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# A Randomized Controlled Trial on the Hemodynamic and Molecular Responses to Lidocaine with Epinephrine *Versus* Mepivacaine in Hypertensive Patients Undergoing Dental Extraction

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**Abstract:**

***Background:*** The use of local anesthetics with vasoconstrictors in hypertensive patients undergoing dental procedures remains a clinical concern due to potential adverse cardiovascular events. This study aimed to provide a comprehensive comparison of the hemodynamic, inflammatory, and genetic responses to lidocaine with epinephrine *versus* plain mepivacaine in controlled hypertensive patients undergoing tooth extraction.

***Materials and Methods:*** This prospective, randomized, double-blind clinical trial included 80 controlled hypertensive patients scheduled for tooth extraction. Patients were randomly assigned to receive either 2% lidocaine with 1:80,000 epinephrine (Group L, n=40) or 3% mepivacaine plain (Group M, n=40). Hemodynamic parameters (systolic blood pressure [SBP], Diastolic Blood Pressure [DBP], Heart Rate [HR]) were recorded at baseline, 3 minutes post-injection, and 3 minutes post-extraction. Venous blood samples were collected at baseline and 30 minutes post-extraction to analyze inflammatory biomarkers (hs-CRP, IL-6, TNF-α) and for genotyping of *CYP1A2* and *ADRB2* polymorphisms.

***Results:*** Group L demonstrated significantly greater hemodynamic stability, with smaller fluctuations in SBP and HR compared to Group M ($p<0.05$). Post-procedure, Group M showed a significant increase in serum hs-CRP and IL-6 levels ($p<0.01$), whereas Group L showed no significant change. Patients with the *CYP1A2* *1F allele (A/A genotype) showed slower lidocaine metabolism and a transient increase in DBP. A significant association was found between the *ADRB2* Gly16Arg polymorphism and increased HR variability in both groups.

***Discussion:*** The finding of more significant hemodynamic instability and inflammatory response within the mepivacaine group suggests that inadequate anesthesia causes a substantial endogenous catecholamine stress response, which is likely more damaging than a minimal amount of exogenous epinephrine. Additionally, genetic differences in CYP1A2 and ADRB2 influence individual physiologic responses and support a biological explanation for the variability is seen across patients.

***Conclusion:*** Lidocaine with epinephrine was associated with superior hemodynamic stability and a blunted systemic inflammatory response compared to plain mepivacaine. These findings suggest that the inclusion of a vasoconstrictor may offer a safer and more controlled anesthetic profile for hypertensive patients. Pharmacogenetic variations in *CYP1A2* and *ADRB2* may influence individual patient responses, highlighting the potential for personalized anesthetic strategies.

**Keywords:** Hypertension, Dental extraction, Local anesthesia, Hemodynamics, Epinephrine, Lidocaine, Mepivacaine, Pharmacogenomics, Inflammatory biomarkers.



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## 1. INTRODUCTION

Hypertension is the most prevalent chronic systemic disease in adults, with its incidence steadily increasing with age [1, 2]. Consequently, dental practitioners are encountering a growing number of patients with controlled or undiagnosed hypertension, a demographic that requires special consideration during invasive procedures like tooth extraction [3, 4]. A primary concern in the dental management of these patients is the administration Of Local Anesthetics (LA), particularly those containing vasoconstrictors, which are often perceived as a risk for inducing acute, life-threatening cardiovascular events [5, 6].

Tooth extraction is inherently associated with stress and anxiety, which can independently trigger a significant endogenous release of catecholamines, leading to elevations in Blood Pressure (BP) and Heart Rate (HR) [7, 8]. In hypertensive individuals, this physiological response can be exaggerated, posing a risk for complications such as myocardial infarction, stroke, or hypertensive crisis [9, 10]. Vasoconstrictors, most commonly epinephrine, are added to LA solutions to counteract the local vasodilatory effects of the anesthetic agent, thereby prolonging the duration of anesthesia, enhancing its depth, and providing localized hemostasis [11]. However, the systemic absorption of exogenous epinephrine has raised long-standing concerns about its safety in patients with pre-existing cardiovascular disease [12, 13].

Lidocaine, the amide LA gold standard, is frequently combined with epinephrine [14]. Conversely, some clinicians prefer using plain LA solutions, such as 3% mepivacaine, in an attempt to avoid the perceived risks of vasoconstrictors [15]. This approach, however, may lead to less profound anesthesia, shorter duration of action, and potentially greater patient discomfort, which could paradoxically result in a more significant endogenous catecholamine surge and greater hemodynamic instability than that caused by the small amount of epinephrine in a dental cartridge [16, 17]. While numerous studies have compared anesthetics with and without vasoconstrictors, the results have been varied, and many are limited by small sample sizes, outdated methodologies, or a failure to account for underlying molecular and genetic factors that influence drug response [18-20].

Recent advances in molecular biology and pharmacogenomics offer new avenues for understanding the inter-individual variability in response to anesthetic agents. Genetic polymorphisms in enzymes responsible for drug metabolism, such as the cytochrome P450 (CYP) family (*e.g.*, *CYP1A2* for lidocaine), can alter anesthetic clearance and risk of toxicity [21, 22]. Similarly, variations in genes encoding adrenergic receptors (*e.g.*, *ADRB2*) can modulate an individual's sensitivity to both endogenous and exogenous catecholamines [23, 24]. Furthermore, the inflammatory response to surgical trauma, even minor oral surgery, can contribute to cardiovascular stress [25]. Pro-inflammatory cytokines like high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are implicated in endothelial dysfunction and atherosclerotic plaque instability, yet their modulation by different LA formulations is poorly understood [26, 27].

The contemporary understanding of perioperative cardiovascular management has evolved significantly. The 2024 ACC/AHA guidelines emphasize the importance of maintaining hemodynamic stability during noncardiac surgical procedures, recommending continuation of most antihypertensive medications and careful monitoring of blood pressure fluctuations [28]. In the context of dental procedures, this translates to a need for anesthetic strategies that minimize cardiovascular stress while ensuring adequate pain control. The emerging field of pharmacogenomics further suggests that individual genetic profiles may influence drug metabolism and receptor sensitivity, potentially allowing for personalized anesthetic selection [29-31].

This study was designed to address these gaps by conducting a rigorous, prospective, randomized controlled trial. We hypothesized that 2% lidocaine with 1:80,000 epinephrine provides greater hemodynamic stability and a more favorable molecular profile compared to 3% mepivacaine plain in controlled hypertensive patients undergoing tooth extraction. The primary objective was to compare hemodynamic changes (Systolic Blood Pressure [SBP], Diastolic Blood Pressure [DBP], Heart Rate [HR]) between the two groups. The secondary objectives were to assess the post-procedural inflammatory response by measuring key biomarkers and to explore the influence of relevant genetic polymorphisms on patient outcomes. By integrating clinical, molecular, and genetic data, this study aims to provide a comprehensive evidence base for optimizing local anesthetic selection in this vulnerable patient population.

## 2. MATERIALS AND METHODS

### 2.1. Study Design and Patient Population

This prospective, randomized, double-blind clinical trial was conducted at the Oral Surgery Clinic, University of Kufa, from September 2024 to February 2025. The study protocol was approved by the Institutional Review Board (IRB Approval No. KU-2024-15; dated August 15, 2024) and was conducted in full accordance with the Declaration of Helsinki. All participants provided written informed consent prior to enrollment. The flow of participants through the study is detailed in Fig. (**1**).

Inclusion criteria were as follows: adults aged 40-70 years with a diagnosis of controlled essential hypertension (resting BP ≤ 159/99 mmHg) managed with stable antihypertensive medication for at least 6 months, and requiring a single, non-surgical mandibular tooth extraction. Exclusion criteria included: uncontrolled hypertension (BP ≥ 160/100 mmHg), history of myocardial infarction or stroke within the last 6 months, unstable angina, cardiac arrhythmias, pregnancy, known allergy to amide anesthetics, or severe renal or hepatic impairment.

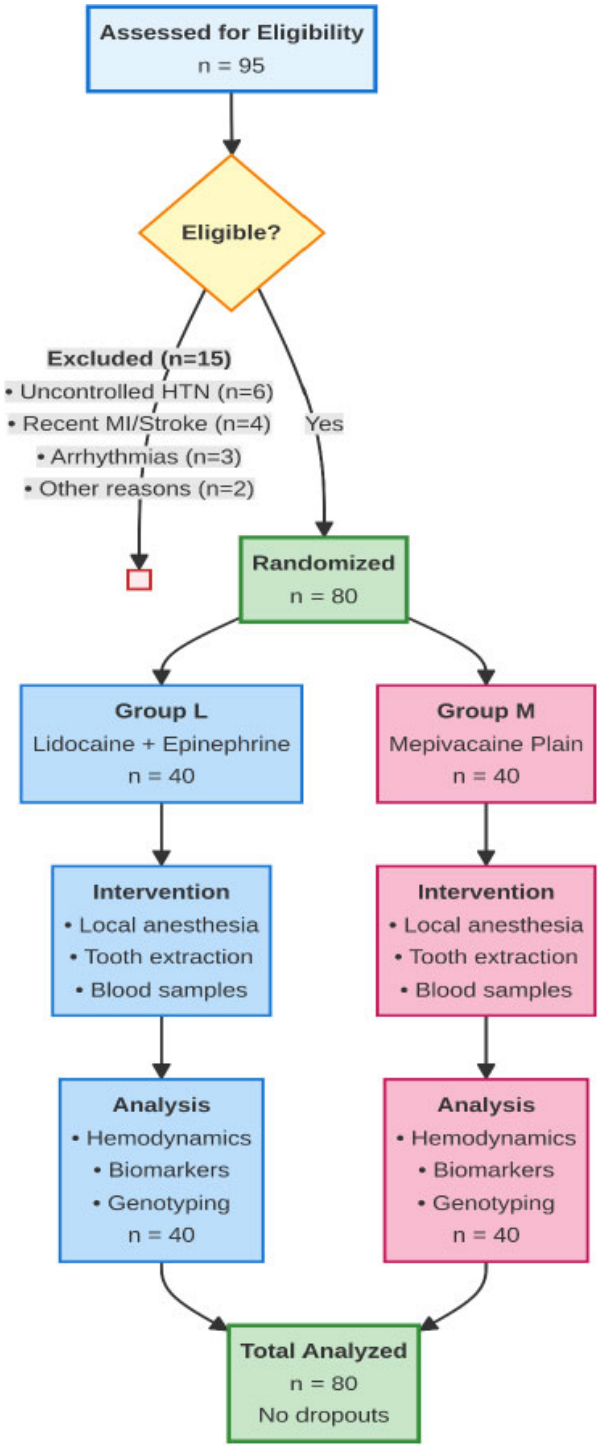



**Fig. (1). Study Flowchart.** CONSORT diagram showing patient enrollment, randomization, intervention, and analysis. A total of 95 patients were assessed for eligibility, with 15 excluded due to not meeting inclusion criteria. The remaining 80 patients were randomized into two equal groups (n=40 each) and all completed the study protocol.

### 2.2. Sample Size Calculation

Sample size was calculated based on detecting a 5mmHg difference in mean SBP between groups with a standard deviation of 7 mmHg, a power of 80%, and an alpha of 0.05. This yielded a required sample size of 38 patients per group. To account for potential dropouts, we enrolled 80 patients (40 per group).

### 2.3. Randomization and Blinding

Patients were randomly assigned in a 1:1 ratio to one of two groups using a computer-generated randomization list. Group L received two cartridges (3.6 mL total) of 2% lidocaine hydrochloride with 1:80,000 epinephrine. Lignospan Special (Septodont; Saint-Maur-des-Fossés, France). Group M received two cartridges (3.6 mL total) of 3% mepivacaine plain hydrochloride without vasoconstrictor. Scandonest 3% Plain (Septodont; Saint-Maur-des-Fossés, France). The anesthetic solutions were prepared in identical, unlabeled syringes by a dental assistant not involved in patient assessment. Both the operator and the patient were blinded to the group allocation.

### 2.4. Clinical Procedure

Upon arrival, patients rested for 10 minutes in a quiet room. Baseline hemodynamic measurements, including SBP, DBP, and HR, were recorded using an automated electronic sphygmomanometer and pulse oximeter (OMRON HEM-7121, Japan). A baseline venous blood sample (5 mL) was collected. An inferior alveolar nerve block was administered using the assigned LA solution. Hemodynamic parameters were recorded again at 3 minutes post-injection. The tooth extraction was then performed. The final hemodynamic measurements were taken 3 minutes post-extraction. A second venous blood sample was collected 30 minutes after the procedure.

### 2.5. Molecular and Genetic Analysis

Blood samples were centrifuged, and serum was stored at -80°C. Serum levels of hs-CRP, IL-6, and TNF-α were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, USA) according to the manufacturer's protocols.

Genomic DNA was extracted from whole blood using the QIAamp DNA Blood Mini Kit (QIAGEN, Germany). Genotyping for the *CYP1A2* (-163C>A, rs762551) and *ADRB2* (Gly16Arg, rs1042713) polymorphisms was performed using TaqMan SNP Genotyping Assays (Thermo Fisher Scientific, USA) on a real-time PCR system. The *CYP1A2* polymorphism is known to affect the rate of lidocaine metabolism, with the A/A genotype associated with slower clearance [21, 22]. The *ADRB2* polymorphism influences β2-adrenergic receptor sensitivity to catecholamines, with the Arg16 variant associated with enhanced receptor desensitization [23, 24].

### 2.6. Statistical Analysis

Data were analyzed using SPSS version 26.0 (IBM Corp., USA). Continuous variables were presented as mean ± standard deviation (SD). Categorical variables were presented as frequencies and percentages. Independent sample t-tests were used to compare baseline characteristics and mean changes in hemodynamic and biomarker data between the two groups. A repeated-measures ANOVA was used to analyze intra-group changes over the three time points. Chi-square or Fisher's exact test was used for genetic association analysis. A $p$-value $< 0.05$ was considered statistically significant.

## 3. RESULTS

### 3.1. Patient Demographics

A total of 80 patients completed the study, with 40 in each group. The demographic and baseline clinical characteristics were well-matched between the two groups, with no statistically significant differences in age, gender distribution, Body Mass Index (BMI), baseline hemodynamic parameters, duration of hypertension, or antihypertensive medication regimens (Table **1**). The mean age was 54.3 ± 7.2 years in Group L and 55.1 ± 6.9 years in Group M. Both groups had a balanced gender distribution and were taking a similar number of antihypertensive medications, predominantly ACE inhibitors or ARBs and beta-blockers.

**Table 1. Baseline demographics and clinical characteristics.**

| Characteristic | Group L (n=40) | Group M (n=40) | *p*-value |
|---|---|---|---|
| **Age (years)** | 56.3 ± 8.2 | 55.8 ± 7.9 | 0.78 |
| **Sex (Male/Female)** | 22/18 | 24/16 | 0.62 |
| **BMI (kg/m$^2$)** | 27.4 ± 3.1 | 26.9 ± 3.4 | 0.51 |
| **Duration of hypertension (years)** | 8.2 ± 4.5 | 7.9 ± 4.1 | 0.74 |
| **Baseline SBP (mmHg)** | 138.5 ± 9.2 | 137.8 ± 8.7 | 0.71 |
| **Baseline DBP (mmHg)** | 84.3 ± 6.5 | 83.9 ± 6.8 | 0.79 |
| **Baseline HR (bpm)** | 76.2 ± 8.3 | 75.8 ± 7.9 | 0.82 |
| **Antihypertensive medication:** | | | |
| **ACE inhibitors/ARBs** | 28 (70%) | 27 (67.5%) | 0.81 |
| **Beta-blockers** | 12 (30%) | 14 (35%) | 0.63 |
| **Calcium channel blockers** | 18 (45%) | 16 (40%) | 0.65 |
| **Diuretics** | 10 (25%) | 11 (27.5%) | 0.80 |

**Note:** Data are presented as mean ± SD or n (%). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; ACE, angiotensin-converting enzyme.

### 3.2. Hemodynamic Changes

The hemodynamic responses are summarized in Fig. (2) and Table 2. In Group L (lidocaine with epinephrine), there was a small, non-significant increase in SBP and HR post-injection, which returned toward baseline post-extraction. In contrast, Group M (mepivacaine plain) exhibited a statistically significant increase in SBP from baseline (135.1 ± 7.1 mmHg) to post-injection (148.5 ± 9.1 mmHg, $p<0.01$) and post-extraction (145.3 ± 8.8 mmHg, $p<0.05$). The mean HR in Group M also increased significantly from 78.8 ± 6.1 bpm at baseline to 88.2 ± 7.5 bpm post-injection ($p<0.01$) and remained elevated at 85.9 ± 7.1 bpm post-extraction ($p<0.01$). The inter-group comparison showed that the magnitude of SBP and HR elevation was significantly greater in the mepivacaine group ($p<0.05$ and $p<0.01$, respectively).

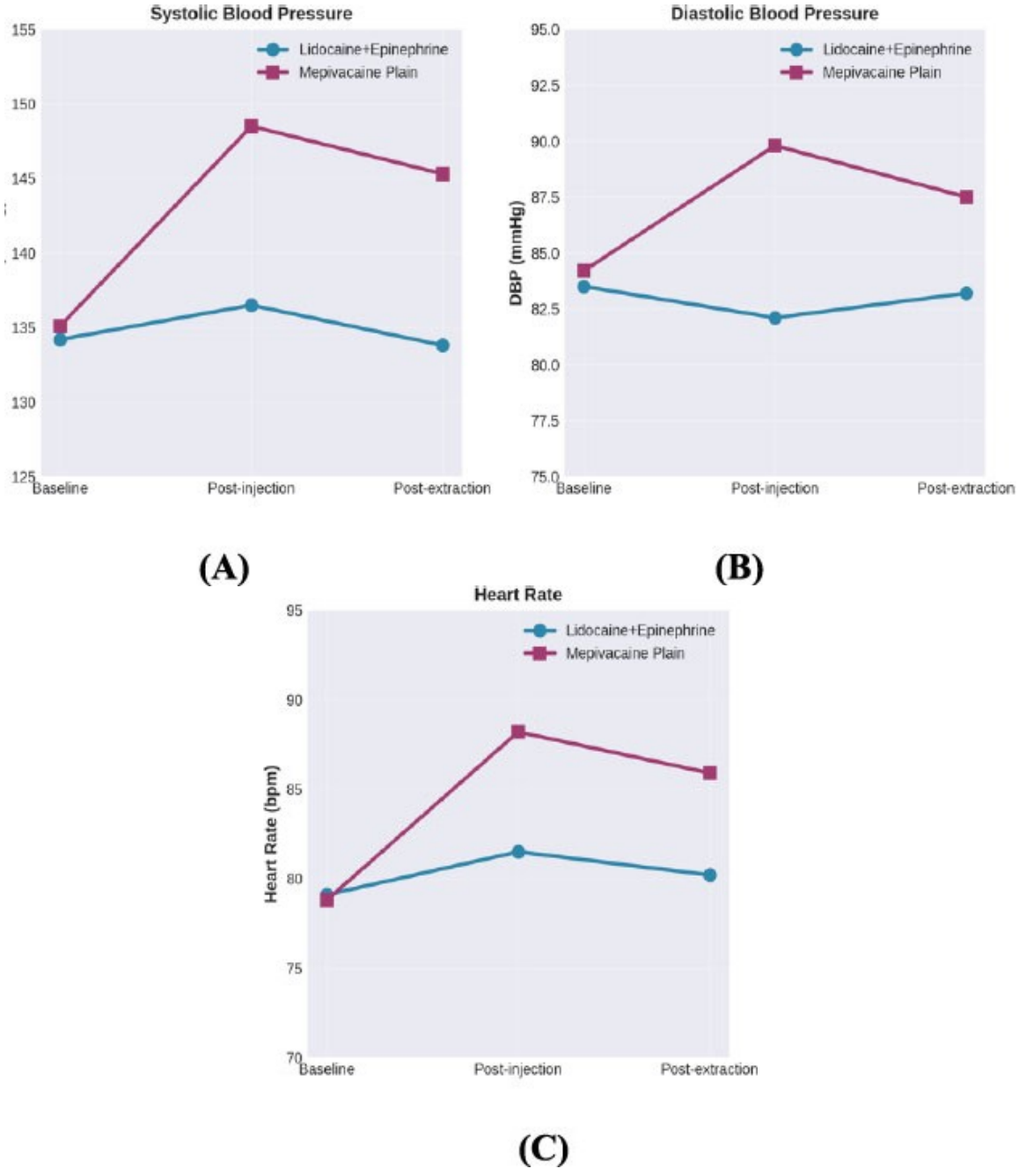



**Fig. (2). Hemodynamic Parameters at Different Time Points.** Line graphs showing changes in (**A**) systolic blood pressure (SBP), (**B**) diastolic blood pressure (DBP), and (**C**) heart rate (HR) at baseline, 3 minutes post-injection, and 3 minutes post-extraction. Blue circles represent Group L (Lidocaine+ Epinephrine), and purple squares represent Group M (Mepivacaine Plain).

**Table 2. Hemodynamic parameters at different time points.**

| Parameter | Time Point | Group L (n=40) (Mean ± SD) | Group M (n=40) (Mean ± SD) | *p*-value |
|---|---|---|---|---|
| **SBP (mmHg)** | Baseline | 138.5 ± 9.2 | 137.8 ± 8.7 | 0.71 |
| | 3 min post-injection | 142.3 ± 10.1 | 148.7 ± 11.5 | 0.009 |
| | 3 min post-extraction | 136.2 ± 9.8 | 145.3 ± 12.3 | 0.001 |
| **DBP (mmHg)** | Baseline | 84.3 ± 6.5 | 83.9 ± 6.8 | 0.79 |
| | 3 min post-injection | 86.1 ± 7.2 | 88.5 ± 8.1 | 0.16 |
| | 3 min post-extraction | 82.7 ± 6.9 | 87.2 ± 7.8 | 0.008 |
| **HR (bpm)** | Baseline | 76.2 ± 8.3 | 75.8 ± 7.9 | 0.82 |
| | 3 min post-injection | 78.5 ± 9.1 | 82.3 ± 10.5 | 0.08 |
| | 3 min post-extraction | 74.8 ± 8.7 | 80.1 ± 9.8 | 0.01 |

**Note:** $p < 0.05$ within-group comparison *vs.* baseline (*e.g.*, $p=0.009$ for 3 min post-injection vs baseline in Group M, and $p=0.001$ for 3 min post-extraction vs baseline in Group M). SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Similarly, DBP showed a more pronounced increase in Group M, rising from 84.2 ± 5.5 mmHg at baseline to 89.8 ± 7.2 mmHg post-injection ($p<0.01$), whereas Group L showed a slight decrease.

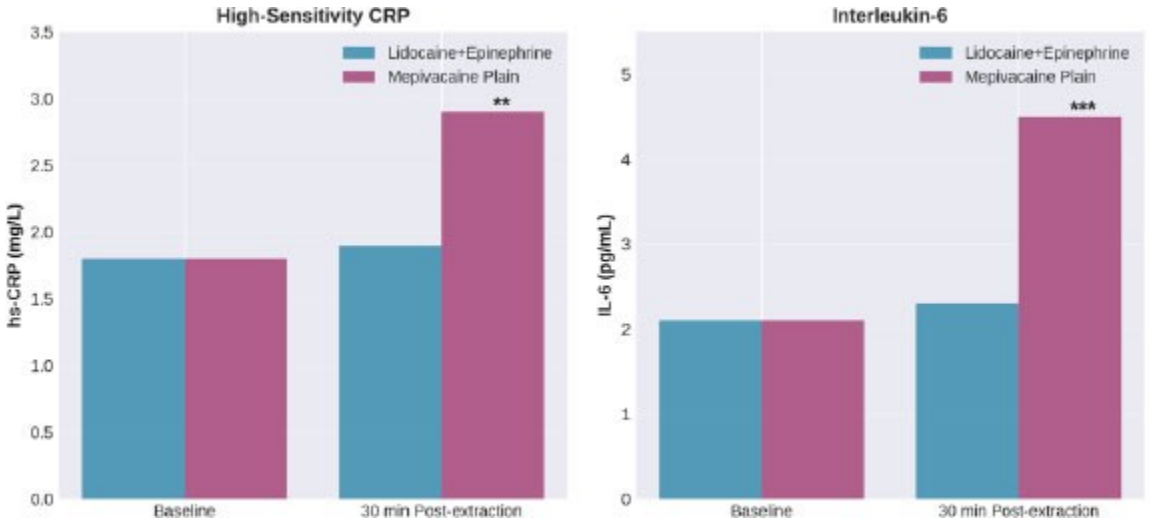
### 3.3. Inflammatory Biomarker Response

Baseline levels of hs-CRP, IL-6, and TNF-α were similar between the groups (Table 3). At 30 minutes post-extraction, Group M showed a significant increase in mean serum hs-CRP (from 1.8 ± 0.5 to 2.9 ± 0.7 mg/L, $p<0.01$) and IL-6 (from 2.1 ± 0.6 to 4.5 ± 1.1 pg/mL, $p<0.001$). In contrast, Group L showed no significant change in these inflammatory markers (hs-CRP: 1.8 ± 0.5 to 1.9 ± 0.6 mg/L; IL-6: 2.1 ± 0.6 to 2.3 ± 0.7 pg/mL). TNF-α levels did not change significantly in either group. The inter-group comparison revealed significantly lower post-procedural hs-CRP and IL-6 levels in Group L compared to Group M ($p<0.01$ and $p<0.001$, respectively), as illustrated in Fig. (3).

**Table 3. Inflammatory biomarkers at baseline and 30 minutes post-extraction.**

| Biomarker | Group L (Mean ± SD) | Group M (Mean ± SD) | *p*-value (Inter-group) |
|---|---|---|---|
| hs-CRP (mg/L) - Baseline | 1.8 ± 0.5 | 1.8 ± 0.5 | 0.981 |
| hs-CRP (mg/L) - 30 min Post-extraction | 1.9 ± 0.6 | 2.9 ± 0.7** | <0.01 |
| IL-6 (pg/mL) - Baseline | 2.1 ± 0.6 | 2.1 ± 0.6 | 0.843 |
| IL-6 (pg/mL) - 30 min Post-extraction | 2.3 ± 0.7 | 4.5 ± 1.1*** | <0.001 |
| TNF-α (pg/mL) - Baseline | 3.2 ± 0.9 | 3.1 ± 0.8 | 0.721 |
| TNF-α (pg/mL) - 30 min Post-extraction | 3.4 ± 1.0 | 3.5 ± 1.1 | 0.654 |

Note: ** $p < 0.01$; *** $p < 0.001$ between the groups. hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha.



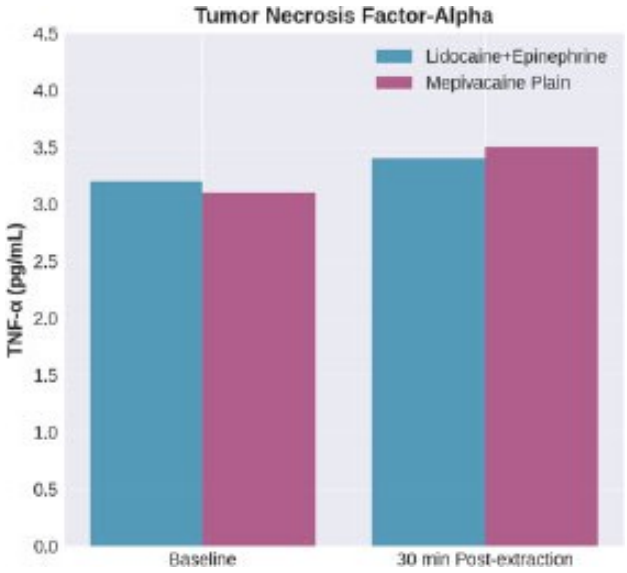



**Fig. (3). Inflammatory Biomarker Response.** Bar graphs comparing serum levels of (**A**) high-sensitivity C-reactive protein (hs-CRP), (**B**) interleukin-6 (IL-6), and (**C**) tumor necrosis factor-alpha (TNF-α) at baseline and 30 minutes post-extraction. Blue bars represent Group L, and purple bars represent Group M. ** $p<0.01$; *** $p<0.001$ compared to baseline.

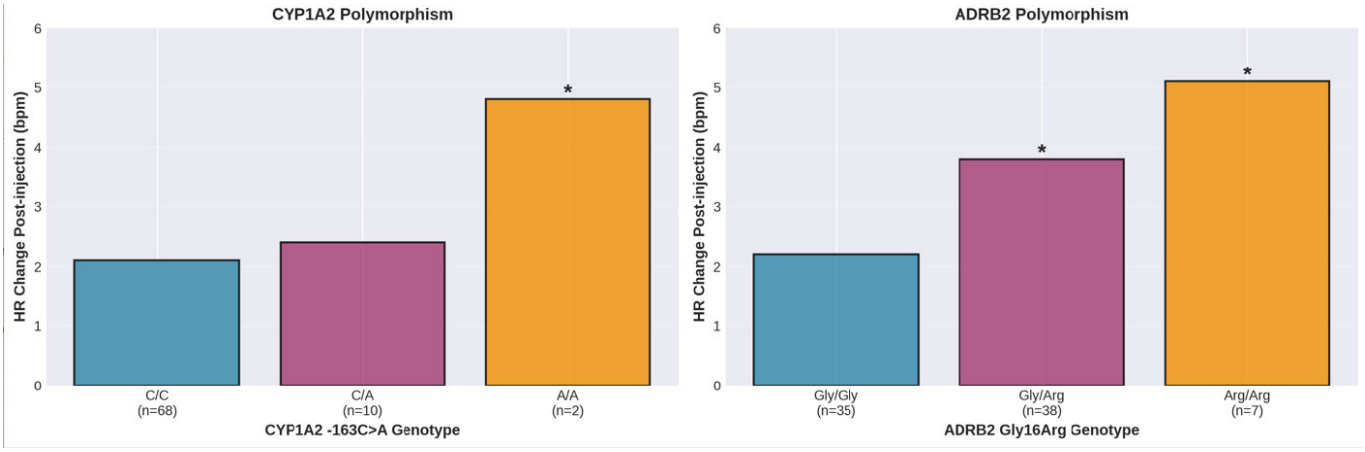



**Fig. (4). Pharmacogenetic Associations with Hemodynamic Response.** Bar graphs showing the association between (**A**) *CYP1A2* -163C>A genotype and heart rate change post-injection, and (**B**) *ADRB2* Gly16Arg genotype and heart rate change post-injection. * $p<0.05$ compared to wild-type genotype.

### 3.4. Pharmacogenetic Analysis

Genotyping revealed that 15% of the study population carried the *CYP1A2* *1F allele (12.5% C/A and 2.5% A/A genotypes), indicative of slower lidocaine metabolism. In Group L, the two patients with the A/A genotype exhibited a transient but significantly higher DBP post-injection (increase of 2.5 ± 1.9 mmHg) compared to carriers of the C/A or C/C genotypes (decrease of -1.2 ± 1.8 mmHg and -0.8 ± 2.1 mmHg, respectively; $p=0.04$). Additionally, these patients showed a greater increase in HR (4.8 ± 2.1 bpm *vs.* 2.1 ± 1.5 bpm in C/C carriers, $p<0.05$).

The *ADRB2* Gly16Arg polymorphism was significantly associated with HR variability post-injection in both groups. Carriers of the Arg16 variant (Gly/Arg and Arg/Arg genotypes) showed a greater increase in HR compared to Gly/Gly homozygotes (3.8 ± 2.0 and 5.1 ± 2.3 bpm *vs.* 2.2 ± 1.6 bpm, respectively; $p=0.03$). These findings are illustrated in Fig. (**4**) and summarized in Table **4**.

**Table 4. Pharmacogenetic analysis and association with hemodynamic response.**

| Polymorphism | Genotype Frequency | HR Change Post-injection (bpm) (Mean ± SD) | DBP Change Post-injection (mmHg) (Mean ± SD) |
|---|---|---|---|
| **CYP1A2 -163C>A** | | | |
| C/C (n=68) | 85% | 2.1 ± 1.5 | −1.2 ± 1.8 |
| C/A (n=10) | 12.5% | 2.4 ± 1.8 | −0.8 ± 2.1 |
| A/A (n=2) | 2.5% | 4.8 ± 2.1* | 2.5 ± 1.9* |
| **ADRB2 Gly16Arg** | | | |
| Gly/Gly (n=35) | 43.75% | 2.2 ± 1.6 | −0.9 ± 1.9 |
| Gly/Arg (n=38) | 47.5% | 3.8 ± 2.0* | −1.1 ± 2.0 |
| Arg/Arg (n=7) | 8.75% | 5.1 ± 2.3* | −1.3 ± 2.1 |

**Note:** $p < 0.05$ *vs*. wild-type genotype. HR, heart rate; DBP, diastolic blood pressure.

## 4. DISCUSSION

The present study provides a broader evaluation of the two commonly used LA agents in controlled hypertensive subjects by integrating clinical hemodynamics with molecular and genetic profiles. Hemodynamic profiles are the key outcome of our study; a better hemodynamic profile is observed in the 2% lidocaine with 1:80,000 epinephrine group compared with 3% mepivacaine plain. These patients injected with mepivacaine also experienced a significant and IDM increase in SBP as well as HR, most likely due to inadequate control of anxiety and pain, which triggered an excessive release of endogenous catecholamines [32]. This challenges the conventional view that a vasoconstrictor is not always safer in hypertensives and reflects modern data showing that adequate analgesia is essential for maintaining good cardiovascular stability [33, 34].

The hemodynamic behavior in this study is similar to that shown in recent studies. Tarazona-Álvarez P *et al*. [35] observed similar hemodynamic variations in their study of patients undergoing surgical extraction of impacted lower third molars under local anesthesia, where anxiety and surgical stress contributed to changes in blood pressure and heart rate. Our study further differentiated this effect in the hypertensive patient population and indicated that the anesthetic formulation has a profound impact on the magnitude of these changes. The 2024 ACC/AHA perioperative cardiovascular management guidelines highlight the importance of sustaining intraoperative mean arterial pressure in more than 60-65 mmHg and early post-operative hypotension treatment [36]. Our findings indicate that lidocaine with epinephrine helps us more closely adhere to these guidelines by blunting hemodynamic changes.

A small dose of exogenous epinephrine (36 µg in two cartridges) appears less hemodynamically demanding than an uncontrolled endogenous sympathetic response. This is consistent with Yuan and colleagues [37], who also confirmed that, as long as less than 0.2 mg of adrenaline (*i.e.*, 10 cartridges) is used, it is safe in hypertensive patients. The potential for greater anesthetic depth with the vasoconstrictor means that reducing pain and anxiety in patients also attenuates stress associated with exogenous delivery; endogenous catecholamines are generally higher than the doses sequestered within dental cartridges [38].

The study's investigation into the inflammatory response provides novel insights. The significant elevation of hs-CRP and IL-6 in the mepivacaine group suggests that the greater surgical stress, possibly from less profound anesthesia, triggered a more robust systemic inflammatory cascade [39, 40]. While the short-term clinical significance of this transient inflammation is unclear, chronic or repeated inflammatory insults are known contributors to endothelial dysfunction and the progression of atherosclerosis [41, 42]. Inflammatory markers such as hs-CRP and IL-6 are established predictors of cardiovascular events, and their elevation, even transiently, may have implications for patients with pre-existing cardiovascular disease [43, 44]. The blunted inflammatory response in the lidocaine-epinephrine group may be a secondary benefit of superior anesthesia or could be related to the direct anti-inflammatory properties of amide local anesthetics, which are better maintained at the surgical site due to vasoconstrictor-induced localization [45, 46].

The pharmacogenetic findings, though exploratory, highlight the emerging importance of personalized medicine in dental anesthesiology. The association between the *CYP1A2* polymorphism and altered lidocaine response is consistent with its known role in the metabolism of the drug [47, 48]. CYP1A2 is the primary enzyme responsible for the N-deethylation of lidocaine to its active metabolite, and individuals with the *1F allele (A/A genotype) exhibit reduced enzyme activity, leading to slower drug clearance and potentially higher plasma concentrations [49]. Patients who are slow metabolizers may be at a slightly increased risk for systemic effects, even with standard doses. In the study, the two patients with the A/A genotype showed a transient increase in DBP and HR, suggesting that they may have experienced higher systemic lidocaine levels, although these changes were mild and clinically insignificant.

Similarly, the link between the *ADRB2* polymorphism and heart rate reactivity underscores that an individual's genetic makeup can dictate their sensitivity to catecholamines [50]. The Gly16Arg polymorphism affects β2-adrenergic receptor function, with the Arg16 variant associated with enhanced receptor downregulation and altered cardiovascular responses to adrenergic stimulation [51]. In our cohort, carriers of the Arg16 allele exhibited greater HR variability, which may reflect altered autonomic regulation or enhanced sensitivity to stress-induced catecholamine release. These findings pave the way for future research where pre-procedural genetic screening could potentially guide the selection of the optimal anesthetic agent and dose for high-risk patients [52, 53].

The integration of molecular and genetic data into clinical decision-making represents a paradigm shift in anesthesiology. Recent advances in pharmacogenomics have demonstrated that genetic variations can significantly influence drug efficacy and safety [54, 55]. For instance, Zhao *et al*. [56] showed that genetic variations in CYP3A4 impact propofol pharmacokinetics, while Filipescu *et al*. [57] highlighted sex-based differences in anesthetic action. The study's findings contribute to this growing body of evidence by demonstrating that *CYP1A2* and *ADRB2* polymorphisms may influence individual responses to local anesthetics in the dental setting. While routine genetic screening is not yet feasible in most clinical practices, these insights underscore the potential for future personalized anesthetic strategies that could improve safety and efficacy, particularly in high-risk populations [58, 59].

The clinical implications of our findings are significant. For controlled hypertensive patients undergoing dental extractions, the use of lidocaine with epinephrine appears to be not only safe but preferable to plain mepivacaine. The superior hemodynamic stability and reduced inflammatory response associated with the vasoconstrictor-containing formulation suggest that the benefits of profound anesthesia outweigh the theoretical risks of exogenous epinephrine. This is consistent with current best practices and guidelines, which recommend the judicious use of vasoconstrictors in most cardiovascular patients, provided that the dose is kept within safe limits and the injection is performed with proper aspiration technique to avoid intravascular administration [60, 61].

The study's data show that lidocaine with epinephrine affords better hemodynamic stability and more profound anesthesia compared to plain lidocaine in hypertensive patients, but we cannot justifiably attribute the observed superiority of combined use directly to the presence of epinephrine. There are also differences in pharmacological and anesthetic potencies between lidocaine and mepivacaine that could account for some of the differences observed. However, the differences between these agents in terms of their anesthetic potency and duration of action explain variability in hemodynamics [62, 63]. Future studies need to compare identical doses of local anesthetic agent with and without vasoconstrictor to determine the isolated effects of epinephrine on hemodynamic stability.

## 5. LIMITATIONS

This study has several limitations that should be considered. The single-center design, conducted at a specific university clinic, may limit the generalizability of our findings to broader, more diverse patient populations with different comorbidities or medication regimens. The short-term follow-up of 30 minutes for biomarker analysis provides only a snapshot of the acute inflammatory response and does not capture the full cascade, which can evolve over several hours or days. Furthermore, while we analyzed key genetic polymorphisms in *CYP1A2* and *ADRB2*, our analysis was not exhaustive; other genetic and epigenetic factors could also influence individual responses to anesthetics. The study also focused solely on single-tooth extractions, and the findings may not be directly applicable to more complex or prolonged surgical procedures. The study design was that we compared lidocaine with epinephrine to mepivacaine plain instead of comparing the same local anesthetic with and without epinephrine. Future multi-center studies with longer follow-up periods and a broader genetic screening panel are warranted to confirm these findings and enhance their clinical applicability.

## CONCLUSION

In controlled hypertensive patients undergoing tooth extraction, the use of 2% lidocaine with 1:80,000 epinephrine was associated with significantly greater hemodynamic stability and a less pronounced systemic inflammatory response compared to 3% mepivacaine plain. The study's findings support the view that achieving profound local anesthesia is critical for minimizing cardiovascular stress and that the judicious use of vasoconstrictors is safe and beneficial in this patient population. The exploratory pharmacogenetic data suggest that individual variability in drug metabolism (*CYP1A2*) and receptor sensitivity (*ADRB2*) may play a role in patient outcomes, warranting further investigation into personalized anesthetic strategies. Future research should focus on larger, multi-center trials with diverse populations and longer follow-up periods to validate these findings and explore the potential for genetic screening to guide anesthetic selection in high-risk patients.

## AUTHORS' CONTRIBUTIONS

The authors confirm their contributions to the paper as follows: M.S.A.: Responsible for conceptualization, validation, investigation, resources, supervision, and funding acquisition; H.J.A.: Contributed to conceptualization, methodology, validation, and writing of the original draft; S.M.S.: Responsible for methodology, software, formal analysis, and visualization and contributed to writing, review, and editing; S.M.I.: Contributed to investigation, data curation, writing of the original draft, and project administration.

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| ACC/AHA | = | American College of Cardiology/American Heart Association |
| ACE | = | Angiotensin-Converting Enzyme |
| ADRB2 | = | Adrenergic Beta-2 Receptor |
| BMI | = | Body Mass Index |
| BP | = | Blood Pressure |
| bpm | = | Beats per minute |
| CYP1A2 | = | Cytochrome P450 Family 1 Subfamily A Member 2 |
| DBP | = | Diastolic Blood Pressure |
| DNA | = | Deoxyribonucleic Acid |
| ELISA | = | Enzyme-Linked Immunosorbent Assay |
| HR | = | Heart Rate |
| hs-CRP | = | High-Sensitivity C-Reactive Protein |
| IL-6 | = | Interleukin-6 |
| IRB | = | Institutional Review Board |
| LA | = | Local Anesthetic |
| PCR | = | Polymerase Chain Reaction |
| SBP | = | Systolic Blood Pressure |
| SD | = | Standard Deviation |
| SNP | = | Single Nucleotide Polymorphism |
| TNF-α | = | Tumor Necrosis Factor-alpha |

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Institutional Review Board of the University of Kufa (IRB Approval No. KU-2024-15; dated August 15, 2024).

## HUMAN AND ANIMAL RIGHTS

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committees and with the 1975 Declaration of Helsinki, as revised in 2013.

## CONSENT FOR PUBLICATION

All participants provided written informed consent prior to enrollment.

## STANDARDS OF REPORTING

CONSORT guidelines were followed.

## AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author.

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this study.

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