



Original

Hemodynamic changes during exodontia in hypertensive and normotensive patients following injection of local anesthetics with and without epinephrine: a prospective comparative study

Abhijith George¹, Mandeep Sharma², Prasanna Kumar³, Sneha Kulkarni³, Vinay Patil⁴ y Jacob John Plackal⁵

¹Department of Head and Neck Surgical Oncology. Lakeshore Hospital. Cochin, India. ²Department of Dentistry. Government Medical College. Kathua, Jammu, India. ³Department of Oral Surgery. KVG Dental College and Hospital. Sullia, India. ⁴Department of Oral and Maxillofacial Surgery. Nanded Rural Dental College & Research Center. ⁵Sri Shankara Cancer Hospital and Research Centre. Basavanagudi, Bangalore, India

INFORMACIÓN DEL ARTÍCULO

Historia del artículo:

Recibido: 19 de junio de 2021

Aceptado: 10 de marzo de 2022

Keywords:

Hemodynamic changes, hypertension, epinephrine, extraction.

A B S T R A C T

Introduction: Hypertensive patients are frequently encountered in routine dental practice and exodontia procedures. Possibility of cardiovascular complications can be anticipated in these patients. This study compares blood pressure, heart rate, and peripheral capillary oxygen saturation, in normotensive and hypertensive patients prior to, during and after dental extractions. **Patients and methods:** A prospective comparative study was carried out in 100 (N = 100) patients between the age group of 40-70 years. 50 patients diagnosed with Stage I hypertension and 50 patients who were normotensives, requiring extraction of tooth were recruited. They were further divided into four groups namely, A, B, C and D, each consisting of 25 (n = 25). Group A included patients with controlled hypertension who were administered local anesthesia with epinephrine, while Group B had patients with controlled hypertension who were administered local anesthesia without epinephrine. Group C had normotensive patients who were administered local anesthesia with epinephrine and normotensive patients who were administered local anesthesia without epinephrine were under group D. The patients were evaluated at preoperative, intra operatively and post-operative interval for blood pressure, heart rate and peripheral oxygen saturation.

Results: The sample consisted of 42 males and 58 females with a mean age of 42.6, 49.9, 40.6 and 31.6 years in group A, B, C and D respectively. Both systolic and diastolic blood pressure was increased after administration of anesthetic in all four group and decreased lower than baseline level after the surgical procedure. Heart rate was also found to be increased in all groups. A significant difference in peripheral oxygen saturation levels between group A and group B was observed post operatively.

Conclusion: The use of epinephrine in local anesthetics have no significant role in altering the blood pressure and heart rate of hypertensive as well as normotensive patients.

*Autor para correspondencia:

Correo electrónico: mandeep.sharma053@gmail.com (Mandeep Sharma).

DOI: [10.20986/recom.2022.1296/2021](https://doi.org/10.20986/recom.2022.1296/2021)

1130-0558/© 2022 SECOM CyC. Publicado por Inspira Network. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Cambios hemodinámicos durante la extracción en pacientes hipertensivos y normotensivos tras la inyección de anestésicos locales con y sin epinefrina: un estudio comparativo prospectivo

R E S U M E N

Palabras clave:

Cambios hemodinámicos, hipertensión, adrenalina, extracción.

Introducción: Con frecuencia, en la práctica dental habitual y en los procedimientos de exodoncia se encuentran pacientes hipertensos. En estos pacientes se pueden anticipar posibles complicaciones cardiovasculares. Este estudio compara la presión arterial, la frecuencia cardíaca y la saturación de oxígeno periférico en pacientes normotensos e hipertensos antes, durante y después de las extracciones dentarias.

Pacientes y métodos: Se realizó un estudio comparativo prospectivo en 100 pacientes (n = 100) entre un grupo de edad de 40-70 años. Se reclutaron 50 pacientes con diagnóstico de hipertensión en estadio I y 50 pacientes normotensos que requirieron extracción dentaria. Se dividieron además en cuatro grupos, A, B, C y D, cada uno de los cuales constaba de 25 (n = 25). El grupo A incluyó pacientes con hipertensión controlada a los que se les administró anestesia local con epinefrina, mientras que el grupo B tenía pacientes con hipertensión controlada a los que se les administró anestesia local sin epinefrina. El grupo C tenía pacientes normotensos a los que se les administró anestesia local con epinefrina y los pacientes normotensos a los que se les administró anestesia local sin epinefrina estaban en el grupo D. En el intervalo preoperatorio, intraoperatorio y postoperatorio se evaluaron la presión arterial, frecuencia cardíaca y saturación de oxígeno periférico de los pacientes.

Resultados: La muestra estuvo formada por 42 hombres y 58 mujeres con una edad media de 42,6, 49,9, 40,6 y 31,6 años en los grupos A, B, C y D, respectivamente. Tanto la presión arterial sistólica como la diastólica aumentó después de la administración de anestésico en los cuatro grupos y disminuyó por debajo del nivel inicial después del procedimiento quirúrgico. También se encontró que la frecuencia cardíaca aumentó en todos los grupos. Después de la operación, se observó una diferencia significativa en los niveles de saturación de oxígeno periférico entre el grupo A y el grupo B.

Conclusión: El uso de adrenalina en anestésicos locales no tiene un papel significativo en la alteración de la presión arterial y la frecuencia cardíaca de pacientes hipertensos y normotensos.

INTRODUCTION

The exponential rise in the life expectancy and the poly morbid states has led to an increase in the high-risk patients in the routine dental practice. The life expectancy of an untreated hypertensive patient decreases by one to two decades. Mild hypertension increases risk of complications like apoplectic or cardiac insult, if left untreated. Thus hypertension, among many other co morbidities, is one of the high-risk groups for routine dental procedures. Hypertensive patients are one of the most commonly encountered patients undergoing exodontia. Chances of cardiovascular complication should be anticipated in these patients during tooth extraction which necessitates the need for a well-equipped dental set up¹.

Monitoring of patient's vitals and general condition is advocated during traumatic extractions of the teeth or if the psychological condition of patient makes such control desirable to enhance safety. Surgeon can acknowledge and identify increased risk situations with prompt diagnosis and can prevent possible complications during oral surgical procedures. Monitoring the hemodynamic changes in a patient permits the surgeon to operate with increased safety as it can prevent emergency situations in clinical practice². Local anesthetic solution used in den-

tistry contains epinephrine which increases the duration and potency of anesthesia. This also reduces the concentration of the anesthetic solution in plasma and improves control over bleeding locally through vasoconstriction³. However, it can induce hemodynamic changes during the surgical exodontia synergistically with other factors, such as anxiety or stress⁴. Adverse cardiac effects and possibility of systemic absorption, has limited its use in cardiac patients. Moreover, due to the possibility of its massive systemic absorption, the use of this drug has been under criticism as it could result in undesirable cardiovascular effects⁴.

Since epinephrine is a vasopressor, it was implicated as an etiological agent in certain clinical cases of hypertension⁵. The hemodynamic and cardiovascular changes caused due to the administration of exogenous epinephrine makes its use a controversy among hypertensive individuals⁶. Monitoring the patient's pulse, blood pressure and peripheral oxygen saturation (SPO₂) before and during procedure increases the safety factor leading to a more relaxed surgical atmosphere and helps relieve dental anxiety in the patient to a certain extent too⁷. There is a lack of evidence comparing the hemodynamic changes in hypertensive and normotensive patients.

This study compares hemodynamic changes namely blood pressure, heart rate, and peripheral capillary oxygen saturation,

in normotensive and hypertensive patients prior to, during and after extraction of the teeth using local anesthesia with and without epinephrine.

MATERIALS AND METHODS

A total of 100 patients (n = 100) between the age group of 40-70 years reporting to the K.V.G Dental College and Hospital, Sullia were recruited. 50 of whom were diagnosed with Stage I hypertension (blood pressure more than 130/86 mmHg and less than 159/99 mmHg) and another 50 having blood pressure in normal physiological ranges, requiring extraction of tooth, during December 2016-December 2019. The study was approved by institutional review board. Criteria for selection of patients are given in Table I.

The subjects were divided into four groups based on ASA (American society of Anesthesiologists) physical status classification⁸ each consisting of 25 patients as follows:

- Group A: patients with controlled hypertension who were administered local anesthesia with epinephrine.
- Group B: patients with controlled hypertension who were administered local anesthesia without epinephrine.
- Group C: normotensive patients who were administered local anesthesia with epinephrine.
- Group D: normotensive patients who were administered local anesthesia without epinephrine.

These patients were evaluated for blood pressure using Electronic Digital Blood Pressure monitor (Omron BP Monitor Upper Arm (Hem 7120), pulse rate and peripheral capillary oxygen saturation using Pulse oximeter (Res Pro-Pulse Oximeter) during preoperatively, intraoperatively and postoperatively.

Local anesthesia (lignocaine with epinephrine 1:80,000, LIGNOX*2 % A and lignocaine plain, LOX*2 %) was used as an anesthetic in a 2 ml syringe (UNOLOK). Standard armamentarium for extraction were also used.

A written informed consent was obtained from all the participants following which an adequate pre-surgical preparation consisting of detailed case history, blood tests wherever indicated and radiographic examination. Baseline blood pressure, pulse rate and SPO₂ was recorded in a tabular form. Local infiltration anesthetic technique was used for achieving anesthesia at the rate of 1 ml per minute at which blood pressure and SPO₂

were also recorded. Simple extraction of the teeth was started 5 minutes following administration of local anesthesia at which point intraoperatively the blood pressure, pulse and SPO₂ was recorded. Postoperatively the blood pressure, pulse and SPO₂ was recorded. Following the procedure standard post-operative instructions were given to the patients along with the antibiotics (when indicated) and analgesics. All extractions and administration of local anesthesia was performed by the same surgeon while the reading of the monitor was recorded in the pro-forma chart by the assistant. The statistical tests used for the analysis were independent sample t test (comparing means of different groups), Repeated measures ANOVA (for comparison between the groups) and Tukey HSD Post-hoc Test for significant results in ANOVA. p < 0.05 is considered as level of significance.

RESULTS

The sample consisted of 42 males and 58 females between ages of 40 to 70, participated in the study. A mean age of 45.96 years in group A, 51.38 in group B, 48.76 in group C and 45.6 in group D. There was no statistically significant difference between age and gender (p > 0.05).

The blood pressure between the groups is given in Table II were slightly higher in intra-operative period but reduced even lower than the baseline post-operatively. In group B, a slight increase in heart rate 102.56 bpm and blood pressure 139.64 mm/Hg during intra operative period. Group C and Group D also followed the same trend of increase in heart rate and blood pressure intra-operatively. Regardless of addition of vasoconstrictor, there was a mild increase in systolic and diastolic pressure after administration of anesthetic in all groups. The hypertensive patients had preoperative systolic and diastolic pressure on a higher side than normotensive patients. Heart rate increased in all groups after administration of local anesthetic. The highest values were recorded intraoperatively in group B (Table III). The SPO₂ remained almost unchanged in all four groups during measurement.

Further comparison between the parameters of all the groups revealed that blood pressure values were significantly higher in groups A and B. There was a statistical difference between hypertensive and normotensive patients irrespective of addi-

Table I. Exclusion and inclusion criteria.

Inclusion criteria	Exclusion criteria
Patients with blood pressure more than 130/86 mmHg and less than 159/99 mmHg (stage I hypertension)	Patient with other systemic illness or co-morbidities and with known allergies to local anesthesia (lignocaine) used in the study
Patients who were diagnosed with hypertension are grouped in Group A and Group B	Patients whose extractions were traumatic or required open method of extraction (trans-alveolar)
Patient with other systemic illness or co-morbidities and with known allergies to local anesthesia (lignocaine) used in the study	Patients with grade 2 or grade 3 tooth mobility
Patients who are not diagnosed with hypertension in whom blood pressure more than 90/60 mmHg and less than 129/85 mmHg are grouped in Group C and Group D.	Patients who required more than 4ml of anesthetic administration
Extraction procedures requiring less than 20 minutes of operatory time.	-----

Table II. Comparison of blood pressure (BP) between the four groups.

Time Interval	Group A	Group B	Group C	Group D	F value	P value
Preoperative (Baseline)						
BP Systolic (mean)	140.88	137	121.6	124.16	53.0558	0.00
BP Diastolic (mean)	88.16	84.52	79.76	79.6	17.1827	0.00
Intra operative						
BP Systolic (mean)	142.56	139.64	123.44	133.6	27.9908	0.00
BP Diastolic (mean)	88.76	85.84	79.76	82.44	18.0605	0.00
Post operative						
BP Systolic (mean)	138.88	136.72	121.88	126.92	37.0112	0.00
BP Diastolic (mean)	87.36	84.92	78.72	78.32	19.5738	0.00

Table III. Comparison of heart rate comparison between the four groups.

Heart rate	Group A	Group B	Group C	Group D	F value	P value
Heart ratepre op (mean)	82.6	80.28	77.2	77.52	2.5249	0.06
Heart rateintra op (mean)	100.48	102.56	90.72	96.48	3.3162	0.0232
Heart ratepost op (mean)	88.24	93.08	81.16	85.28	3.8374	0.0121

tion of epinephrine in hypertensive patients in their systolic blood pressure ($p = 0.00$). Comparison of change in the values after injection of anesthetic are explained by plot of means in Figures 1 and 2. Heart rate values increased intraoperatively in all the groups with a significant difference between Group B vs. Group C intra and post operatively (Figure 3). There was a statistically significant difference between group A (98.91) and group B (97.92) in postoperative SPO2 with comparison of changes illustrated in Figure 4 ($p = 0.04$).

DISCUSSION

Epinephrine is the principal vasoconstrictor being used in local anesthetic solution. The localized vasodilator effects of lignocaine in subcutaneous and submucosal vessels are counteracted by epinephrine which causes vasoconstriction in the surrounding tissues. This vasoconstriction of tissues decreases the bleeding at surgical site and increases efficacy of anesthesia while reducing the plasma concentration of anesthetic agent being used and therefore decreased systemic toxicity⁹. Furthermore, bleeding control can be very useful as it improves visibility and access at surgical site¹. Many clinicians do not use epinephrine in hypertensive patients and patients having cardiac complications. The systemic absorption of epinephrine and its adverse cardiac effects thereafter limits its use in such patients^{10,11}. Factors responsible for such a hyper dynamic cardiovascular response may include pain at the injection site, intravascular injection, psychogenic stress, drug interaction, or systemic absorption of the epinephrine¹². Previous investigations have revealed that the inclusion of vasoconstrictor causes the arterial plasma epinephrine concentration to double but meantime was also associated with cardiovascular stability in young healthy patients. Many investigators have concluded that

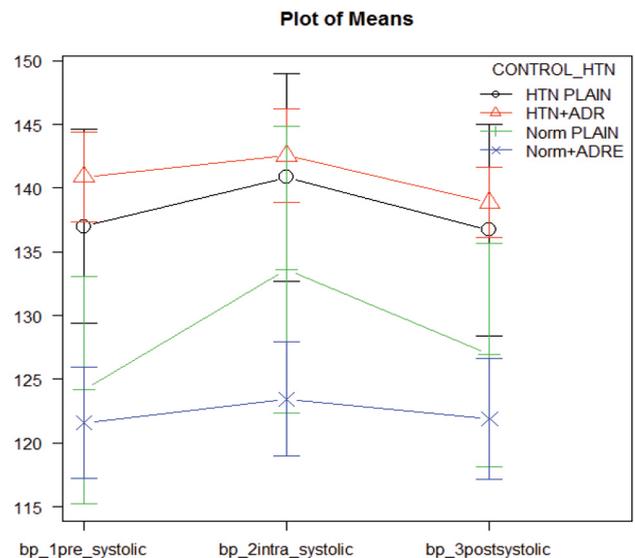


Figure 1. The trends in the fluctuations of mean blood pressure over time in each group are demonstrated by the slopes of the graph.

local anesthetic solutions containing epinephrine are usually well tolerated by patients with mild and moderate degrees of cardiovascular disease¹³⁻¹⁶. Anxiety, stress and pain during dental treatment results in release of endogenous catecholamines which can result in unacceptable cardiovascular effects¹⁷. On the contrary, some studies show that rapid absorption of exogenous epinephrine result in this increase rather than the endogenous release of catecholamines^{18,19}. Blood pressure is affected in the same way by vasoconstrictors as well as by other factors

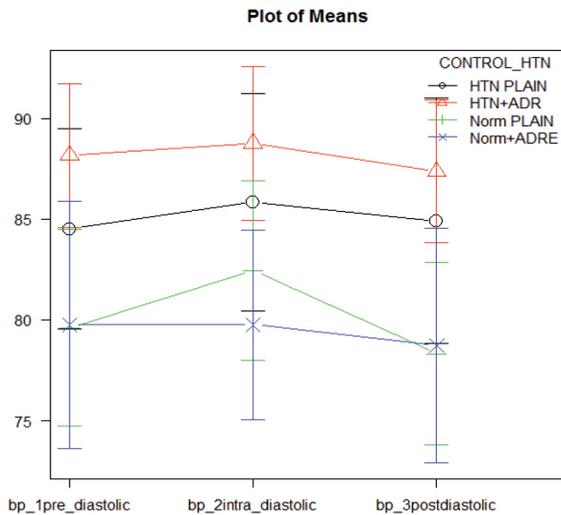


Figure 2. The alteration follow the same pattern in all the four groups.

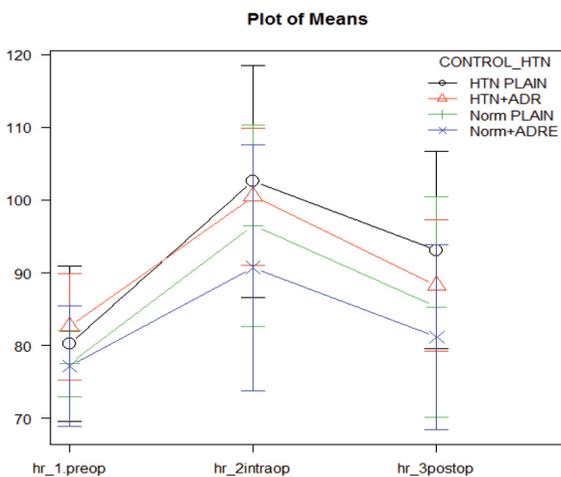


Figure 3. The trends in the fluctuations of heart rate over time in each group are demonstrated by the slopes of the graph.

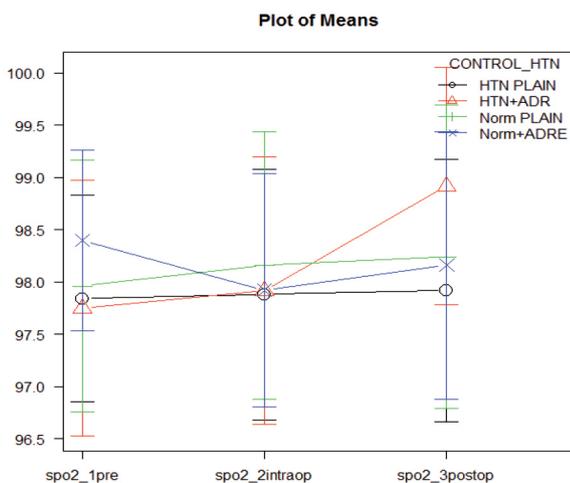


Figure 4. The trends in the fluctuations of SPO₂ over time in each group are demonstrated by the slopes of the graph.

such as stress and anxiety²⁰. So, hypertensive patients constitute an important risk group.

Patients that were considered hypertensive in this study were those who were previously diagnosed by a physician and have their blood pressure presently well controlled with antihypertensive medication at the time of this study. As per the ASA (American Society of Anesthesiologist) physical status classification, this group of patients belonged to class II. In our study mean age of 45.96 years in group A, 51.38 in group B, 48.76 in group C and 45.6 in group D was found. There was no statistically significant difference between age and gender ($p > 0.05$).

Both systolic and diastolic blood pressure increased slightly after administration of anesthetic in all four group regardless of addition of vasoconstrictor and decreased after the surgical procedure to levels even lower than those recorded at baseline. Since the increase was also noticed in patients who were given plain anesthetic, it can be attributed to the release of endogenous catecholamines due to the pain, anxiety and stress of the procedure. Our study results were in accordance to the results reported by Nichols²¹. In another study, a steady but insignificant increase in systolic blood pressure was observed in hypertensive subjects after administration of anesthesia in both lignocaine epinephrine and plain lignocaine groups³.

Gungormus and Buyukkurt in their study found out that no significant change is seen in the blood pressure of hypertensive patients following administration of epinephrine-containing 2 % articaine²². Matsumura et al demonstrated that catecholamine present in local anesthetic solution caused an increase in blood pressure and pulse rate²³. The hypertensive patients in this study failed to respond to a great extent to lignocaine-epinephrine than plain lignocaine injection.

On comparing intraoperative systolic blood pressure, there was a statistically significant results between groups A and C, A and D, B and C, B and D and C and D. We concur that there is a significant difference between hypertensive and normotensive patients irrespective of addition of epinephrine in hypertensive patients in their systolic blood pressure. Also, there is significant difference in normotensive patients who received anesthetic with epinephrine. The mean intraoperative systolic blood pressure was more in normotensive patients receiving plain local anesthetic as compared with patients administered local anesthetic with epinephrine. This may be attributed to reduced action of local anesthetic leading to reduced pain control and due to the vasodilating action of systemically absorbed local anesthetic leading directly or indirectly through release of endogenous catecholamines to the circulation. Post-operative systolic and diastolic pressure followed the same trend as their intraoperative measurement. However, Significant difference in systolic pressure between hypertensive groups and normotensives groups was observed. But there is no significant difference between groups C and D, indicating that addition of epinephrine has no effect on diastolic blood pressure of normotensive patients. Based on this finding, it may be said that it is beneficial to use local anesthesia with vasoconstrictor for patients with controlled hypertension, provided all precautions to prevent inadvertent intravascular injection are undertaken by the care provider. The observed increase can further be attributed to factors such as psychological and physical stress, including that from painful stimuli, and patient anxiety since increased levels were observed in these groups. Other studies have shown

slight variation from these results. Ogunlewe et al found no changes in the blood pressure and pulse rate response following injection of local anesthetic with epinephrine in hypertensive patients²⁴. With Gungormus and Buyukkurt and Meyer reporting similar results^{22,25}.

Heart rate increased in all groups after administration of local anesthetic. The highest values were recorded intraoperatively in group B (hypertensive patients administered with plain local anesthetic). In all groups the heart rate returned back close to baseline reading postoperatively. In analysis there was a significant difference between group B and group C. But it is of less relevance as there was no statistical difference between groups A and group B and between group C and group D. But from the plot of mean heart rate we concur that both preoperative and intraoperative heart rates were higher in hypertensive patients as compared with normotensive patients. Also, the increase in heart rate cannot be attributed to the addition of epinephrine or hypertension as it increases almost equally in all four groups. The study conducted by Tolas et al., observed a significant increase in circulating epinephrine concentration, almost doubling plasma epinephrine concentration after injecting local anesthetic with 1:100000 epinephrine while no significant increase was noted in subjects who received injections of plain local anesthetic although the hemodynamic variables were stable²⁶. They concluded that epinephrine in conjunction with local anesthesia was associated with cardiovascular stability in young healthy patients and the increased plasma epinephrine results from the rapid absorption of exogenous epinephrine. The study conducted by Baguena et al. in Spanish population found significant changes in heart rate and blood pressure due to anxiety and fear related issues²⁰. Alemany-Martínez et al. reported changes in heart rate were affected by pain, individual factors such as age, gender, hypertension, previous experience with dental treatments, and psychological response²⁷. In his study, males showed higher blood pressure values than females, while the latter showed higher pulse rate values and anxiety levels. In another study pulse rate remained stable or decreased during local analgesia and peaked during exodontia and then decreased 10 minutes after treatment. Also this study shows a transient period of bradycardia immediately after injection of local anesthesia which contradicts the results of our study in which there is a steady increase in heart rate following local anesthesia administration in all the groups. Yokobayashi et al found that administration of local analgesic lowers the pulse rate and infiltration was more significant than block analgesia in this regard²⁸. The results of our study were in agreement with the study conducted by Abraham-Inpijn et al who reported tachycardia > 120 beats/min with a maximum value of 154 beats/min during treatment²⁹. In a study which evaluated changes in heart rate during third molar surgery, the

lowest heart rates were recorded in the waiting room, in the dental chair, during anaesthesia, when applying surgical drapes, during suturing, and at the end of the procedure. The highest values were obtained during the time-out procedure, incision, and alveolotomy which is similar to our study³⁰.

The SPO₂ remained almost unchanged in all four groups during measurement. There was a statistically significant difference between group A and group B in postoperative SPO₂. But there was no significance in preoperative and intraoperative SPO₂ between the groups. From this data, we concur that there may be a correlation of SPO₂ between hypertensive patients administered with epinephrine. The SPO₂ have increased considerably postoperatively in patients administered local anesthetic with epinephrine than all other groups, whereas it has remained almost constant for hypertensive and normotensive patients administered with plain local anesthetic. Similar results were obtained in a study by Silvestre et al who did not observe any significant differences in oxygen saturation but had also remained insignificant in postoperative period¹⁶ (Table IV). Some studies have shown transient hypoxia after administration of local anesthesia³¹.

However, further studies with larger sample size are warranted to substantiate our results. Also, we acknowledge the potential for adverse cardiovascular effects by adrenergic stimulation in high-risk patients when a vasoconstrictor is used. That is the reason we have included only stage I hypertensive patients in Group A and B. Patients with higher blood pressure than stage I were excluded from our study. The type of vasoconstrictor combined with the local anesthetic and the total dose injected will be important clinically.

CONCLUSION

The use of epinephrine in local anesthetics have no significant role in altering the blood pressure and heart rate of stage I hypertensive as well as normotensive patients. The Systolic blood pressure increases in normotensive patients administered with plain local anesthetics than when local anesthetics is given with epinephrine. Addition of epinephrine has an effect on post-operative SPO₂ in hypertensive patients. Oxygen saturation increases in patients administered local anesthetic with epinephrine.

CONFLICTS OF INTEREST/COMPETING INTERESTS

The authors have no relevant conflicts of interest/competing interests.

Table IV. Comparison of oxygen saturation between the four groups.

SPO ₂	Group A	Group B	Group C	Group D	F value	P value
SPO ₂ pre op (mean)	97.8	97.84	98.4	97.96	1.6182	0.1902
SPO ₂ intra op (mean)	97.84	97.88	97.92	98.16	0.3416	0.7953
SPO ₂ post op (mean)	98.91	97.92	98.16	98.24	2.8454	0.0417

FUNDING

- The authors did not receive support from any organization for the submitted work.
- No funding was received to assist with the preparation of this manuscript.
- No funding was received for conducting this study.
- No funds, grants, or other support was received.

REFERENCES

1. Rhodus NL, Little JW. Dental management of the patient with cardiac arrhythmias: an update. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2003;96(6):659-68. DOI: 10.1016/s1079-2104(03)00380-9.
2. Arrigoni J, Lambrecht JT, Filippi A. Cardiovascular monitoring and its consequences in oral surgery. *Schweiz Monatsschr Zahnmed.* 2005;115(3):208-13.
3. Sisk AL. Vasoconstrictors in local anesthesia for dentistry. *Anesth Prog.* 1992;39(6):187-93.
4. Replogle K, Reader A, Nist R, Beck M, Weaver J, Meyers WJ. Cardiovascular effects of intraosseous injections of 2 percent lidocaine with 1:100,000 epinephrine and 3 percent mepivacaine. *J Am Dent Assoc.* 1999;130(5):649-57. DOI: 10.14219/jada.archive.1999.0274.
5. Tolas AG, Pflug AE, Halter JB. Arterial plasma epinephrine concentrations and hemodynamic responses after dental injection of local anesthetic with epinephrine. *J Am Dent Assoc.* 1982; 104(1):41-3. DOI: 10.14219/jada.archive.1982.0114.
6. Brown MJ. The role of epinephrine in essential hypertension in man. In: Paton W., Mitchell J., Turner P. (eds) *IUPHAR 9th International Congress of Pharmacology.* London: Palgrave; 1984.
7. Bader JD, Bonito AJ, Shugars DA. Cardiovascular Effects of Epinephrine in Hypertensive Dental Patients: Summary. 2002 Mar. In: *AHRQ Evidence Report Summaries.* Rockville (MD): Agency for Healthcare Research and Quality (US); 1998-2005. 48.
8. Dripps RD. New classification of physical status. *Anesthesiol.* 1963;24:111.
9. Le SH, Tonami K, Umemori S, Nguyen LT, Ngo LT, Matak S. The potential of heart rate variability for exploring dental anxiety in mandibular third molar surgery. *Int J Oral Maxillofac Surg.* 2018;47(6):809-15. DOI: 10.1016/j.ijom.2018.01.019.
10. Toju K, Shiraishi K, Hakozaki T, Isosu T, Murakawa M. Plasma ropivacaine concentration following ultrasound-guided subcostal transversus abdominis plane block in adults. *J Anesth.* 2015;29(1):146-8. DOI: 10.1007/s00540-014-1864-0.
11. Corvetto MA, Echevarría GC, De La Fuente N, Mosqueira L, Solari S, Altermatt FR. Comparison of plasma concentrations of levobupivacaine with and without epinephrine for transversus abdominis plane block. *Reg Anesth Pain Med.* 2012;37(6):633-7. DOI: 10.1097/AAP.0b013e31826c330a.
12. Naguib M, Magboul MM, Samarkandi AH, Attia M. Adverse effects and drug interactions associated with local and regional anaesthesia. *Drug Saf.* 1998;18(4):221-50. DOI: 10.2165/00002018-199818040-00001.
13. Niwa H, Sugimura M, Satoh Y, Tanimoto A. Cardiovascular response to epinephrine-containing local anesthesia in patients with cardiovascular disease. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2001;92(6):610-6. DOI: 10.1067/moe.2001.118903.
14. Elad S, Admon D, Kedmi M, Naveh E, Benzki E, Ayalon S, et al. The cardiovascular effect of local anesthesia with articaine plus 1:200,000 adrenalin versus lidocaine plus 1:100,000 adrenalin in medically compromised cardiac patients: a prospective, randomized, double blinded study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2008;105(6):725-30. DOI: 10.1016/j.tripleo.2008.02.005.
15. Nusstein J, Berlin J, Reader A, Beck M, Weaver JM. Comparison of injection pain, heart rate increase, and postinjection pain of articaine and lidocaine in a primary intraligamentary injection administered with a computer-controlled local anesthetic delivery system. *Anesth Prog.* 2004;51(4):126-33. DOI: 10.2344/0003-3006(2006)53[126:TEOASI]2.0.CO;2.
16. Silvestre FJ, Salvador-Martínez I, Bautista D, Silvestre-Rangil J. Clinical study of hemodynamic changes during extraction in controlled hypertensive patients. *Med Oral Patol Oral Cir Bucal.* 2011;16(3):e354-8. DOI: 10.4317/medoral.16.e354.
17. Kobilansky C, Lanzinger I, Philippu A. Release of endogenous catecholamines in the nucleus tractus solitarii during experimentally induced blood pressure changes. *Naunyn Schmiedeberg Arch Pharmacol.* 1988;337(2):125-30. DOI: 10.1007/BF00169238.
18. Singewald N, Schneider C, Philippu A. Effects of blood pressure changes on the catecholamine release in the locus coeruleus of cats anaesthetized with pentobarbital or chloralose. *Naunyn Schmiedeberg Arch Pharmacol.* 1993;348(3):242-8. DOI: 10.1007/BF00169151.
19. Rood JP, Cannell H. Plasma levels of lignocaine after peri-oral injections of two different concentrations. *Pharmacol Ther Dent.* 1978;3(1):45-7.
20. Baguena JC, Chiva F. Effects of anesthetics for dental use about blood pressure and heart rate. *Rev Eur Odontostomatol.* 1999;5:291.
21. Nichols C. Dentistry and hypertension. *J Am Dent Assoc.* 1997; 128(11):1557-62. DOI: 10.14219/jada.archive.1997.0096.
22. Gungormus M, Buyukkurt MC. The evaluation of the changes in blood pressure and pulse rate of hypertensive patients during tooth extraction. *Acta Med Austriaca.* 2003;30(5):127-9.
23. Matsumura K, Miura K, Kurokawa H, Abe I, Takata Y. Lack of association between QT dispersion and blood pressure response during dental surgery. *Clin Exp Pharmacol Physiol.* 2001;28(9):748-51. DOI: 10.1046/j.1440-1681.2001.03514.x.
24. Ogunlewe MO, James O, Ajuluchukwu JN, Ladeinde AL, Adeyemo WL, Gbotolorun OM. Evaluation of haemodynamic changes in hypertensive patients during tooth extraction under local anaesthesia. *West Indian Med J.* 2011;60(1):91-5.
25. Meyer FU. Haemodynamic changes under emotional stress following a minor surgical procedure under local anaesthesia. *Int J Oral Maxillofac Surg.* 1987;16(6):688-94. DOI: 10.1016/s0901-5027(87)80054-1.
26. Tolas AG, Pflug AE, Halter JB. Arterial plasma epinephrine concentrations and hemodynamic responses after dental injection of local anesthetic with epinephrine. *J Am Dent Assoc.* 1982; 104(1):41-3. DOI: 10.14219/jada.archive.1982.0114.
27. Alemany-Martínez A, Valmasada-Castellón E, Berini-Aytés L, Gay-Escoda C. Hemodynamic changes during the surgical removal of lower third molars. *J Oral Maxillofac Surg.* 2008; 66(3):453-61. DOI: 10.1016/j.joms.2007.06.634.
28. Yokobayashi T, Nakajima T, Yagata H, Yatabe Y. Changes of heart rate during administration of local anesthetics in the oral region. *J Oral Surg.* 1977;35(12):961-7.
29. Abraham-Inpijn L, Borgmeijer-Hoelen A, Gortzak RA. Changes in blood pressure, heart rate, and electrocardiogram during dental treatment with use of local anesthesia. *J Am Dent Assoc.* 1988;116(4):531-6. DOI: 10.14219/jada.archive.1988.0318.
30. Hollander MH, Schortinghuis J, Vissink A. Changes in heart rate during third molar surgery. *Int J Oral Maxillofac Surg.* 2016; 45(12):1652-7. DOI: 10.1016/j.ijom.2016.08.004.
31. Ashkenazi M, Greenberg BP, Sarnat H. Severe hypoxia following local anesthesia in a sedated patient: case report. *Pediatr Dent.* 1998;20(5):359-60.