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Usporedba intramuskularno primijenjenog i inhaliranog epinefrina: eksperimentalno istraživanje

A Comparison of Intramuscular Versus Inhaled Epinephrine in Humans: A Pilot Study

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Sažetak
Svrha: Intravenozna ili intramuskularna primjena epinefrina preporučuje se u slučaju sistemske anafilaksije. Zadatak je bio procijeniti njegovu razinu u plazmi nakon intramuskularne primjene u mišić bukcinator u odnosu prema razini nakon inhalacije. **Ispitanici i postupci:** U ovom eksperimentalnom istraživanju na ljudima mjerile su se koncentracije epinefrina prije intramuskularne primjene ili inhalacije te nakon njih, uz intramuskularnu injekciju fiziološke otopine te intravenoznu primjenu epinefrina kao negativnu i pozitivnu kontrolu. **Rezultati:** Najviše vrijednosti bile su nakon intramuskularne primjene - maksimalna razina u plazmi iznosila je 3367,2 pg/ml. Nakon inhalacije epinefrina razina je bila 151,89 pg/ml. **Zaključak:** U slučaju respiratornog poremećaja, ako je uzrok anafilaksija, može biti korisna inhalacijska primjena epinefrina. Kod teških kardiovaskularnih reakcija, ako nije dostupan venski put, jedini je način primjene intramuskularna titracija epinefrina. Mišić bukcinator korisno je mjesto za stomatologe koji se susreću sa slučajevima anafilaksije.

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Ključne riječi
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Uvod

Anafilaktički šok jedno je od najtežih hitnih stanja u stomatološkoj praksi, a može rezultirati opstruktivnom oteklinom gornjih dišnih puteva, astmatičnim stanjem ili kolapsom kardiovaskularnog sustava te smrću. Brzo venski injiciran epinefrin može spasiti život (1-9). Tijekom anafilaktičkog šoka često nije moguć intravenozni pristup na koji se može primijeniti epinefrin, pa se kao prva alternativa u liječenju smatra intramuskularna primjena 0,5 mg adrenalina za odrasle te 0,01 mg/kg tjelesne mase za djecu (10). Također se kao jednostavno liječenje preporučuje inhalacija epinefrina, posebice kod dišnih komplikacija tijekom anafilaksije. Kod

Introduction

Anaphylactic shock is one of the most dangerous emergencies in dental practice. Anaphylaxis may result in obstructive swelling of the upper airway, status asthmaticus or collapse of the cardiovascular system, resulting in death. Rapidly injected epinephrine by the intravenous route could be life saving (1-9). During anaphylactic shock an intravenous access may not available for application of epinephrine. Therefore intramuscular injection of 0.5 mg adrenaline for adults and 0.01 mg/kg body weight for children is regarded as first-line treatment as an alternative (10). Epinephrine inhalation has also been suggested as an easy treatment especially

astmatične epizode epinefrin se primjenjuje putem inhalatora te je to neinvazivna i jednostavna alternativa ubodu (12-14). Zamjenska je metoda i autoinjektor epinefrina za intramuskularnu primjenu u anterolateralni dio prepone. Zbog centralizacije cirkulacije kod anafilaksije, inhalacija epinefrina mogla bi biti bolji odabir, posebice u slučajevima s dodatnim respiratornim problemima.

Svrha istraživanja bila je procijeniti razine epinefrina u plazmi nakon intramuskularne primjene u mišić bukcinator - područje poznato stomatolozima, u usporedbi s epinefrinom koji se dobivao inhalatorom s protokom i neprestanim dotokom kisika tijekom postupka.

Ispitanici i postupci

Trojica autora dobrovoljno su pristali biti i ispitanici (Tablica 1.). Istraživanje je obavljeno nakon pristanka lokalnoga Etičkog povjerenstva. Dvojica sudionika bili su nepušači (prvi i treći), a lijekove nije uzimao nitko. Svaki je ispitanik bio tek nakon tjedan dana na različitim eksperimentalnim testovima, a svi su obavljeni u 8 sati kako bi se izbjegli cirkadijski učinci. Danju, dok se obavljalo ispitivanje, nitko nije konzumirao kofein i nikotin. Bilježile su se sljedeće varijable: puls (bilo), krvni tlak, razina epinefrina u plazmi te osobne popratne pojave, poput tremora i gastrointestinalnih tegoba (mučnina ili povraćanja).

Nakon postavljanja intravenskog katetera (BD Venflon™ 18 GA, 1,2x45 mm, Polymed AG, Glattbrugg, Švicarska) u desnu kubitalnu venu te tlakomjera (NAIS Blood Pressure Watch, Polymed AG, Glattbrugg, Švicarska) na lijevu podlakticu, ispitanici su 15 minuta mirovali u stomatološkom stolcu. Zatim im je na početku mjerenja bila izvađena krv Vacutainerom (1,95 mmol/l glutationa i 5,0 mmol/l etilenglikolne tetraacetične kiseline (EGTA) - Becton Dickinson AG, Basel, Švicarska). Sljedeći uzorci bili su uzeti pet, deset i dvadeset minuta nakon primjene

for airway complications during anaphylaxis. During an asthma episode the inhalation of epinephrine from a dose inhaler has been used as a non-invasive, user-friendly alternative to an injection (12-14). An epinephrine autoinjector for intramuscular injection in the anterolateral aspect of the thigh in an alternative method. Due to a centralized circulation during anaphylaxis inhalation of epinephrine may be more valuable in cases with additional respiratory problems.

The purpose of this pilot study was to evaluate epinephrine plasma levels after intramuscular injection into the buccinator muscle, a familiar area for the dentist, in comparison to inhaled epinephrine. This was achieved with an oxygen flow driven inhaler which allows a continuous supply of oxygen to the epinephrine inhalation.

Methods

Three authors of this study volunteered as test persons (Table 1). The study was performed with approval of the local ethics committee. Two participants were nonsmokers (1 and 3), none of the participants was under any other medication. Each subject underwent different experimental tests only after an interval of one week. All experiments commenced at 8 a.m. to exclude possible circadian effects. Participants abstained from ingestion of caffeine containing drinks or nicotine on the study day. The following variables were recorded: heart rate, blood pressure, plasma epinephrine and subjective side effects like tremor, palpitations or gastrointestinal symptoms, i.e. nausea or vomitus.

After insertion of an intravenous catheter (BD Venflon™ 18 GA, 1.2x45 mm, Polymed AG, CH-Glattbrugg) into the right cubital vein for blood sampling and positioning a blood pressure cuff (NAIS Blood Pressure Watch, Polymed AG, CH-Glattbrugg) at the left forearm, the participants rested for 15-minutes in the sitting position in a dental chair. Afterwards a blood sample was drawn with a Vacutainer (1.95 mmol/l glutathione und 5.0 mmol/l ethylene glycol tetraacetic acid (EGTA), Becton

Tablica 1. Antropometrijski parametri ispitanika
Table 1 Anthropometric parameters of test persons

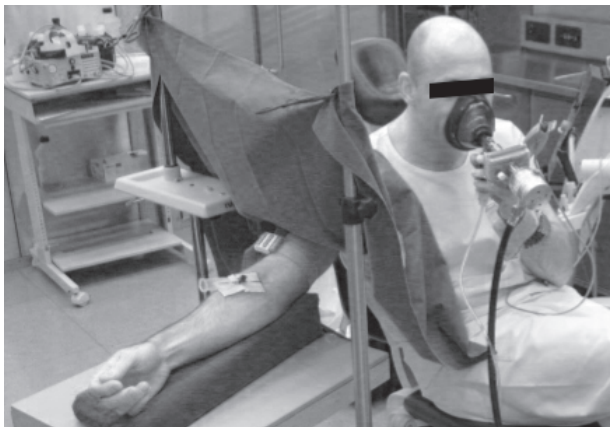
	Spol • Sex	Starost • Age (godina • years)	Težina • Weight (kg)	Visina • Height (cm)	Indeks tjelesne mase • Body Mass Index
Ispitanik 1 • Subject 1	muški • male	44	84	182	25.36
Ispitanik 2 • Subject 2	muški • male	28	65	175	21.23
Ispitanik 3 • Subject 3	muški • male	33	68	182	20.53

epinefrina. Mjerenja pulsa i tlaka bila su obavljena na početku te tri, pet, deset, petnaest, dvadeset te dvadeset i pet minuta nakon primjene epinefrina.

Uzorci su zatim bili uskladišteni na ledu te unutar 45 minuta centrifugirani (2500 okr/mim, Sigma Centrifuge, Vitaris AG, Baar, Švicarska) na temperaturi od 4°C. Plazma je bila uklonjena i do analize spremljena na -70°C. Razina epinefrina u plazmi određivala se visokorezolutnom tekućom kromatografijom (HPLC) s elektrokemijskom detekcijom, prema ranije opisanom postupku (15 -16).

Prema intramuskularnom protokolu injicirano bilo je 0,3 ml epinefrin-hidroklorida (Sintetica S.A., Mendrisio, Švicarska) u 1 mg/ml (ukupna doza 300 μg) intraoralno u mišić bukcinator. Poštujući inhalacijski protokol bilo je primijenjeno 15 ml epinefrin-tartrata 1 mg/ml (ukupna doza 15 mg) tijekom 15 minuta i to pomoću inhalatora s protokom kisika (Cirrus Nebuliser code 1501, Intersurgical Ltd, Wokingham, Berkshire, Velika Britanija) spojenog na T-spojku (Intersurgical Ltd. Code 1986) i oživljavač s kisikom (Mediline GCE Norden AB, Malmö, Švedska) s maskom AMBU veličine III 12l O_2/min pri normalnoj frekvenciji disanja (12-15 udisaja/min - Slika 1.). Kako bi se izbjegla kontaminacija uzoraka krvi epinefrinom aerosolom, oni su tijekom inhalacije bili izolirani kompresom.

Kao negativna kontrola bilo je uporabljeno 0,3 ml fiziološke otopine koja se injicirala intramuskualrno. Dodatno, da bi se procijenila postignuta promjena razine epinefrina tijekom intravenozne injekcije, jedan od autora pristao je intravenski primiti lijek i (2x 0,15 ml i 1x 0,3 ml epinefrin-hidroklorida razrijeđenog na 0,1 mg/ml (Sintetica S.A., Mendrisio, Švicarska). Dobivao ga je u minutnim frakcijama, a ukupna je doza iznosila 60 μg, (Tablica 2.). U tom su se slučaju, zbog pretpostavljenog kratkog poluvremena epinefrina, uzorci uzimali u kraćim razdobljima, naime nakon jedne, tri i pet minuta.



Slika 1. Eksperiment
Figure 1 Experimental setting

Dickinson AG, CH-Basel) at time 0'. Further blood samples were taken 5, 10, and 20 minutes after epinephrine application. The measurements of heart rate and blood pressure were recorded at 0', 3', 5', 10', 15', 20', and 25'.

The samples were stored on ice and underwent centrifugation (2500 rpm, Sigma Centrifuge, Vitaris AG, CH-Baar) at 4°C within 45 minutes. The plasma was removed and stored at -70°C until it was analyzed. Plasma epinephrine was determined by high-performance liquid chromatography (HPLC) with electrochemical detection (EC), as described and validated previously (15-16).

Within the intramuscular injection protocol 0.3 ml epinephrine hydrochloride (Sintetica S.A., CH-Mendrisio) 1 mg/ml (total dose 300 μg) was injected intra orally into the right buccinator muscle. Within the inhalation protocol subjects inhaled 15ml epinephrine tartrate 1 mg/ml (total dose 15 mg) for 15 minutes by use of an oxygen flow driven inhaler (Cirrus Nebuliser code 1501, Intersurgical Ltd, Wokingham, UK-Berkshire) connected to a T-piece (Intersurgical Ltd. Code 1986) and an oxygen demand valve resuscitator (mediline GCE Norden AB, S-Malmö) with an AMBU mask size III 12l O_2/min at normal breathing frequency (12-15 breaths/min, Figure 1). To avoid a contamination of the blood sampling system with epinephrine by the aerosol, it was isolated by a surgical cloth during the inhalations.

0.3 ml of normal saline solution (Sintetica S.A., CH-Mendrisio) injected intramuscularly served as a negative control. Additionally, to evaluate the order of magnitude of epinephrine levels achievable during intravenous epinephrine injection, one of the authors volunteered to receive the medication intravenously (2x 0.15 ml and 1x 0.3 ml of epinephrine hydrochloride diluted to 0.1 mg/ml (Sintetica S.A., CH-Mendrisio) injected in fractions during one minute, total dose 60 μg, Table 2). In this case due to the assumed short half-time of the epinephrine, blood samples were taken after 1, 3, and 5 minutes.

Tablica 2. Apsorpcija epinefrina nakon različitih načina primjene
Table 2 Epinephrine absorption after different administration routes in

	Intramuskularno • Intramuscular	**Inhalacija • Inhalation**	**Intravenozno • Intravenous**	**Fiziološka otopina • Saline-Solution**
Epinefrin • Epinephrine (ml)	0.3	15	0.03	0.3
$C_{bazalni}$ • C_{basal} (pg/ml)	51.84	54.9	47.58	53.07
C_{max} (pg/ml)	3367.2	151.89	2734.02	69.54
T_{max} (min)	5	5	1	-

Rezultati

Koncentracija epinefrina u plazmi

Srednja vrijednost epinefrina u plazmi prije primjene intramuskularno ili inhalacijom iznosila je 53,07 pg/ml, odnosno 49,41 pg/ml. Nakon primjene fiziološke otopine iznosila je 53,07 pg/ml, no maksimum od 69,54 pg/ml postigla je unutar pet minuta (Tablica 2.). Nakon intravenske injekcije epinefrina naglo je rasla koncentracija (početna 47,58 pg/ml). Maksimalna koncentracija u plazmi nakon intravenske primjene 60μg epinefrina iznosila je 2734,02 pg/ml (Tablica2.).

Nakon intramuskularne injekcije 0,3 mg epinefrina, koncentracija u plazmi narasla je nakon pet minuta s bazalnih 53,07 pg/ml na 1886,7 pg/ml (Slika 2a.). Deset minuta kasnije koncentracije su kod svih ispitanika pale ispod 1240,7 pg/ml. Posljednji uzorak krvi, uzet dvadeset minuta nakon primjene, pokazao je povećanje bazalnih koncentracija za sedam do petnaest puta.

Nakon inhalacije epinefrina bazalna razina kod prvoga ispitanika porasla je na 151,89 pg/ml i to do pet minuta nakon prestanka inhalacija. Kod trećeg ispitanika bilo je uočeno blago povećanje (Slika 2b.) - najviša razina postignuta je nakon 10 minuta, a kod drugoga sudionika se smanjila.

Results

Plasma epinephrine concentration

Median baseline plasma epinephrine concentrations before administration of epinephrine by intramuscular or inhalation routes were 53.07 pg/ml and 49.41 pg/ml, respectively. Plasma epinephrine baseline before intramuscular injection of saline solution was 53.07 pg/ml. After saline injection the plasma concentration of epinephrine achieved a maximum of 69.54 pg/ml within 5 minutes (Table 2). The intravenous injection of epinephrine showed a rapid increase of epinephrine plasma concentration (baseline 47.58 pg/ml). The maximum plasma concentration after 60 μg epinephrine administered intravenously was 2734.02 pg/ml (Table 2).

After the intramuscular injection of 0.3 mg epinephrine, the plasma concentrations of epinephrine increased from median basal values of 53.07 pg/ml to a median of 1886.7 pg/ml after 5 minutes (Figure 2a). After 10' concentrations decreased in all participants to below 1240.7 pg/ml. The last blood sample drawn at 20' showed a 7 to 15-fold increase of the basal concentrations.

After epinephrine inhalation plasma levels in subject 1 increased to 151.89 pg/ml within 5 minutes after terminating the inhalations. In subject 3 only a mild increase (Figure 2b) was observed and peak was reached after 10 minutes while in subject 2 a decrease was reported.

Slika 2a. Utjecaj injekcije epinefrina na razinu u plazmi
Figure 2a Effect of epinephrine injection on plasma level

Slika 2b. Utjecaj inhalacije epinefrina na razinu u plazmi
Figure 2b Effect of epinephrine inhalation on plasma levels

Promjene pulsa (bila)

U prvoj minuti nakon intramuskularne primjene epinefrina, rast pulsa bio je stalan sve do vrhunca nakon tri minute i iznosio je 34 otkucaja u minuti (kod prvoga ispitanika, a kod trećega se dogodio blagi porast (sedam otkucaja u minuti - Slika 3a.). Prvom ispitaniku puls je tijekom prvih 5 minuta nakon injekcije samo blago pao, a kod drugoga brzo. Nakon deset minuta bio je na normalnoj razini. Inhalirani epinefrin uzrokovao je samo blagi porast (13 otkucaja u minuti) u prvih pet minuta kod prvoga i drugoga ispitanika. Kod trećega je puls pao. I u tom je slučaju povratak na normalnu razinu uočen nakon deset minuta (Slika 3b.). Kod drugoga ispitanika puls je počeo ponovno rasti nakon deset do dvadeset minuat, ali nije bila postignuta razina prvog porasta.

Heart rate change

Within the first minute after intramuscular application of epinephrine a consistent increase of heart rate to reach the peak after 3 minutes up to 34 beats per minute (bpm) (subject 1). In participant 3 only a slight elevation (7 bpm, Figure 3a) was observed. Subject 1 showed in the first 5 minutes after injection only a slowly decline of the heart rate in subject 2 the decline was rapidly. After 10 minutes heart rates had returned to baseline. Inhaled epinephrine caused only a very slight elevation of heart rate (13 bpm) in the first 5 minutes in subjects 1 and 2. In participant 3 heart rate even decreased. In this case return to baseline values was recorded within 10 minutes after epinephrine administration as well (Figure 3b). In subject 2 the heart rate began to rise again after 10 minutes up to 20 minutes. The first peak was not reached.

Slika 3a. Promjene bila nakon intramuskularne primjene epinefrina
Figure 3a Heart rate changes after intramuscular epinephrine injection

Slika 3b. Promjene bila nakon inhalacije epinefrina
Figure 3b Heart rate changes after epinephrine inhalation

Promjene krvnoga tlaka

Sistolički krvni tlak

Obje metode primjene epinefrina uzrokovale su porast sistoličkoga krvnog tlaka - intramuskularna metoda rezultirala je porastom tijekom prve tri minute, a inhalacijska unutar prvih pet minuta, no nakon intramuskularne primjene porast je bio znatno veći (medijan 18 mmHg, Slika 4a). Nakon intramuskularne primjene vrijednosti krvnog tlaka do desete minute bile su jednake. Nakon početnoga blagog porasta koji je bio najveći u desetoj minuti, kod dvojice ispitanika dogodio se još jedan i to dvadeset minuta kasnije (Slika 4b.).

Dijastolički krvni tlak

Intramuskularna primjena blago ga je povećala iznad početne vrijednosti. Najveće povećanje (od 14 mmHg) bilo je zabilježeno kod drugoga ispitanika i to pet minuta nakon primjene. Zatim je sli-

Blood pressure change

Systolic blood pressure

Both methods of administration caused an increase in the systolic blood pressure, with the intramuscular method within the first 3 minutes and with inhalation within the first 5 minutes, distinctly more after intramuscular administration (median 18 mmHg, Figure 4a). The amount of the blood pressure values up to the tenth minute were equal after intramuscular injection. After an initial slight increase to reach the peak at 10 minutes, another mild increase could be measured in two test subjects after 20 minutes following the inhalation (Figure 4b).

Diastolic blood pressure

Intramuscular injection induced only a mild increase to values above baseline. The highest increase of 14 mmHg was measured in subject 2 after 5 minutes and after a slow decrease till minute

Slika 3a. Promjene krvnog tlaka nakon intramuskularne primjene epinefrina (točke su medijan, stupići raspon)
Figure 3a Blood pressure changes after intramuscular injection of epinephrine (dots indicate median, bars indicate range)

Slika 3b. Promjene krvnog tlaka nakon inhalacije epinefrina (točke su medijan, stupići raspon)
Figure 3b Blood pressure changes after inhalation of epinephrine (dots indicate median, bars indicate range)

jedio pad do petnaeste minute i ponovni porast do dvadesete (+13 mmHg - Slika 4a.). Nakon inhalacije najveći je porast bio kod drugoga ispitanika (27 mmHg) i to u prvih pet minuta, a zatim je tlak padao do dvadesete minute (Slika 4b.).

Popratne pojave

Nakon intramuskularne injekcije 0,3 mg epinefrina svi su ispitanici istaknuli brzu pojavu tremora prstiju i palpitacija. To je nestalo nakon 20 do 25 minuta. Nakon inhalacije epinefrina dvojica su ispitanika navela tremor, a jedan palpitacije, no simptomi su nestali za 10 do 15 minuta. Srčanih aritmija nije bilo. Ni jedan ispitanik nije naveo gastrointestinalne tegobe. Nakon intramuskularne injekcije nije bilo nekroze mišića.

Rasprava

Nemogućnost brze primjene epinefrina smatra se najvažnijim čimbenikom koji pridonosi smrti pacijenata s anafilaksijom (1,2,11). Njegovo alfa-adrenergično djelovanje povećava perifernu vaskularnu otpornost, krvni tlak i perfuzije koronarnih arterija, beta-1-adrenergično djelovanje dovodi do kronotropne, batomotropne i inotropne aktivnosti srčanog mišića, a beta-2-adrenergično djelovanje završava bronhodilatacijom (17,18).

Kako nije bilo kontrole fiziološkom otopinom kod svakog ispitanika, pretpostavka je bila da je kod prvoga ispitanika prirođena razina epinefrina u plazmi od 69,54 pg/ml nakon primjene fiziološke otopine reprezentativni podatak.

No, analitička metoda HPLC-EC ne razlikuje epinefrin proizveden u adrenalnoj meduli od ono-

15 a second peak was reached at 20 minutes (+13 mmHg, Figure 4a). After inhalation the maximum increase in pressure could be measured in subject 2 (27 mmHg) already in the first 5 minutes followed by a slow decline of all values to baseline after 20 minutes (Figure 4b).

Side effects

After intramuscular injection of 0.3 mg epinephrine all subjects reported a rapid onset of finger tremor and palpitations. After 20 to 25 minutes these side effects were not any more noticed. After inhalation of epinephrine two of the three test persons noticed tremor and one subject palpitations. These symptoms subsided after 10 to 15 minutes. No cardiac arrhythmias were observed. No subject complained about gastrointestinal symptoms. No muscle necrosis was observed after the intramuscular injection.

Discussion

Failure to administer epinephrine promptly has been identified as the most important factor contributing to death in patients with anaphylaxis (1,2,11). Its α-adrenergic effects result in increased peripheral vascular resistance, blood pressure and coronary artery perfusion. While its β_1-adrenergic effects increase the chronotropic, bathomotropic and inotropic hearth activity, the β_2-effects result in bronchodilatation (17,18).

In the absence of a saline control for each of the study subjects, the assumption was made that the endogenous epinephrine plasma concentration of 69.54 pg/ml obtained after the intramuscular saline injection by subject 1 would be representative. However, using the HPLC-EC analytical method, the epinephrine produced endogenously in the ad-

ga koji se primijenjuje kao lijek. Učinkovitost ekstrakcije bila je 70 do 80 %. Niža razina detekcije epinefrina uz pomoć toga postupka iznosila je 5 pg/ml (19).

Intravenski primijenjen epinefrin kod prvoga je ispitanika brzo povećao koncentraciju, a s terminalnom eliminacijom poluvremena od 30 do 35 sekundi brzo se i smanjio.

Maksimalna koncentracija u plazmi nakon intravenske primjene 60 μg epinefrina gotovo da je dosegnula intramuskularne razine (i.v. doza iznosila je samo petinu, 2734,02 pg/ml u odnosu na 3367,2 pg/ml - Tablica 2.). Slične razine u plazmi opažene su i u istraživanju Simonsa i suradnika (20). Autori su izmjerili maksimalnu koncentraciju u plazmi od 2136 ± 351 pg/ml 8 ± 2 min nakon intramuskularne primjene 0,3 mg epinefrina i to u obliku bolusa u trenutku kada su bili prepoznati ozbiljni znakovi anafilaksije. Sistemska se apsorpcija u tom trenutku može poboljšati lokalno masažom ili toplinom. Prema našim podacima nakon intramuskularne primjene epinefrina očite su kardiovaskularne reakcije. Inicijalni porast pulsa (medijan +24 ,9 %) i sistoličkoga krvnog tlaka (medijan +7,7 mmHg) mogli su biti potaknuti očekivanjem, stresom ili bolovima povezanima s ubodom. Inhalirani epinefrin prouzročio je umjerene promjene pulsa i sistoličkoga krvnog tlaka.

Inhalacija epinefrina inhalatorom preporučuje se kao korisna alternativa intramuskularnoj injekciji ako se pacijenti boje uboda, već su doživjeli umjerenu anafilaksiju, ili su u ranijim epizodama imali jače respiratorne simptome negoli vaskularne (14,21,22). Primjena epinefrina inhalacijom otopine razrijeđene do 1 mg/ml, može se odabrati u liječenju mukozalnih oteklina ili opstrukcije dišnih puteva te bronha.

Naše je istraživanje pokazalo blago povećanje koncentracije u plazmi tijekom prvih 20 minuta nakon inhalacije 15 mg epinefrina u odnosu prema kontroli. Poznato je da kod dobre inhalacijske tehnike <10 % inhalirane doze dopire u dublje dijelove respiratornog trakta (23). Simons i suradnici u svojem su istraživanju (24) obrađivali i inhalaciju kod djece (maksimum u plazmi nakon 32 ± 62 minute 1822 ± 413 pg/ml). Ti podaci ne mogu se ponoviti u eksperimentalnim uvjetima te je upitno bi li uopće porasla koncentracija u plazmi nakon duljeg razdoblja mjerenja. Ne zna se može li inhalirani epinefrin pomoći u kod anafilaksije s dominantno vaskularnim simptomima. Prema sadašnjim spoznajama taj je oblik primjene učinkovit kod primarnog udara na

renal medulla cannot be distinguished from exogenously administered epinephrine. The extraction efficiency was 70-80%. The lower limit of detection of epinephrine using this assay was 5 pg/ml (19).

Epinephrine injected intravenously in subject 1 showed a rapid increase of the plasma concentration and with a terminal elimination half-life of 30-35 seconds also a fast decrease. The maximum plasma concentration after 60 μg epinephrine administered intravenously reached near the levels observed after intramuscular administration (i.v. dose was only one-fifth as high, 2734.02 pg/ml vs. 3367.2 pg/ml; Table 2). Similar plasma peaks were found by another study of Simons et al. (20). The authors showed a plasma concentration maximum of 2136 ± 351 pg/ml after 8 ± 2 min with 0.3 mg epinephrine i.m. as a single dose administered into the deltoideus muscle. The intramuscular injection should be performed by bolus once serious signs of anaphylaxis have been recognized. Systemic absorption can then be assisted by local massage and heat if necessary. Our data show an obvious cardiovascular reaction after epinephrine has been administered intramuscularly. The initial increases in heart rate (median +24.9 %) and in systolic blood pressure (median +7.7 mmHg) may, in part, have been evoked by expectation, stress or pain in connection to the injection. Inhaled epinephrine caused only moderate enhancement of heart rate as well as systolic blood pressure.

Inhalation of epinephrine by use of an inhalation device is recommended by some authors as a useful alternative to the intramuscular injection in patients who are afraid of injections, or who experienced previous mild episodes of anaphylaxis, or whose previous episodes have resulted in respiratory rather than vascular symptoms (14,21,22). Epinephrine application by inhaling a solution diluted to 1 mg/ml may be used for treatment of mucosal swelling of the airways or bronchial obstruction.

In our study only a slight increase of plasma concentration was detected during the first 20 minutes after inhalation of 15 mg epinephrine compared to the control. It is known that <10% of the inhaled dose reaches the deeper respiratory tract even with a good inhalation technique (23). The study group of Simons et al. (24) tested also the inhalative application form in children (plasma maximum after 32 ± 62 min with 1822 ± 413 pg/ml). These results could not be reproduced using the experimental conditions above and it is questionable if there would be an increase in plasma concentration after a longer measurement period of inhalation using our tech-

respiratorni trakt (25). Inhalator koji je spojen na T-dio s kisikom može simultano davati i kisik i epinefrin. Osoblje treba podučiti kao se treba koristiti tom napravom, posebice u hitnim slučajevima kao što je anafilaksija. Tim se rezultatima ne može procijeniti ukupna potrebna doza kod težeg oticanja dišnih puteva. Osim toga, tijekom anafilaktičke reakcije kod pacijenata se može dogoditi bronhospazma ili laringealni edem s respiratornim poremećajem (26). Biodostupnost epinefrina u takvoj situaciji vjerojatno je manja negoli kod zdravih ljudi.

Zaključak

Kod respiratornog poremećaja uzrokovanog anafilaksijom mogla bi biti korisna primjena epinefrina inhalacijom (27,28), posebice ako nije moguće uspostaviti venski put (zbog premalo rutine u akutnoj situaciji). U skladu s literaturom, ovo istraživanje potvrđuje da inhalirani epinefrin, barem dijelovi čestica koje stvara protok kisika (kirurški ovlaživač; 76 % čestica manje je od 5μm kod protoka kisika od 8l/min), nije prikladan za stabilizaciju kardiovaskularnog sustava tijekom anafilaksije (29). Vidljive kardiovaskularne reakcije na anafilaksiju, ako nije dostupan venski put, mogu se kontrolirati samo titracijom epinefrina intramuskuralno. Za hitna stanja u stomatološkoj ordinaciji najprikladnija je, čini se, primjena epinefrina intramuskularno u tkivo mišića bukcinatora, osobito ako nije moguće uspostaviti venski put.

Potrebna su daljnja istraživanja na većem broju pacijenata, kako bi se mogao procijeniti klinički utjecaj.

nique. It is arguable if inhaled epinephrine application might also be helpful in cases of anaphylaxis with predominant vascular symptoms. According to the present knowledge this type of application is very effective by primary impacts of the anaphylaxis on the respiratory tract (25). With an oxygen flow driven inhaler connected to T-piece and an oxygen demand valve resuscitator it is possible to administer oxygen simultaneously to epinephrine. Easy handling of the device supports its use. Staff should be trained to use a demand valve, particularly in urgent situations such as anaphylaxis. The results presented here cannot estimate the total dose required in cases of massive swelling in the airways. Furthermore during an anaphylactic reaction patients may present with bronchospasm or laryngeal edema with respiratory distress (26). Bioavailability of epinephrine would presumably be more limited than in healthy people.

Conclusion

In cases of respiratory distress when anaphylaxis is a possible cause, at first the application of epinephrine by inhalation may be of value (27, 28), especially when intravenous access cannot be used (i.e. due to a lack of routine during an acute situation). In accordance to the pertinent literature, the present study confirms that inhaled epinephrine, at least at the particles size generated by oxygen flow (Intersurgical Nebuliser: 76% of particles sized less than 5μm at oxygen flow of 8l/min), is not suitable to stabilize the cardiovascular system in a state of anaphylaxis (29). Manifest major cardiovascular reactions according to anaphylaxis without availability of a venous access can only be treated by titration of epinephrine given intramuscularly. For the dental office emergency treatment the intramuscular injection of epinephrine into the buccinator muscle of the respective patient seems to be a feasible method for dentists in cases when an intravenous line cannot be established. Further studies on larger series are needed to determine the clinical impact.

Abstract
Purpose: The intravenous or intramuscular administration of epinephrine is recommended treatment in systemic anaphylaxis. The goal was to evaluate epinephrine plasma levels after intramuscular injection into the buccinator muscle in comparison to inhaled epinephrine. **Methods:** In this pilot study in humans, we measured plasma epinephrine concentrations before and after epinephrine administration by intramuscular injection, or by inhalation, with intramuscular saline and intravenous epinephrine as the negative and positive controls, respectively. **Results:** Peak plasma epinephrine concentrations were higher after epinephrine was injected intramuscularly with a maximum plasma epinephrine concentration of 3367.2 pg/ml. After administration by inhalation epinephrine peak level was 151.89 pg/ml. **Conclusions:** In cases of respiratory distress when anaphylaxis is a possible cause, at first the application of epinephrine by inhalation may be of value. Manifest major cardiovascular reactions according to anaphylaxis without availability of a venous access can only be treated by titration of epinephrine intramuscularly. The buccinator muscle is a useful site for dentists involved on treatment of anaphylaxis.

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Key words
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