Methemoglobin Levels in Generally Anesthetized Pediatric Dental Patients Receiving Prilocaine Versus Lidocaine

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The purpose of this study was to measure and compare peak methemoglobin levels and times to peak methemoglobin levels following the use of prilocaine and lidocaine in precooperative children undergoing comprehensive dental rehabilitation under general anesthesia. Ninety children, 3–6 years of age, undergoing dental rehabilitation under general anesthesia were enrolled and randomly assigned into 3 equal groups: group 1, 4% prilocaine plain, 5 mg/kg; group 2, 2% lidocaine with 1 : 100,000 epinephrine, 2.5 mg/kg; and group 3, no local anesthetic. Subjects in groups 1 and 2 were administered local anesthetic prior to restorative dental treatment. Methemoglobin levels (SpMET) were measured and recorded throughout the procedure using a Masimo Radical-7 Pulse Co-Oximeter (Masimo Corporation, Irvine, Calif, RDS-1 with SET software with methemoglobin interface). Data were analyzed using chi-square, one-way analysis of variance (ANOVA), and Pearson correlation (significance of $P < .05$). Group 1 had a significantly higher mean peak SpMET level at 3.55% than groups 2 and 3 at 1.63 and 1.60%, respectively. The mean time to peak SpMET was significantly shorter for group 3 at 29.50 minutes than that of group 1 at 62.73 and group 2 at 57.50 minutes. Prilocaine, at 5 mg/kg in pediatric dental patients, resulted in significantly higher peak SpMET levels than lidocaine and no local anesthetic. In comparison to no local anesthetic, the administration of prilocaine and lidocaine caused peak SpMET levels to occur significantly later in the procedure.

Key Words: Methemglobin; Methemoglobinemia; Prilocaine; Lidocaine.

Local anesthetics are essential medications for the treatment of most dental diseases. They have been used for over 100 years for the management of perioperative dental pain in both adults and children. It is difficult to overstate the importance that local anesthetics have played in the development of the dental profession.[1]

The availability of a variety of local anesthetics for the provision of dental care enables dental practitioners to select the local anesthetic based on the patient's medical history and the requirements of the treatment to be performed.[2] As with every medication, each local anesthetic has unique pharmacological properties and specific benefits and risks when selected for use in dental treatment.[3] An important risk with some injectable local anesthetics is the formation of methemoglobin.[4,5]

There are currently 5 injectable local anesthetics prepared for and marketed to the dental profession:

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articaine, bupivacaine, lidocaine, mepivacaine, and prilocaine.[2,3,6,7] Lidocaine is the prototypical amide local anesthetic agent and remains the most commonly used dental local anesthetic in the US with a 60% US market share.[2,3] Although it has a smaller market share in the US, prilocaine is also an effective amide local anesthetic.[2] Prilocaine sales represent approximately 6% of the US dental local anesthetic market.[2,3] Lidocaine and prilocaine have both been reported to induce the formation of methemoglobin.[5,8] However, there is no direct evidence supporting the claims that lidocaine definitively induces the formation of methemoglobin.[4] In fact, the extent of the formation of methemoglobin has not been reported for either local anesthetic.

Hemoglobin is a protein molecule that constitutes about one third of the red blood cell volume. Hemoglobin has 3 major roles in the red blood cell: (1) to transport oxygen from the lungs to all peripheral cells, thus serving their metabolic needs; (2) to carry carbon dioxide, a by-product of cellular metabolism, from the peripheral cells to the lungs where it is removed by exhalation; and (3) to act as a buffer for the body's acid-base system. The hemoglobin molecule includes 4 porphyrin rings, each of which contains an atom of iron in the ferrous state (Fe^{2+}). These 4 molecules in hemoglobin are known as heme groups. The iron in the ferrous state in the heme groups allows hemoglobin to optimally transport oxygen and carbon dioxide in a physiologic manner.[4]

Methemoglobin is a form of hemoglobin in which 1 or more of the ferrous ions found in the 4 heme groups have been oxidized to become ferric ions (Fe^{3+}). The presence of the ferric ion(s) alters the molecular shape and function of the newly formed methemoglobin. This conformational change of the new molecule inhibits its ability to bind oxygen and causes it to bind a water molecule instead. In comparison to hemoglobin, methemoglobin has an increased affinity for its bound oxygen and a decreased affinity for any unbound oxygen. Consequently, less oxygen is transported and released to peripheral tissues, which can result in tissue hypoxia.[4,8–10] Furthermore, with less oxygen being released in the periphery, the affinity for carbon dioxide is reduced. As a result, less carbon dioxide is removed from the tissues and peripheral acidosis may ensue.[4]

Human physiologic blood levels of methemoglobin normally range between 0% and 2% as a result of the oxidation of hemoglobin by the prototypical oxidant oxygen. The human body has several protective physiologic mechanisms that reduce methemoglobin to hemoglobin. The continuous reduction of methemoglobin to hemoglobin by these physiologic systems aids in maintaining homeostasis of the oxygen delivery system in the body. The predominant enzyme system for the reduction of methemoglobin to hemoglobin is nicotinamide adenine dinucleotide–dependent methemoglobin reductase (also known as cytochrome-b5 reductase). An alternate enzyme system that plays a lesser role in methemoglobin reduction and reduces only a small fraction of methemoglobin to hemoglobin is nicotinamide adenine dinucleotide phosphate–methemoglobin reductase. Biochemical pathways that use ascorbic acid and glutathione are also involved in reducing oxidized hemoglobin, but to an even smaller extent.[4,8,9,11,12]

When an individual is exposed to an exogenous oxidizing agent of sufficient dosage and potency, the rate of methemoglobin formation can overwhelm the protective reduction mechanisms. This results in higher than normal blood levels of methemoglobin, causing the condition known as acquired methemoglobinemia.[4,11] Examples of medications that may cause elevated methemoglobin levels include nitrates (nitroglycerin), nitrites (amyl nitrite), antiemetics (metoclopramide), antibiotics (trimethoprim, sulfonamides, and dapsone), and local anesthetics (prilocaine and benzocaine).[4,8–10,12] The liberal use of benzocaine in infant teething gels and topical anesthetic sprays is a concern.[4,5,8–10,12] Exposure to industrial agents can also cause acquired methemoglobinemia.[8,9,11]

The severity of the signs and symptoms of acquired methemoglobinemia is directly proportional to the amount of methemoglobin present in the blood. Healthy individuals are usually asymptomatic when methemoglobin levels are below 15%. Signs of tissue hypoxia, such as cyanosis, usually become evident when the levels range between 15% and 20%.[4,8–10,12] As methemoglobin blood levels increase, oxygenated blood changes color from bright red to chocolate brown.[8,9,12] When blood levels between 20% and 30% are achieved, individuals may develop mental status changes, such as headaches, fatigue, dizziness, and syncope. Levels of 30–50% can cause confusion, tachycardia, and tachypnea. At levels greater than 50%, dysrhythmias, seizures, coma, acidosis, and death can occur.[4,8–10,12] Patients with compromised oxygen transport disorders, such as anemia, cardiovascular disease, lung disease, or sepsis, or with abnormal hemoglobins (ie, carboxyhemoglobin, sulfhemoglobin, or hemoglobin found in sickle cell disease) may experience moderate to severe symptoms with methemoglobin levels as low as 5%.[12]

Treatment for symptomatic acquired methemoglobinemia includes the administration of a 1% solution of methylene blue at 1–2 mg/kg given intravenously over 5 minutes. This may be repeated if symptoms do not resolve in 20–30 minutes. Methylene blue does not directly reduce the oxidized hemoglobin. Methylene blue is first reduced by the enzyme nicotinamide adenine dinucleotide phosphate–methemoglobin reductase to

Table 1. Study Groups

Study Group	*Local Anesthetic Agent to Be Administered*	*Dosage, mg/kg*
1 (n = 30)	4% prilocaine plain	5
2 (n = 30)	2% lidocaine with 1:100,000 epinephrine	2.5
3 (n = 30) (negative control)	No local anesthetic	—

leukomethylene blue, which then reduces the methemoglobin to hemoglobin.[4,5,8,9]

Although dental clinicians are often aware that the formation of methemoglobin is induced by specific dental local anesthetics, they are less aware of the induced levels and toxic manifestations that may ensue.[4,12] Research has been conducted on the levels of methemoglobin formed following the use of injectable local anesthetics for routine medical surgical procedures. However, there has been little research conducted on methemoglobin formation associated with the administration of injectable local anesthetics for dental treatment.[13–15] Based on the widespread use of local anesthetics in dentistry and their ability to potentially cause methemoglobinemia, dental practitioners need more information on the disorder and its toxic manifestations. It is particularly important that dental clinicians treating pediatric dental patients use dosing guidelines that preclude clinical toxicity.

The purpose of this study was to measure and compare the peak (maximum) methemoglobin levels achieved and the lengths of time to peak methemoglobin levels following the use of injectable prilocaine and lidocaine during comprehensive dental rehabilitation in precooperative children treated under general anesthesia.

METHODS

This study was approved by the Institutional Review Board of Loma Linda University, Loma Linda, California, and was registered with ClinicalTrials.gov (Clinical Trials.gov identifier: NCT01402869). Convenience sampling was used to recruit the participation of 90 subjects that were scheduled to undergo comprehensive dental rehabilitation under general anesthesia at the Koppel Special Care Dentistry Center at Loma Linda University School of Dentistry (an accredited outpatient surgery center). Parental/legal guardian informed consent was obtained for all participating subjects. Subject inclusion criteria were (a) American Society of Anesthesiologists (ASA) I or II health status; (b) age greater than 3 years but less than 6 years; and (c) weight between 10 and 25 kg. Subject exclusion criteria included children not in the need of restorative dental treatment under general anesthesia and/or with a body mass index (BMI) less than the 5th or greater than the 95th percentile for their age and gender.

Following enrollment in the study, subject gender, age in months, weight, height, BMI (BMI = [weight (kg) ÷ height^2 (cm^2)] × 10,000), and ASA health status were noted and documented. Subjects were randomly assigned into 3 groups: group 1, 4% prilocaine plain (n = 30); group 2, 2% lidocaine with 1 : 100,000 epinephrine (n = 30); and group 3, no local anesthetic (n = 30) (Table 1). After induction of general anesthesia (using 4–5 mg/kg of ketamine HCl with 0.1 mg/kg of midazolam and 4 μg/kg of glycopyrrolate administered intramuscularly or 8% sevoflurane with 70% nitrous oxide as a mask induction) and the placement of vital sign sensors (electrocardiogram leads, pulse oximeter sensor, temperature probe, and sphygmomanometer cuff), a peripheral intravenous line was started. A Masimo Radical-7 pediatric, nondisposable pulse co-oximeter sensor (Masimo Corporation, Irvine, Calif, Model DCIP-dc12; Figure 1) was then placed on the ring finger of the right hand of each subject. An alternate digit was selected if necessary. The sensor was then connected to a Radical-7 Pulse Co-Oximeter (Masimo, RDS-1 with SET software with methemoglobin interface; Figure 2). Utilizing the Radical-7 Pulse Co-Oximeter, the pulse rate, hemoglobin saturation, perfusion index, and methemoglobin as a percentage of total hemoglobin (SpMET) were continuously monitored and recorded at 10-second intervals (device-specified interval) throughout the dental examination and treatment. The time of device placement and baseline SpMET were both recorded.

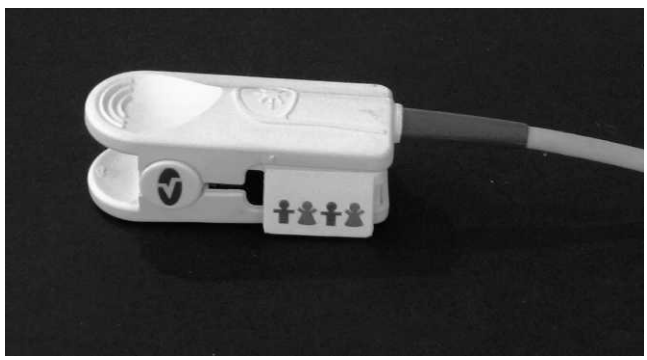

Figure 1. Masimo Radical-7 pediatric, nondisposable, pulse co-oximeter sensor.

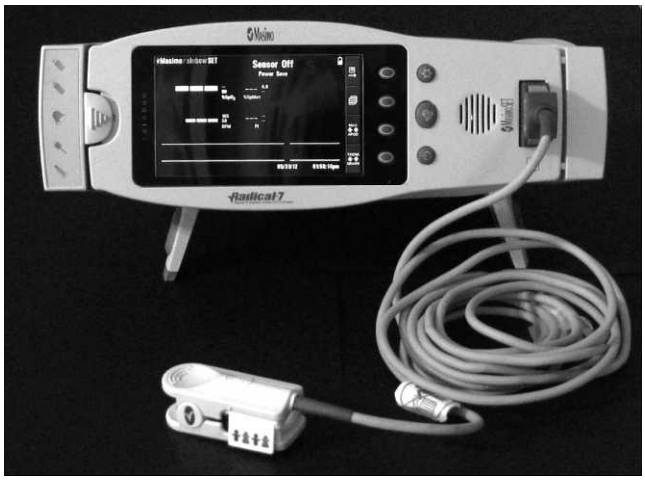

Figure 2. Masimo Radical-7 Pulse Co-Oximeter.

When measuring methemoglobin blood levels, research has shown pulse co-oximetry technology to have a high degree of agreement with traditional blood specimen analysis methods.[15–18] In a study conducted by Feiner et al,[18] the Masimo Radical-7 Pulse Co-Oximeter was determined to have a mean bias (Masimo Radical-7 methemoglobin measurement [SpMET] minus arterial blood methemoglobin value [%MetHb]) and precision (SD of the bias) of 0.16 and ±0.83%, respectively, over an oxygen saturation range of 74–100% and a methemoglobin range of 0.4–14.4%.

Following the placement of the oropharyngeal screen or throat pack, for open airway or intubation, respectively, the completion of the radiographs, the oral examination, and the prophylaxis, local anesthetic was administered to subjects assigned to groups 1 and 2. Group 1 subjects were administered 5 mg/kg of 4% prilocaine plain (4% Citanest Plain Dental, Novocol Pharmaceutical of Canada, Inc, Cambridge, Ontario, Canada) and group 2 subjects were administered 2.5 mg/kg of 2% lidocaine with 1 : 100,000 epinephrine (lidocaine HCl 2% and epinephrine 1 : 100,000 injection, Novocol; Table 1). Local anesthetic dosages to be administered were prepared using a standardized milligram per millimeter scale for the 1.7- and 1.8-mL dental local anesthetic cartridges. The local anesthetic was administered by the operating dentist at a single point in time prior to the restorative procedures via infiltration at 1 or more sites in the maxilla and mandible based upon the procedures to be completed. The time of local anesthetic administration was recorded.

Group 3 subjects served as a negative control group and did not receive local anesthetic for dental rehabilitation. If the dental examination identified that a group 3 subject was in need for 1 or more dental tooth extractions, the patient was withdrawn from the study and any needed local anesthetic was administered by the operating dental clinician.

For all subjects, SpMET was monitored and recorded by the Radical-7 until subject movement precluded further monitoring (usually in the recovery room). The time of the removal of the Radical-7 sensor was recorded.

In the unlikely event that methemoglobin levels were to rise above 15% or the subject to become symptomatic, the attending dentist anesthesiologist was prepared to administer intravenous methylene blue at a dosage of 1–2 mg/kg, the accepted treatment for symptomatic methemoglobinemia.[4]

Electronic data for each subject was transferred from the Radical-7 Pulse Co-Oximeter to Microsoft Excel (Microsoft Office 2010, Microsoft Corporation, Redmond, Wash) using Masimo TrendCom software (V3.5.1.7). Peak SpMET, length of time to peak SpMET (length of time from the local anesthetic administration [groups 1 and 2] or start of restorative procedures [group 3] to the time peak SpMET was observed), and delta SpMET (change in SpMET level from baseline to peak SpMET) were determined using the electronic Radical-7 data and documented for all subjects.

Variables analyzed included subject gender, age, weight, BMI, ASA health status, airway management method, location of sensor placement, dosage of local anesthetic, baseline SpMET, peak SpMET, length of time to peak SpMET, delta SpMET, and total monitoring time of SpMET. Prior to data analysis, BMIs (numerical values) were categorized into 3 groups based upon the corresponding percentiles for age and gender using the Centers for Disease Control and Prevention's body mass index-for-age percentile charts for males and females.[19,20] BMI categories were as follows: category 1, BMI between the 5th and 35th percentiles; category 2, BMI between the 35th and 65th percentiles; and category 3, BMI between the 65th and 95th percentiles. Data analysis included descriptive and inferential statistics using SPSS 20 (Statistical Package for the Social Sciences, IBM SPSS Inc, Chicago, Ill). Inferential statistical tests included chi square test, one-way ANOVA with least significant difference post hoc test, and Pearson correlation. The statistical level of significance was set at $P < .05$.

RESULTS

Parental/legal guardian consent was obtained for 104 Koppel Special Care Dentistry Center patients. Thirteen consented patients were excluded from the study because of BMIs that were less than the 5th percentile (5 patients) or greater than the 95th (8 patients) for their

Table 2. Study Group Demographics: Age, Weight, BMI*

	Age, mo		*Weight, kg*		*BMI*	
Study Group	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Group 1: prilocaine	50.97	9.84	17.17	2.94	15.62	1.12
Group 2: lidocaine	50.77	10.19	17.24	2.78	15.69	1.08
Group 3: no LA	50.63	8.43	17.19	2.96	15.60	1.03
Total	50.79	9.41	17.20	2.86	15.64	1.07
P	.99		.99		.95	

* One-way analysis of variance with least significant difference post hoc test with significance set at $P < .05$. BMI indicates body mass index; LA, local anesthetic.

age and gender. One subject was withdrawn from group 3 because 1 or more dental tooth extractions were required. The final sample consisted of 90 subjects (group 1: $n = 30$, group 2: $n = 30$, and group 3: $n = 30$). The sample was comprised of 45 males and 45 females with a mean sample age of 50.79 months, a mean weight of 17.20 kg, and a mean BMI of 15.64 (Table 2).

A majority of the subjects ($n = 75$, 73.3%) were of ASA I health status with the remainder ($n = 15$, 16.7%) being of ASA II health status (Table 3) with health conditions including, but not limited to, controlled asthma, innocent heart murmur, or seizure disorder. Airway management under general anesthesia for the sample population consisted of an open airway technique in 62.2% ($n = 56$) and nasal intubation in 37.8% ($n = 34$). The Masimo Radical-7 sensor was placed on the right ring finger in 97.8% ($n = 88$) of the subjects. The sensor was placed on the right middle finger and the large toe of the right foot in 2 subjects because of inaccessibility of the right ring finger.

As summarized in Tables 2 and 3, data analysis indicated that subjects were evenly distributed among the groups and the 3 groups were similar in their descriptive characteristics. One-way analysis of variance tests indicated that there were no significant differences among the study groups in the categories of age, weight, and BMI (numerical value; Table 2). Additionally, according to chi-square tests, there were no significant differences among the 3 groups with regard to gender, ASA health status, and BMI percentile (Table 3).

The groups were similar with mean baseline SpMET values between 0.80% and 0.90% ($P = .95$; Table 4). However, the study groups differed with regard to the measured peak SpMET levels. Group 1 subjects had significantly higher peak SpMET levels than subjects in groups 2 and 3 ($P < .001$). There was no major difference in the peak SpMET levels between groups 2 and 3 ($P = .89$). The mean peak SpMETs of groups 1, 2, and 3 were 3.55, 1.63, and 1.60%, respectively (Table 4 and Figure 3). No subjects in any group developed clinical symptoms of methemoglobinemia or exceeded a SpMET level of 15%. The maximum observed SpMET level in any one subject in this study was 6.90%, which occurred in a group 1 subject. The ranges for the peak SpMET levels of the groups were as follows: 1.10–6.90% for group 1, 0.10–2.60% for group 2, and 0.40–2.50% for group 3.

Similar to peak SpMET levels, data analysis indicated that group 1 had a significantly higher mean delta SpMET value than groups 2 and 3 ($P < .001$). There was no significant difference in the delta SpMET values between groups 2 and 3 ($P = .92$). The mean delta SpMET of group 1 was 2.73% whereas those of groups 2 and 3 were 0.78% and 0.76%, respectively (Table 4 and Figure 4).

When considering the lengths of time to peak SpMET levels, there was a significant difference observed among the 3 groups (Table 4). Peak SpMET levels were observed significantly later in the dental treatment for subjects in groups 1 and 2 than for subjects in group 3 ($P < .001$). Groups 1 and 2 had similar mean time lengths

Table 3. Study Group Demographics: Gender, ASA Health Status, and BMI Percentile*

	Gender, No. (%)		*ASA Health Status, No. (%)*		*BMI Percentile Category, No. (%)*		
Study Group	*Male*	*Female*	*I*	*II*	*1*	*2*	*3*
Group 1: prilocaine	11 (36.7)	19 (63.3)	26 (86.7)	4 (13.3)	11 (36.7)	6 (20.0)	13 (43.3)
Group 2: lidocaine	18 (60.0)	12 (40.0)	25 (83.3)	5 (16.7)	6 (20.0)	14 (46.7)	10 (33.3)
Group 3: no LA	16 (53.3)	14 (46.7)	24 (80.0)	6 (20.0)	6 (20.0)	12 (40.0)	12 (40.0)
Total	45 (50.0)	45 (50.0)	75 (83.3)	15 (16.7)	23 (25.6)	32 (35.6)	35 (38.9)
P	.18		.79		.21		

* Chi-square test with significance set at $P < .05$. ASA indicates American Society of Anesthesiologists; BMI, body mass index; and LA, local anesthetic.

Table 4. Study Group Methemoglobin Levels*

	Baseline SpMET, %		Peak SpMET, %		Delta SpMET, %		Time to Peak SpMET, min		Total Time of SpMET Monitoring, min	
Study Groups	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Group 1: prilocaine	0.82	0.39	3.55	1.22	2.73	1.23	62.73	23.78	90.83	27.14
Group 2: lidocaine	0.85	0.35	1.63	0.52	0.78	0.44	57.50	30.67	96.57	29.25
Group 3: no LA	0.84	0.43	1.60	0.45	0.76	0.48	29.50	20.36	67.50	18.28
Total	0.83	0.39	2.26	1.22	1.42	1.22	49.91	29.00	84.97	29.06
P	.952		<.001†		<.001†		<.001†		<.001†	

* One-way analysis of variance with least significant difference post hoc test with significance set at $P < .05$. SpMET indicates methemoglobin as a percentage of total hemoglobin; LA, local anesthetic.

† *P* value indicated statistically significant difference among the 3 groups.

to observed peak SpMET levels, with values of 62.73 and 57.50 minutes, respectively ($P = .43$). The mean time length to the observed peak SpMET levels in group 3 was 29.50 minutes. In addition, there was also a significant difference among the study groups with regard to total time length of SpMET monitoring (Table 4). The mean total time of SpMET monitoring was significantly shorter for group 3 ($P < .001$) at 67.50 minutes than that of group 1 at 90.83 minutes and group 2 at 96.57 minutes.

No significant correlations were noted between subject age, weight, BMI (numerical value), and dosage of local anesthetic with the variables of peak SpMET levels, delta SpMET values, and times to peak SpMET levels among any of the groups. Furthermore, no significant correlations were noted between subject gender and BMI percentile and the variables of peak SpMET levels, delta SpMET values, and times to peak SpMET levels.

DISCUSSION

Acquired methemoglobinemia is a rare but potentially life-threatening condition that may occur following the absorption of adequate amounts of certain chemicals or medicines. Methemoglobinemia remains a complication of treatment in both the medical and dental professions despite advances in understanding its pathogenesis and diagnosis.[4,12] Of the injectable local anesthetics marketed in the dental profession, only prilocaine is well documented to induce the formation of methemoglobin and cause acquired methemoglobinemia. However, the levels and extent of toxicity following the administration of prilocaine used in the dental profession have not been reported. Lidocaine has been suggested to cause acquired methemoglobinemia.[5,13–15] However, there is inconsistent evidence demonstrating the ability of lidocaine to oxidize hemoglobin to methemoglobin.[4,5] This research specifically addresses a gap in the current literature by examining the ability and extent to which the injectable dental local anesthetics prilocaine and lidocaine (with epinephrine) induce the formation of

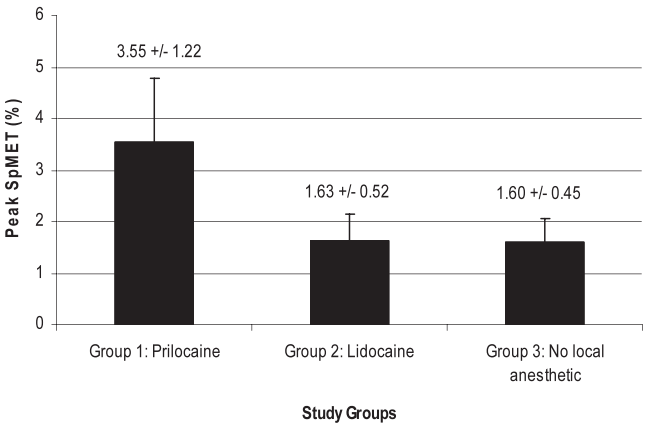

Figure 3. Mean peak methemoglobin levels.

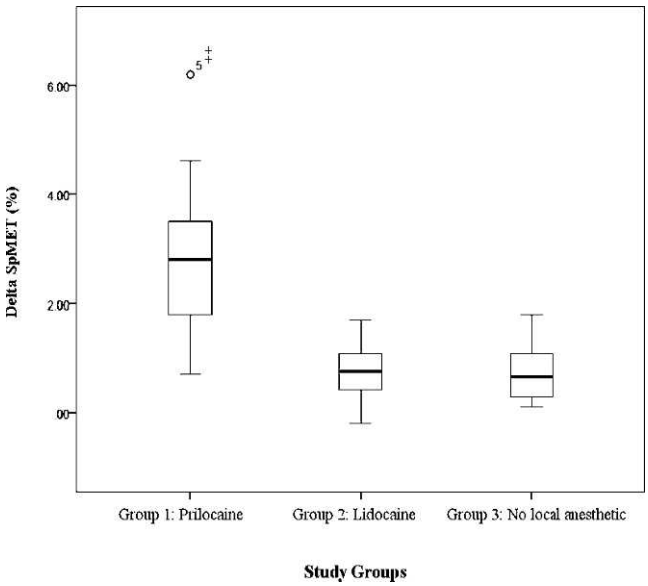

Figure 4. Delta methemoglobin values. ‡ The maximum delta SpMET value observed in Group 1 was in subject 5 with a value of 6.2%.

methemoglobin. The purpose of this study was to measure and compare peak methemoglobin levels and length of time to peak methemoglobin levels in precooperative children who received prilocaine or lidocaine during complete dental rehabilitation under general anesthesia.

Methemoglobin is a dose-dependent toxin; the signs and symptoms of acquired methemoglobinemia are proportional to the amount of methemoglobin present in the blood. Thus, the extent of the compromised oxygen delivery and the carbon dioxide removal in the peripheral tissues is directly related to the fraction of hemoglobin that is oxidized.[4] However, the development and severity of acquired methemoglobinemia (levels >2%) is unpredictable and can vary from person to person following the administration of the same dose of a causative agent.[4,8–10] Many drugs that induce the formation of methemoglobin are not direct causative agents. Instead these drugs are metabolized into agents that oxidize hemoglobin to methemoglobin. Examples of some drugs that produce metabolites that are active oxidizers include prilocaine, benzocaine, and dapsone.[9,21] Variations among individuals in the metabolism of methemoglobin-causative agents and physiologic reduction mechanisms of methemoglobin to hemoglobin result in variable blood concentrations of methemoglobin.[9] In addition, the percentage of oxidized hemoglobin, and thus the severity of the symptoms of methemoglobinemia, varies with the absorption of the causative agent, its site of administration, and the presence of potential risk factors for methemoglobinemia.[10]

Evidence supporting the oxidation of hemoglobin to methemoglobin following the use of prilocaine has been clearly demonstrated.[5,8,13–15] In the human body, prilocaine is metabolized into o-toluidine and nitrosotoluidine, both of which are responsible for the oxidation of hemoglobin to methemoglobin.[4] According to a retrospective study by Guay,[5] prilocaine was associated with 68 out of 242 (28%) of the literature's documented episodes of acquired methemoglobinemia. It was not specified if the prilocaine in these prilocaine-associated episodes of acquired methemoglobinemia contained vasoconstrictor. As a result of her findings, Guay[5] suggested that a dosage of prilocaine as low as 2.5 mg/kg in children could induce clinically symptomatic methemoglobinemia in some individuals. The ability of prilocaine to induce the formation of methemoglobin and cause symptomatic methemoglobinemia following its use for regional anesthesia was directly demonstrated by Vasters and colleagues.[14] They observed that a dose of either 300 or 400 mg of prilocaine administered during major knee surgery caused an average methemoglobin level of 2.7%, with values ranging between 0.9% and 15.4%. Vasters et al[14] also demonstrated that the extent of methemoglobin formation following the administration of prilocaine is unpredictable and highly variable among individuals. However, Vasters et al[14] concluded that following the use of prilocaine for regional anesthesia, a higher dose, younger age, female gender, and a higher concentration of prilocaine were the most important predictive factors for developing high levels of methemoglobin.[14]

As stated by Guay,[5] the ability of lidocaine to cause methemoglobinemia is "…less well demonstrated" than that of other agents. Guay[5] reported that lidocaine (she did not report if the lidocaine anesthetic contained vasoconstrictor) was associated with 12 out of 242 (~5%) of the literature's documented cases of acquired methemoglobinemia. However, 8 of the 12 cases were associated with the concomitant administration of oxidizing agents and 1 episode was associated with chronic abuse of topical lidocaine gel. Only 3 of the documented lidocaine-associated cases of methemoglobinemia occurred after the administration of appropriate dosage and clinical application of lidocaine. However, Guay[5] did not report the levels of methemoglobin observed in these 3 episodes, nor did she indicate if the patients developed clinical symptoms of acquired methemoglobinemia. As suggested by Trapp et al,[4] neither the literature nor its extensive clinical use support lidocaine as an oxidizer of hemoglobin or as causative agent of methemoglobinemia.

The manufacturer of prilocaine and the American Dental Association (ADA) recommend a maximum allowable dosage of 4% prilocaine plain of 8 mg/kg or 600 mg if ≥70 kg.[22,23] The American Academy of Pediatric Dentistry (AAPD) endorses a maximum safe dosage of prilocaine (plain or with epinephrine) of 6 mg/kg or 400 mg.[24] The manufacturer of lidocaine and the ADA recommend a maximum allowable dosage of 2% lidocaine with 1 : 100,000 epinephrine of 7 mg/kg or 500 mg in both adults and children.[23,25] The maximum allowable dosage of lidocaine (with or without epinephrine) recommended by the AAPD is 4 mg/kg or 300 mg.[24] The dosages of prilocaine and lidocaine administered in this study (4% prilocaine plain, 5 mg/kg, and 2% lidocaine with 1 : 100,000 epinephrine, 2.5 mg/kg; Table 1) were chosen as they allow for typical and adequate volumes of local anesthetic (0.75–1.5 dental cartridges) to be deposited at multiple sites in the maxilla and mandible in this patient population as needed for the dental treatment. Furthermore, the dosages of the local anesthetics were selected as they are both below the manufacturer's, ADA's, and the AAPD's recommended maximum allowable dosages.[22–25] Lastly, when concentration differences of the local anesthetic solutions are taken into consideration, the dosages selected allow for equivalent volumes of the 2 agents to be administered

when calculated upon weight. The decision to use 2% lidocaine with 1 : 100,000 epinephrine versus solutions with more or less epinephrine was based on the fact that 2% lidocaine with 1 : 100,000 epinephrine is the most commonly used and the prototypical local anesthetic in dentistry.[2]

The results of this study showed that peak methemoglobin levels observed in precooperative children following the administration of 5 mg/kg of 4% prilocaine plain were significantly greater than peak methemoglobin levels observed in children who received 2.5 mg/kg of 2% lidocaine with 1 : 100,000 epinephrine, as well as those who did not receive local anesthetic (Table 4). These results can be further confirmed by comparing delta methemoglobin levels and baseline methemoglobin values of the 3 groups. Baseline methemoglobin levels were similar for all study groups, whereas delta methemoglobin levels were significantly greater following the administration of prilocaine than lidocaine and no local anesthetic (Figure 4). This demonstrates that the increased peak methemoglobin levels observed in the prilocaine subjects were not due to elevated baseline methemoglobin values, but were rather the result of definitive changes in methemoglobin levels over the baseline values.

The maximum methemoglobin level observed in this study was 6.90% and occurred in a subject who received prilocaine. No subjects in any group developed clinical symptoms of methemoglobinemia. Data analysis indicated that the mean peak methemoglobin level of the prilocaine group was 3.55% (Table 4). This mean peak level is above the normal physiologic methemoglobin range (0–2%), but is below the clinical symptomatic range of acquired methemoglobinemia ($\geq$15%). These results are consistent with previous reports that demonstrate that prilocaine is capable of inducing acquired methemoglobinemia.[10–12] Furthermore, the results from this study suggest that at a dosage of 5 mg/kg, 4% prilocaine will not cause symptomatic acquired methemoglobinemia in precooperative children undergoing dental treatment in the absence of exposure to other oxidants of hemoglobin as previously suggested by Guay.[5]

The mean peak methemoglobin level of the lidocaine group was 1.63%. This was similar to the mean peak methemoglobin level of the no local anesthetic group at 1.60% (Table 4). These results suggest that lidocaine with epinephrine does not increase methemoglobin levels above physiologic norms. In contrast to previous suggestions that lidocaine oxidizes hemoglobin to methemoglobin, these results imply that lidocaine (with epinephrine) does not oxidize hemoglobin and does not cause acquired methemoglobinemia. However, it may be more appropriate to state that lidocaine may oxidize hemoglobin to a small extent, but if the protective physiologic reduction mechanisms are functioning properly, methemoglobin levels greater than 2% do not occur. In evaluating the results of this study, one must also take into account that the lidocaine used in this study contained epinephrine. One can suggest that the epinephrine slows that systemic uptake of the lidocaine, thus slowly releasing lidocaine into the circulatory system where it can then be metabolized by the liver. Consequently, the body is not exposed to high levels of lidocaine at any one time and protective methemoglobin reduction mechanisms are not overwhelmed. However, as the effects of the epinephrine decrease, more lidocaine is released into circulation and a small quantity of methemoglobin is formed. Perhaps systemic epinephrine offers some degree of protection against the formation of acquired methemoglobinemia.

One must question why there was an increase in methemoglobin levels from the baseline values of approximately 0.75% for both the lidocaine group and the no local anesthetic group. This information suggests that perhaps additional agents that were administered during the procedure, such as oxygen and intravenous and/or inhalation general anesthetics, were oxidizing hemoglobin to a mild extent. Further research is required to determine if the additional agents used during dental treatment under general anesthesia oxidize hemoglobin with a resulting small increase in methemoglobin.

In this study, the time elapsed to peak methemoglobin levels was significantly longer for the prilocaine (62.73 minutes) and lidocaine (57.50 minutes) groups than the no local anesthetic group (29.50 minutes) (Table 4). One can infer that the delay to the peak methemoglobin level in the prilocaine group in comparison to the no local anesthetic group is likely due to the metabolism of the prilocaine into its oxidative metabolites that must occur prior to the oxidation of hemoglobin. If lidocaine with epinephrine was responsible for the oxidation of hemoglobin to methemoglobin in this study, one would expect a greater length of time to peak methemoglobin for the lidocaine group than that of both the prilocaine group and the no local anesthetic group due to the vasoconstriction caused by the epinephrine and the delayed rate of systemic uptake of the medication. However, this was not observed. Furthermore, as the lidocaine group and the no local anesthetic group did not differ in their mean peak methemoglobin values, one could again surmise that lidocaine with epinephrine does not oxidize hemoglobin and the small quantity of methemoglobin formed in both groups 2 and 3 is caused by an additional agent administered during general anesthesia. It may also be relevant to suggest that the systemic epinephrine administered with the lidocaine reduces the rate of methemoglobin formation caused by

any alternative agent and results in a delay in the small amount of methemoglobin formed.

When evaluating total methemoglobin monitoring in this study, it was evident that total monitoring time was significantly shorter for the no local anesthetic group at 67.50 minutes than for the prilocaine and lidocaine groups at 90.83 and 96.57 minutes, respectively (Table 4). It is possible that the children in the no local anesthetic group required fewer dental restorative procedures than the children in the prilocaine and lidocaine groups. It is also likely that children in the no local anesthetic group had shorter monitoring times as a result of faster wake-ups following general anesthesia. Perhaps the subjects were less comfortable with regard to pain control following the procedures and were less inclined to sleep during recovery. This may be an area worthy of future examination.

One of this study's limitations was the inability to control total methemoglobin monitoring time. Subjects varied in the number and extent of restorative procedures required. Furthermore, the different operating clinicians varied in their speed and skill. Toxic methemoglobin levels and associated symptoms may be immediate or may also be delayed several hours after exposure to an oxidizing agent because of varying rates of absorption and metabolism of the agent.[14] Perhaps higher peak methemoglobin levels would have been observed in this study if monitoring had been continued for several hours or if levels had been measured the following day. Another limitation of this study was that it was restricted to precooperative children. Results may not be generalized to older children or adults. Lastly, it would have been preferable to compare methemoglobin levels following the administration of local anesthetics that contained equivalent concentrations of epinephrine to avoid potential complications associated with rates of absorption. However, prilocaine is not manufactured in a solution that contains epinephrine in a concentration of 1 : 100,000.[2]

Future studies should be conducted that compare methemoglobin levels following the administration of a larger variety of local anesthetics: lidocaine with epinephrine, lidocaine without epinephrine, prilocaine with epinephrine, prilocaine without epinephrine. This will further clarify the involvement of local anesthetics and epinephrine in oxidizing hemoglobin. Other studies may wish to evaluate the time frame to which prilocaine, as used for dental treatment, causes elevated methemoglobin levels. Additional investigations should evaluate the role of oxygen and all other medicines administered during general anesthesia in the formation of methemoglobin.

In summary, 4% prilocaine plain, when administered at a dosage of 5 mg/kg in precooperative children undergoing comprehensive dental rehabilitation under general anesthesia, resulted in methemoglobin levels that were significantly greater than those produced by lidocaine with epinephrine and no local anesthetic. Additionally, in the absence of exposure to other known hemoglobin oxidizers and any hemoglobinopathies, prilocaine resulted in methemoglobin levels that were above those considered to be physiologically normal. In contrast, 2% lidocaine with 1 : 100,000 epinephrine at a dosage of 2.5 mg/kg did not increase peak methemoglobin levels in comparison to those who did not receive local anesthetic. As no subject in this study developed symptomatic methemoglobinemia following the administration of prilocaine or lidocaine, results suggest that at the dosages used in this study, these injectable local anesthetics are appropriate for use in precooperative children undergoing dental treatment. However, because of the ability of prilocaine to cause methemoglobin levels above physiologic norms, prilocaine should be used with caution in children who have hemoglobinopathies and/or those who are receiving additional oxidizing agents. Furthermore, the results demonstrated that in comparison to the no local anesthetic group, peak methemoglobin levels occurred significantly later in the dental procedure following the administration of prilocaine or lidocaine with epinephrine. The times to peak methemoglobin values were similar for the 2 local anesthetics in that they occurred approximately 60 minutes after their administration.

CONCLUSIONS

From this study, in precooperative children undergoing comprehensive dental rehabilitation under general anesthesia, the following conclusions can be made:

1. A 4% solution of prilocaine plain administered at a dosage of 5 mg/kg resulted in significantly higher peak methemoglobin levels than lidocaine with 1 : 100,000 epinephrine and no local anesthetic.
2. A 2% solution of lidocaine with 1 : 100,000 epinephrine administered at a dosage of 2.5 mg/kg did not result in peak methemoglobin levels greater than no local anesthetic.
3. The administration of 4% prilocaine plain and 2% lidocaine with 1 : 100,000 epinephrine caused peak methemoglobin values to occur significantly later in the dental procedure in comparison to those who did not receive local anesthetic.

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