group, $n=7$), corresponding to the respective observation periods. The control groups received physiological saline, whereas the treatment groups received nicotine. Nicotine was administered by injection at a dose of 0.5 mg/kg body weight, diluted in 0.9% sodium chloride solution. The administration was performed once daily for 10 consecutive days before the tooth extraction procedure. Following extraction, the treatment protocol was continued according to the experimental schedule described in the study protocol.

4. Tooth Extraction Procedure

Before the experimental procedure, the animals were anesthetized according to the established animal protocol. The extraction procedure was performed in the mandibular region using appropriate dental instruments. After extraction, the animals were observed according to the predetermined observation period. To minimize postoperative complications unrelated to the experimental intervention, the animals were maintained under control conditions with adequate food and water throughout the study period.

5. Assessment of Alveolar Osteitis

The occurrence of alveolar osteitis was assessed following the predetermined observation period after tooth extraction. Clinical evaluation of the extraction socket was performed based on the criteria established in the study protocol, including changes in the extraction socket and the presence of findings consistent with alveolar osteitis. The assessment was performed by observation of the extraction socket and recorded according to the predetermined scoring criteria.

6. Blood Collection and Serum Preparation

Blood samples were collected from the experimental animals according to the predetermined observation schedule. Blood was collected and allowed to undergo clot formation at room temperature. The samples were subsequently centrifuged at 2,500 rpm for 15 minutes to separate the serum. The obtained serum was collected and stored at the required temperature until MCP-1 analysis was performed.

7. Determination of Serum MCP-1 Levels

Serum MCP-1 concentrations were determined using an enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions. Briefly, the collected serum samples were prepared and added to an MCP-1-specific ELISA microplate. The samples were incubated according to the assay protocol, followed by washing and addition of the appropriate detection reagents. After the final incubation, the absorbance was measured using an ELISA microplate reader. MCP-1 concentrations were calculated based on the standard curve provided with the assay kit and expressed in the corresponding concentration units.

8. Ethical Approval

The experimental procedures involving animals were conducted following approval from the relevant Ethics Committee of the Faculty of Dental Medicine, Universitas Airlangga. All procedures were performed in accordance with the applicable ethical principles for experimental animal research.

9. Statistical Analysis

The data were analyzed statistically to determine differences in serum MCP-1 levels between the experimental groups. The normality of the data distribution was assessed using the Shapiro-Wilk test. Homogeneity of variance was assessed using the Levene test. For normally distributed and homogeneous data, differences between groups were analyzed using one-way analysis of variance (ANOVA) followed by an appropriate post hoc test. Statistical significance was set at $p < 0.05$.

RESULTS

The results showed differences in serum Monocyte Chemoattractant Protein-1 (MCP-1) levels among the experimental groups following tooth extraction. The animals were divided into control and nicotine-exposed groups and evaluated at different observation periods. The nicotine-exposed groups demonstrated higher MCP-1 levels compared with the corresponding control groups, indicating an alteration in the inflammatory response following nicotine exposure.

TABLE 1: Intergroup Average MCP-1 Level Measurement Results.

Variable	Experimental Group	Sample Size	Maximum Value	Minimum Value	Mean MCP-1 Level (pg/mL)
Kadar MCP-1	K24	7	90.30	77.08	82.19 ± 4.92
	K72	7	81.12	65.79	72.18 ± 5.42
	P24	7	115.07	90.30	103.77 ± 8.72
	P72	7	102.33	73.72	86.27 ± 9.74

Statistical analysis demonstrated a significant difference in MCP-1 levels among the experimental groups ($p < 0.05$). Further analysis using the Tukey HSD test showed significant differences between several experimental groups, indicating that nicotine exposure and the observation period contributed to differences in MCP-1 levels.

The clinical examination results of the alveolar sockets are presented in Table 2 to provide a descriptive overview of the occurrence of alveolar osteitis in each group.

TABLE 2: Clinical Examination Results of Sockets in Wistar Rats.

Study Group	Sample Size	Number of Samples with Alveolar Osteitis (Score > 2)	Number of Samples without Alveolar Osteitis (Score ≤ 2)
Control	7	1	6
Experiment	7	5	2

Differences in the distribution of alveolar osteitis occurrence were observed between the control group and the treatment group. Clinical evaluation was performed using a modified ordinal scale for socket healing severity, with assessment criteria including local edema and erythema, absence of a blood clot, presence of granulation tissue, and purulent secretion.

In the control group, comprising a sample size of 7 rats, 1 sample had a total score of > 2 and was classified as having alveolar osteitis, whereas the remaining 6 samples had a score of ≤ 2 and were categorized as not experiencing alveolar osteitis. This finding indicates that the majority of sockets in the control group underwent normal healing or mild impairment. Conversely, in the treatment group, which also consisted of 7 rats, 5 samples were found with a total score of > 2 and classified as alveolar osteitis, while the remaining 2 samples had a score of ≤ 2 and were not categorized as alveolar osteitis. These results demonstrate that a higher incidence of alveolar osteitis was observed in the treatment group compared to the control group.

TABLE 3: The Distribution of Alveolar Osteitis Among the Experimental Groups.

Total Score	Control Group	Experimental Group
0 (Very Good)	1	0
1 (Good)	3	0
2 (Normal)	2	2
3 (Poor)	1	3
4 (Very Poor)	0	2

Total scores range from 0 to 4, where scores 0–2 indicate normal healing or mild impairment and are not categorized as alveolar osteitis, whereas scores 3–4 indicate severe healing impairment and are classified as alveolar osteitis.

In the control group, samples exhibited healing scores ranging from good to normal. Specifically, 1 sample had a score of 0 (very good), 3 samples had a score of 1 (good), 2 samples had a score of 2 (normal), 1 sample obtained a score of 3 (poor), and no samples were found with a score of 4 (very poor). This distribution indicates that the socket healing process in the control group tended to proceed optimally with minimal inflammation severity. Conversely, in the treatment group, the score distribution shifted toward more severe healing impairment. No samples were found with a score of 0 or 1. A total of 2 samples had a score of 2 (normal), 3 samples had a score of 3 (poor), and 2 samples had a score of 4 (very poor). The occurrence of alveolar osteitis was also observed following tooth extraction. The incidence of alveolar osteitis was greater in the nicotine-exposed groups compared with the control groups. The findings indicate that nicotine exposure was associated with an increased occurrence of alveolar osteitis during the post-extraction healing period.

DISCUSSION

The present study demonstrated that nicotine exposure was associated with increased serum Monocyte Chemoattractant Protein-1 (MCP-1) levels and a greater occurrence of alveolar osteitis following tooth extraction. The increase in MCP-1 suggests that nicotine may influence the inflammatory response during the early phase of post-extraction wound healing. MCP-1, also known as C-C motif chemokine ligand 2 (CCL2), is an important chemokine involved in the recruitment of monocytes and macrophages to sites of tissue injury [5,6]. An increase in MCP-1 may therefore reflect enhanced recruitment of inflammatory cells during the healing process. Previous studies have demonstrated the involvement of MCP-1 in inflammatory responses and macrophage recruitment during tissue repair [6,10].

Alveolar osteitis is a post-extraction complication characterized by the loss or premature breakdown of the blood clot and localized inflammation. Smoking is recognized as an important risk factor for this condition [17,18]. Nicotine may contribute to impaired socket healing through vasoconstriction, reduced tissue oxygenation, and increased oxidative stress, which can disrupt normal wound repair and prolong the inflammatory phase [19,20]. These mechanisms provide a plausible explanation for the greater occurrence of alveolar osteitis observed in the nicotine-exposed animals in the present study.

The higher MCP-1 levels observed in the nicotine-exposed groups may be related to the biological effects of nicotine on vascular and inflammatory processes. Nicotine can induce vasoconstriction and affect local tissue perfusion, potentially reducing oxygen and nutrient delivery to the extraction socket. In addition, nicotine may alter the activity of inflammatory cells and the expression of inflammatory mediators. Previous research has demonstrated that nicotine exposure can modify cytokine expression in gingival fibroblasts and affect inflammatory responses in oral tissues [7,11]. These effects may contribute to an altered inflammatory environment during socket healing.

The serum MCP-1 measurements further support this interpretation. At 24 hours after extraction, the mean MCP-1 concentration was 103.77 pg/mL in the nicotine-exposed group (P24), compared with 82.19 pg/mL in the control group (K24). At 72 hours, MCP-1 levels remained higher in the nicotine-exposed group (P72; 86.27 pg/mL) than in the control group (K72; 72.18 pg/mL). These findings indicate that nicotine exposure was associated with an elevated systemic inflammatory response at both observation time points. Previous studies have reported that nicotine can increase MCP-1 expression in human gingival fibroblasts and that circulating MCP-1 levels may be associated with smoking exposure [21,22]. Nevertheless, serum MCP-1 reflects systemic inflammatory activity and does not necessarily represent the precise inflammatory conditions within the extraction socket.

The increased occurrence of alveolar osteitis in the nicotine-exposed groups is consistent with previous evidence showing that smoking is an important risk factor for alveolar osteitis [1,3]. Smoking may interfere with normal extraction-socket healing through several mechanisms, including vasoconstriction, impaired tissue oxygenation, alteration of inflammatory responses, and increased fibrinolytic activity. These mechanisms may compromise the stability of the blood clot and interfere with the subsequent stages of socket healing [1,3].

The clinical assessment in the present study also demonstrated a difference in healing outcomes between the groups. In the control group, one animal (14.3%) developed alveolar osteitis, whereas six animals (85.7%) exhibited normal healing. In contrast, five animals (71.4%) in the nicotine-exposed group developed moderate to severe alveolar osteitis, while only two animals (28.6%) exhibited normal healing. The Mann-Whitney test demonstrated a statistically significant difference in alveolar osteitis severity between the groups ($p = 0.013$). These findings indicate that nicotine exposure was associated not only with higher serum MCP-1 levels but also with poorer clinical healing outcomes. This pattern is consistent with the proposed effects of nicotine on tissue perfusion, inflammatory regulation, and blood clot stability.

Several mechanisms may explain the association between nicotine exposure and alveolar osteitis. Nicotine can affect vascular function and inflammatory responses, potentially interfering with the normal healing process [8,11]. In addition, alveolar osteitis is strongly associated with excessive fibrinolytic activity, which can result in premature breakdown or loss of the blood clot within the extraction socket. The disruption of the blood clot may subsequently interfere with the progression of normal socket healing and contribute to the clinical development of alveolar osteitis [4,12]. A possible connection between inflammatory signaling and clot instability may involve downstream IL-6 activity. In experimental studies, MCP-1 induced IL-6 production in human smooth muscle cells, whereas IL-6 stimulated plasminogen activator activity in human dental pulp cells. These findings provide a biologically plausible pathway, but IL-6 and fibrinolytic activity were not measured in the present study, so this mechanism cannot be confirmed in the current rat model [15,16].

At the molecular level, MCP-1 binds to the CCR2 receptor on monocytes and promotes their migration toward sites of tissue injury. This recruitment is a physiological component of wound healing because inflammatory cells help remove cellular debris and support tissue repair. However, excessive or prolonged inflammatory signaling may interfere with the transition from the inflammatory phase to the proliferative phase. Nicotine-associated increases in MCP-1 may therefore contribute to sustained inflammatory-cell recruitment and an altered healing environment [21,23].

The involvement of NF- κ B-related inflammatory signaling and IL-6 provides a potential link between chemokine activity and increased fibrinolysis, although the individual steps in this pathway require further investigation in the context of nicotine-induced alveolar osteitis [23,24].

The relationship between increased MCP-1 levels and alveolar osteitis observed in this study may indicate that an altered inflammatory response contributes to impaired post-extraction healing. Although MCP-1 has an important physiological role in recruiting monocytes and macrophages during tissue repair, excessive or prolonged inflammatory activity may interfere with the progression from the inflammatory phase to subsequent stages of wound healing. DiPietro et al. demonstrated that MCP-1 plays an important role in macrophage recruitment during wound healing, supporting the role of this chemokine in the inflammatory response to tissue injury [5].

The temporal changes in MCP-1 levels provide additional insight into the inflammatory response. MCP-1 concentrations decreased between 24 and 72 hours in both groups, suggesting a temporal decline in the early inflammatory response. However, MCP-1 remained higher in the nicotine-exposed group at 72 hours than in the corresponding control group. This persistent difference may indicate that nicotine exposure alters the magnitude or resolution of the inflammatory response. Previous experimental research has reported that MCP-1 expression may peak during the early stages of inflammation and subsequently decline during tissue repair [25]. Nevertheless, the present study cannot establish whether the observed changes resulted from delayed inflammatory resolution, altered chemokine production, or other systemic effects of nicotine.

The findings also suggest that the effect of nicotine on post-extraction healing is not limited to a local mechanical disturbance of the blood clot. Rather, nicotine may influence the biological processes involved in inflammation and tissue repair. Nicotine has been reported to modify inflammatory mediator expression in gingival fibroblasts, suggesting that exposure to nicotine can alter the local inflammatory microenvironment [7]. In addition, alterations in MCP-1 levels have been reported in smokers with periodontal disease, further supporting a potential association between tobacco exposure and MCP-1-mediated inflammatory responses [8].

Prolonged inflammation may also interfere with the formation of granulation tissue, angiogenesis, and collagen deposition. Nicotine-induced vasoconstriction and oxidative stress may further compromise oxygen delivery and the repair capacity of the injured tissue [19,20]. In addition, an imbalance in macrophage activity may affect the transition from predominantly pro-inflammatory responses toward reparative processes. These mechanisms could contribute to delayed socket healing; however, macrophage phenotypes, angiogenesis, fibroblast activity, and collagen deposition were not directly

evaluated in the present study and should therefore be regarded as potential explanations rather than demonstrated mechanisms.

The observed increase in MCP-1 following nicotine exposure may therefore represent part of the inflammatory response associated with impaired extraction-socket healing. However, MCP-1 is not necessarily a direct causal marker of alveolar osteitis. Its elevation may reflect inflammatory-cell recruitment occurring during the healing process. Therefore, the relationship between MCP-1 and alveolar osteitis should be interpreted as an association within the experimental conditions of this study rather than definitive evidence of a causal pathway.

The association between serum MCP-1 and clinical alveolar osteitis severity further supports the potential relevance of this chemokine to post-extraction inflammatory changes. Spearman correlation analysis demonstrated a statistically significant positive relationship between serum MCP-1 levels and clinical socket severity ($p < 0.05$). This finding suggests that higher MCP-1 concentrations were associated with poorer clinical healing outcomes in experimental animals. It is also consistent with the findings of Rodrigues et al. (2011), who described more pronounced tissue inflammation in an experimental animal model of alveolar osteitis [26]. Furthermore, Øyri et al. (2021) reported increased MCP-1 and IL-6 levels in alveolar sockets affected by alveolar osteitis compared with contralateral sites [27]. Cahyani et al. (2024) also reported an association between nicotine exposure, increased serum IL-6, fibrinolytic activity, and impaired alveolar wound healing [28]. Collectively, these findings support the potential involvement of inflammatory mediators in alveolar osteitis, although differences in experimental models and measured outcomes should be considered when comparing the studies.

Overall, the results indicate that nicotine exposure is associated with changes in MCP-1 levels and an increased occurrence of alveolar osteitis after tooth extraction. These findings provide further evidence that nicotine may interfere with post-extraction healing through modulation of the inflammatory response. Further studies are required to clarify the molecular pathways linking nicotine exposure, MCP-1 regulation, macrophage recruitment, and the development of alveolar osteitis.

Several limitations should be considered when interpreting these findings. First, MCP-1 was measured at only two time points, 24 and 72 hours after extraction. Although these time points provide information about the early inflammatory response, they do not capture the full progression of socket healing through the subsequent proliferative and remodeling phases. Additional observations at earlier and later time points, such as 6 hours, 48 hours, 5 days, and 7 days, could provide a more comprehensive understanding of MCP-1 dynamics. Second, only serum MCP-1 was measured.

Assessment of MCP-1 expression in the extraction-socket tissue could provide more direct evidence of local inflammatory activity. Finally, IL-6 concentrations, fibrinolytic activity, histopathological changes, angiogenesis, and macrophage phenotypes were not evaluated. Further studies incorporating these parameters, alongside different nicotine doses and exposure durations, are needed to clarify the mechanisms connecting nicotine exposure, inflammatory regulation, and alveolar osteitis.

CONCLUSIONS

This study demonstrates that nicotine exposure significantly increases MCP-1 levels and elevates the risk of developing alveolar osteitis. The nicotine-exposed groups exhibited higher MCP-1 levels and a greater incidence of alveolar osteitis compared with the control groups. These findings suggest that nicotine enhances inflammatory responses, thereby impairing post-extraction socket healing.

To further elucidate the mechanisms involved, future studies should evaluate local MCP-1 tissue expression alongside serum levels and expand the observation time points (e.g., 6 h, 48 h, 5 days, and 7 days) to capture complete inflammatory dynamics. Additional investigations incorporating varying nicotine dosages, exposure durations, and histopathological analysis are recommended to determine the critical thresholds affecting socket healing. Clinically, these findings highlight the vital importance of patient education regarding smoking cessation before and after tooth extraction as an essential preventive strategy against alveolar osteitis.

COMPLIANCE WITH ETHICAL STANDARDS

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